SEVENTH FRAMEWORK PROGRAMME "COOPERATION"

THEME "HEALTH"

PRIMA-eDS – Project Final Report

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Final Report

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Table of Contents

List of abbreviations

ATC-Code	anatomical therapeutic chemical code
CDSR	cochrane database of systematic reviews
CMR	comprehensive medication review
COPD	chronic obstructive pulmonary disease
cRCT	cluster randomised controlled trial
CRF	case report form
CRN-NWC	clinical research network north west coast
DARE	database of abstracts of reviews of effects
EbM	evidence based medicine
EbMeDS	evidence based medicine electronic decision support

eCMR	electronic comprehensive medication review
eCRF	electronic case report form
eDS	electronic decision support
EHR	electronic health record
EQuiP	European Society for Quality and Safety in Family Practice
GCP	good clinical practice
GIN	Guidelines International Network
GP	General practitioner, general practice
ICD10	international statistical classification of diseases version 10
ISRCTN	international standard randomised controlled trial number
KKS	Koordinierungszentrum für Klinische Studien (clinical trial centre)
MAI	medication appropriateness index
NOAC	new oral anticoagulant
NP	nurse practitioner
NSAID	nonsteroidal antiinflammatory drug
PICOS	population-intervention-comparator-study design
PIM	potentially inappropriate medication
PM	person month
RCT	randomised controlled trial
SDMC	safety and data monitoring committee
SNRI	serotonin noradrenalin reuptake inhibitor
SOP	standard operating procedure
SR	systematic review
SSRI	selective serotonin reuptake inhibitor
SVeMG	scuola veneta di medicina generale
VKA	vitamin K antagonist
WP	work package

1 Final Publishable Summary Report

1.1 Executive Summary

Polypharmacy constitutes an increasing problem in older multimorbid patients. The prevalence of polypharmacy in the population >75 years has been found to be between 25 and 50%. While there exists only limited evidence regarding the benefit, the evidence regarding potential harm of polypharmacy is increasing. Thus polypharmacy and inappropriate prescribing have been shown to increase the risk of adverse drug events, and contribute substantially to morbidity, hospitalization, and mortality. An Austria study found that 10% of hospitalizations of patients >70 years are directly related to an adverse drug event. This clearly indicates that there is a strong need to reduce inappropriate drug prescription. Diverse heterogeneous approaches to reduce polypharmacy and inappropriate prescribing have been proposed, but none of these have been evaluated regarding practicability in primary care and clinically relevant endpoints within a sufficiently powered randomized controlled trial. The most popular approach to reduce inappropriate prescribing is at present the implementation of Potentially Inappropriate Medication (PIM)-lists as like the Beers-List. These lists are based on Delphi-rounds of experts (mostly pharmacologists and geriatricians) and not on evidence derived from clinical studies, and they never have been shown to have any effect on clinical outcome. Other approaches include the STOPP-criteria of Gallagher 2008, updated in 2015, or the Medication Appropriateness Index (MAI). None of these tools have been sufficiently evaluated regarding clinical outcome, and they are hardly applicable in every day practice. Using a combination of these methods, we found in a study of 169 primary care patients from 22 practices an average of 2.7 inappropriate medications per patient. But physicians in every day clinical practice, and especially general practitioners (GPs) are unable to do thorough medication reviews with their patients due to knowledge gaps and limited time. Therefore in the PRIMA-eDS project, we developed an electronic decision support (eDS) tool to assist physicians and patients to avoid inappropriate medication and polypharmacy, and to identify prescriptions where risks outweigh possible benefits of the drug treatment. This tool is based on current best evidence to optimize treatment of those diseases that are most common in elderly patients like cardiovascular disease, heart failure, hypertension, atrial fibrillation, diabetes mellitus type 2, musculoskeletal disorders, COPD, and mental diseases. We collated this evidence from Duodecim's Evidence based Medicine Guidelines and several systematic reviews and transformed it into recommendations to optimize drug treatment of multimorbid older patients. These recommendations were integrated in the existing EbMeDS electronic decision support together with various commercially available databases to check medication for renal dosing, interactions, indications, contraindications and potential adverse drug events. The tool was then evaluated in a cluster randomized controlled trial with 3904 patients >75 years taking at least 8 different medications. The trial revealed a trend towards a reduction of the composite endpoint of mortality and first hospitalisation in intention to treat analysis, and a significant reduction of this endpoint in per protocol analysis. Also, a significant reduction in the number of drugs prescribed to the patients in the intervention group could be shown. Qualitative and quantitative usability analysis of the tool revealed that it must be integrated in existing electronic health records for wider use. Overall, the PRIM-eDS-tool could be shown to be a promising approach to deal with the increasing problem of polypharmacy in our society. It will help to reduce inappropriate prescribing and improve health and outcome in older patients with polypharmacy.

1.2 Project Context and Objectives

1.2.1 Context of the PRIMA-eDS-project

The prevalence of chronic comorbidity and multimorbidity is substantial, and affects more than half of the population > 75 years of age. The patterns of chronic multimorbidity include mainly the following diseases: cardiovascular disease (including coronary heart disease, cerebrovascular disease and peripheral vascular disease), heart failure, hypertension, atrial fibrillation, diabetes mellitus type 2, musculoskeletal disorders including pain, COPD, and mental diseases like depression and dementia, with heart failure showing the highest rate of comorbidity, being accompanied by an average of 2.9 additional chronic diseases. As a result of multimorbidity, polypharmacy seems to be ever increasing as guideline adherence regarding drug treatment of chronic disease is recommended by policymakers and medical colleges. Depending on definitions and setting between 25 and 50% of all patients > 75 years are exposed to five or more drugs. The benefits of drugs are usually shown in studies including mostly younger subjects without comorbidity and multiple medications. The patients involved in clinical trials usually are characterized by a life expectancy of many years. Therefore the results of these studies may not be applied to older comorbid patients on polypharmacy and with reduced life expectancy. It has been shown that most clinical practice guidelines do not modify or discuss the applicability of their recommendations for older patients with multiple comorbid diseases, and following all the guidelines might lead to distinct polypharmacy with increased risk of adverse reactions and interactions between drugs, outweighing the potential benefits of drug treatment.

According to a systematic review including all settings, the overall adverse drug event (ADE) rate lies at a median of 14.9% per 1000 person-months and increases with age and polypharmacy. In a recent systematic review focusing particularly on the primary care setting, we found the prevalence rate for ADEs to be about 10% in prospective studies. Up to 50% of these ADEs are judged to be preventable. Various international studies found a hospitalisation rate due to adverse drug events between 2.4 and 16.6%, depending largely on the age-group evaluated. Polypharmacy and inappropriate medication have been shown to contribute substantially to the burden of morbidity, hospitalisation and death.

According to the 2017 drug prescribing report of the AOK (German statutory health insurance) 78.7% of all prescriptions are handed to patients by primary care physicians (primary care physicians in Germany are General Practitioners and General Internists). Any intervention aimed at the reduction of polypharmacy will therefore be most effective, if the professional group of primary care physicians is targeted. Although there exists only limited evidence regarding the benefit of guideline-recommended drugs in polymorbid older patients, GPs are reluctant to discontinue medication initiated by specialists and hospital physicians. Recently, distinct guidelines to deal with polypharmacy have been developed, but physicians are insecure in the reduction of polypharmacy, and there is significant risk of legal consequences when deviating from guidelines dealing with single diseases. Also, it may take too much time to convince patients that they should discontinue drugs they have been prescribed by a specialist. Adequate tools and an easily accessible knowledge base to aid GPs and patients in their shared decision to reduce polypharmacy do not exist.

1.2.2 Objectives of PRIMA-eDS

With the background of the increasing problem of polypharmacy regarding health outcomes and the inability of primary care physicians as the main prescribers of polypharmacy to deal with this problem, PRIMA-eDS set out to develop a usable solution for every day practice in the form of electronic decision support. After the development of the tool, this new approach to dealing with inappropriate prescribing and polypharmacy has been tested in a randomized controlled trial.

In detail, the objectives of PRIMA-eDS were as follows:

- to carry out a series of systematic reviews of the literature, evaluating and defining current best evidence regarding the pharmacological treatment of elderly patients with multiple chronic diseases, specifically addressing the problem of polypharmacy in the treatment of the most common chronic diseases in elderly populations,

- to develop an electronic decision support tool (PRIMA-eDS-tool) based on existing EbMeDS-technology developed by Duodecim ltd. to aid physicians and patients to make use of current best evidence when coming to a shared decision regarding multiple drug treatment of the most common chronic diseases in elderly populations,

- to test the efficacy of the PRIMA-eDS-tool in an appropriately powered, multinational, multicentre cluster-randomised controlled trial with a composite of hospital admission and mortality as the primary endpoint, the number of prescribed drugs as secondary endpoint, and mortality and adverse drug events as safety endpoints,

- to optimise the PRIMA-eDS-tool with the results of a qualitative and quantitative usability test and the randomised controlled trial, and make it available for widespread use within and outside of Europe.

1.2.2.1 Objective 1: Gathering current best evidence

First, we aimed to gather current best evidence to optimize treatment of those diseases that are most common in elderly patients like cardiovascular disease, heart failure, hypertension, atrial fibrillation, diabetes mellitus type 2, musculoskeletal disorders, COPD, and mental diseases. We carried out a series of systematic reviews of the literature focused on the treatment of multiple chronic diseases in the primary care setting. We made use of existing reviews (e.g. Cochrane-reviews) and guidelines and checked these reviews and guidelines for applicability and validity regarding their use in an elderly multimorbid population. A further systematic review focused on existing strategies and tools to reduce polypharmacy like the Garfinkel-algorithm, the Beers list, the STOPP-criteria, the medication appropriateness index (MAI) and others. Our systematic reviews were carried out with highest standards in methodology as described by the Cochrane Handbook 5.1.0. Objective 1 was the main focus of Work Package 2 of the PRIMA-eDS-project.

1.2.2.2 Objective 2: Development and implementation of the eDS-tool

Secondly, we used the evidence obtained in Objective 1 to develop a sustainable electronic decision support (eDS) tool to reduce polypharmacy and inappropriate medication in older patients that can be easily applied in daily primary care practice. The ttol was based on the existing EbMeDS-technology developed by Duodecim ltd. (www.ebmeds.org). EbMeDS uses predefined decision rules and risk estimation functions based on patient data from the electronic health record, and current best evidence to aid physicians and patients in their shared decision making about optimal therapy.

In the PRIMA-eDS-project, diagnoses, medication, and patient baseline data like laboratory test results, renal function, weight, height etc. were transferred to a pseudonomized electronic case report form (eCRF) online which interacted online with the web-based eDS-tool thus providing alerts to the physician, if a specific medication should be avoided or discontinued according to current best evidence. The tool not only supports the GP in the reduction of polypharmacy and inappropriate medication, but also helps to convince the patient when medication should be discontinued for the better, and at the same time provides forensic assurance in the form of background evidence, if discontinuation is contradictory to existing mono-disease guidelines. Objective 2 was the main focus of Work Packages 3-4 of the PRIMA-eDS-project.

1.2.2.3 Objective 3: Evaluation of the eDS-tool

Thirdly, we set out to compare the clinical outcome of existing treatment regimens (applying polypharmacy in the treatment of multimorbidity, i.e. usual care) with the PRIMA-eDS-aided drug regimen reducing polypharmacy and inappropriate prescribing in a multinational, multicentre randomised controlled trial (RCT). From the studies of Garfinkel we have preliminary evidence that the prudent reduction of polypharmacy is beneficial to the patient, but the algorithm Garfinkel used in his study has not been proven to be effective in a randomized controlled trial. There is also limited evidence that Beers' criteria characterizing inappropriate medication for the elderly are associated with adverse outcome, but this evidence is mostly based on retrospective cohort studies. Similarly, the STOPP-criteria have been shown to be associated with adverse drug events, but it has never been shown convincingly that their application reduces ADEs. In the PRIMA-eDS-trial we set out to prove that the prudential reduction of polypharmacy in the targeted diseases by avoiding inappropriate and non-evidence-based medication in older populations leads to a reduction of the hospital admission rate and adverse events and improves quality of life and mental as well as physical functioning. We intend to achieve the reduction of polypharmacy by eliminating non-evidence based drug therapy and prioritising medication in case of possibly dangerous drug-drug-interactions in a standardized fashion by using the PRIMA-eDS-tool developed for objective 2. Objective 3 was the main focus of Work Packages 5-9 of the PRIMA-eDS-project.

1.2.2.4 Objective 4: Optimization of the eDS-tool and dissemination

Fourthly, we evaluated the PRIMA-eDS-trial and continuously updated and optimized the PRIMA-eDS-tool with the findings of the RCT and continuous evidence-updates. The optimized tool is available as "Comprehensive Medication Review" by Duodecim ltd. and will be disseminated for widespread general utilization in Europe and outside Europe. Objective 4 was the main focus of Work Packages 10-12 of the PRIMA-eDS-project.

1.3 Main S&T results/foregrounds

1.3.1 Gathering the evidence and development of the PRIMA-eDS-tool

1.3.1.1 Systematic reviews

We prepared a set of systematic reviews (SRs) on the drugs which are the most commonly prescribed to older people and which are associated with an increased risk of hospitalization due to adverse

events in this population. The selection of the drugs was done using national prescription databases as well as published studies identified in the literature.

To shorten the review process while maintaining highest quality according to the Cochrane-handbook we developed a distinct methodology. A template for a systematic review study protocol to be used for all reviews carried out within PRIMA-eDS was developed. We then developed Standard Operating Procedures (SOP) for the reviewers to follow, with the aim to standardize our review work.

We aimed at including SRs, meta-analyses, clinical trials and observational studies which included a sufficient number of participants aged 65 years old and older (mean age ≥ 65 or > 80% studies with mean age ≥ 65 or subgroup analysis by age for SRs; >80% participants aged ≥ 65 or subgroup analysis by age for original studies) and which evaluated clinically relevant endpoints. A stepwise approach was carried out for the selection of studies including the following searches: search 1 (systematic reviews and meta-analyses from 2 databases: Cochrane Database of Systematic Reviews [CDSR] and Database of Abstracts of Reviews of Effects [DARE]), search 2 (systematic reviews and meta-analyses from 4 databases: MEDLINE, EMBASE, Health Technology Assessment Database, International Pharmaceutical Abstracts database), search 3A (individual studies meeting inclusion criteria from excluded studies in search 1 and/or 2), search 3B (intervention and observational studies from 4 databases: MEDLINE, EMBASE, Health Technology Assessment Database, International Pharmaceutical Abstracts database). Additional references which were excluded but considered of interest for the development of recommendations were also collected. Each consecutive step of the search strategy was only employed if the preceding step did not yield sufficient results to collate the evidence and derive recommendations.

Each SR has been undertaken by two independent reviewers who have followed the reviews' protocol and the SOP using piloted excel documents to report the selection of studies, data extraction and quality appraisal. Validated instruments have been used to evaluate the quality of the included studies. Recommendations on when to discontinue or adjust the dose of one of the studied drugs have been developed by the researchers using GRADE methodology. Approximately 2 or 3 team meetings per SR were necessary for the development of recommendations, in which the researchers involved in each SR as well as clinicians and senior researchers took part. Recommendations were developed using a standardized wording schema providing information about the strength of the recommendation and the quality of the evidence. Once recommendations had been developed, they were peer reviewed by a team of experts in evidence based medicine provided by DMP.

Twenty-one SRs on 17 drug classes have been performed. In total, 210 articles have been included (59 SR or MA, 97 CIS, 54 OS), the number of included references per drug class ranging from 0 to 28. The inclusion of studies due to subgroup analysis by age was frequent; information on comorbidity and concomitant use of other drugs was often not available. Often reported outcomes were mortality, hospitalization, cardiovascular events including stroke, adverse drug event, and safety. The quality of the studies included ranged from very low to high.

Forty-two recommendations to discontinue or reconsider the use of the studied drugs or to adjust their doses have been. The quality of the evidence was often downgraded because it was based on subgroup analyses; the strength of the recommendations was most frequently weak. Fifty references were additionally taken into consideration.

Table 1 displays the overview of SRs as well as the information on the number of studies identified in each search, the number of studies included, excluded, considered of interest, and the number of recommendations developed for each SR.

Table 1: Systematic reviews on drug treatment for the development of PRIMA-eDS-stop-recommendations

Drug groups (condition)	Search 1	Search 2	Search 3.A	Search 3.B	Excluded full-texts	Included articles	Additional references of interest	Recommendations
β-blockers (hypertension)	130	232	19	NN	132	5 (4 RCT, 1 MA)	3 CR, 1 RCT	3
β-blockers (heart failure)	82	187	17	NN	54	6 (1 SR, 1 MA, 2 OS, 2 RCT)		0
NSAIDs (musculoskeletal disorders)	38	204	229	NN	184	27 (5 SR, 7 RCT, 15 OS)	1 PIM list	1
Statins (prevention of cardiovascular disease)	78	122	NN	NN	73	8 (7 MA, 1 HTA Review)	1 Review, 1 MA, 1 RCT	1
Thiazides (heart failure)	42	101	16	947	43	0	1 OS, 1 CR, 1 NR, 1 CG	1
Thiazides (oedema)								1
Thiazides (hypertension)	188		242	NN	234	35 (5 OS, 29 RCT, 1 CT)		3
Calcium antagonists (angina)	24	43	2	880	71	2 (1 RCT, 1 OS)	1 MA; 1 CG	2
Calcium antagonists (hypertension)	156	217	86	NN	134	5 (3 RCT, 2 OS)	1 PIM list	2
High ceiling diuretics (heart failure, oedema, hypertension, liver failure, and renal failure)	103		19	2456	37	3 OS		2
Platelet aggregation inhibitors (cerebral infarction and prevention of cerebral infarction and transient ischaemic attack, peripheral artery occlusive disease, coronary disease)	713		150	NN	194	28 (11 SR, 15 RCT, 2 OS)	1 MA	3
VKA/NOACs (thromboembolism in atrial fibrillation)	102 update: 77	217 update: 59	NN	NN	90 update: 17	26 (15 MA, 5 CR, 2 SR, 4 indirect comparisons)	0	0
Vitamin K antagonists (deep vein thrombosis/lung embolism)	74	67	23	1905	164	10 (1 SR, 9 RCT)	8 references from Guidelines	1
NOACs (deep vein thrombosis/lung embolism)							1 EO, 1 PIM list	4
Metformin (type 2 diabetes)	76	82	64	649	201	3 (2 RCT, 1 OS)	1 CG	4
Gliptins (type 2 diabetes)	19	27	9	627	236	16 (1 MA, 12 RCT, 3 OS)	1 MA, 2 RCT, 2 OS, 1 SA	1
Pioglitazone (type 2 diabetes)	58	48	16	NN	52	1 (MA)	1 CR, 1 RCT, 1 MA, 2 SR&MA, 1 NR	1
Sulfonylureas + glinides (type 2 diabetes)	38	61	75	NN	71	2 (2 OS)	1 CR	2
Insulin (type 2 diabetes)	197	283	47	NN	90	8 (5 OS, 3 RCT)	1 PA, 2 RCT, 5 OS	3
Nitrates (angina)	126		30	NN	40	3 (2 RCT, 1 OS)	1 CG	1
Digoxin (heart failure)	42	84	83	NN	44	4 (2 RCT, 2 CT)		1
Opioids	670		37	NN	139	18 (2 MA, 1 SR, 3 CT, 12 OS)	1 CG	3

Legend: The values included in the table are numbers of studies. CG=Clinical Guideline; CR=Cochrane Review; CT=Clinical trials; EC=expert consensus; EO=expert opinion; HTA=Health technology assessment; MA= Meta-analysis; NN=not necessary; NR=narrative review; NSAIDs=Nonsteroidal anti-inflammatory drugs; OS=observational study; PIM= potentially inappropriate medication; RCT=randomized controlled trial; SA=safety assessment; SR=Systematic review; VKA/NOACs=vitamin K antagonists/new oral anticoagulants

Table 2 presents a sample of 12 recommendations developed for 5 drug-indication pairs, in the way they have been incorporated into the tool.

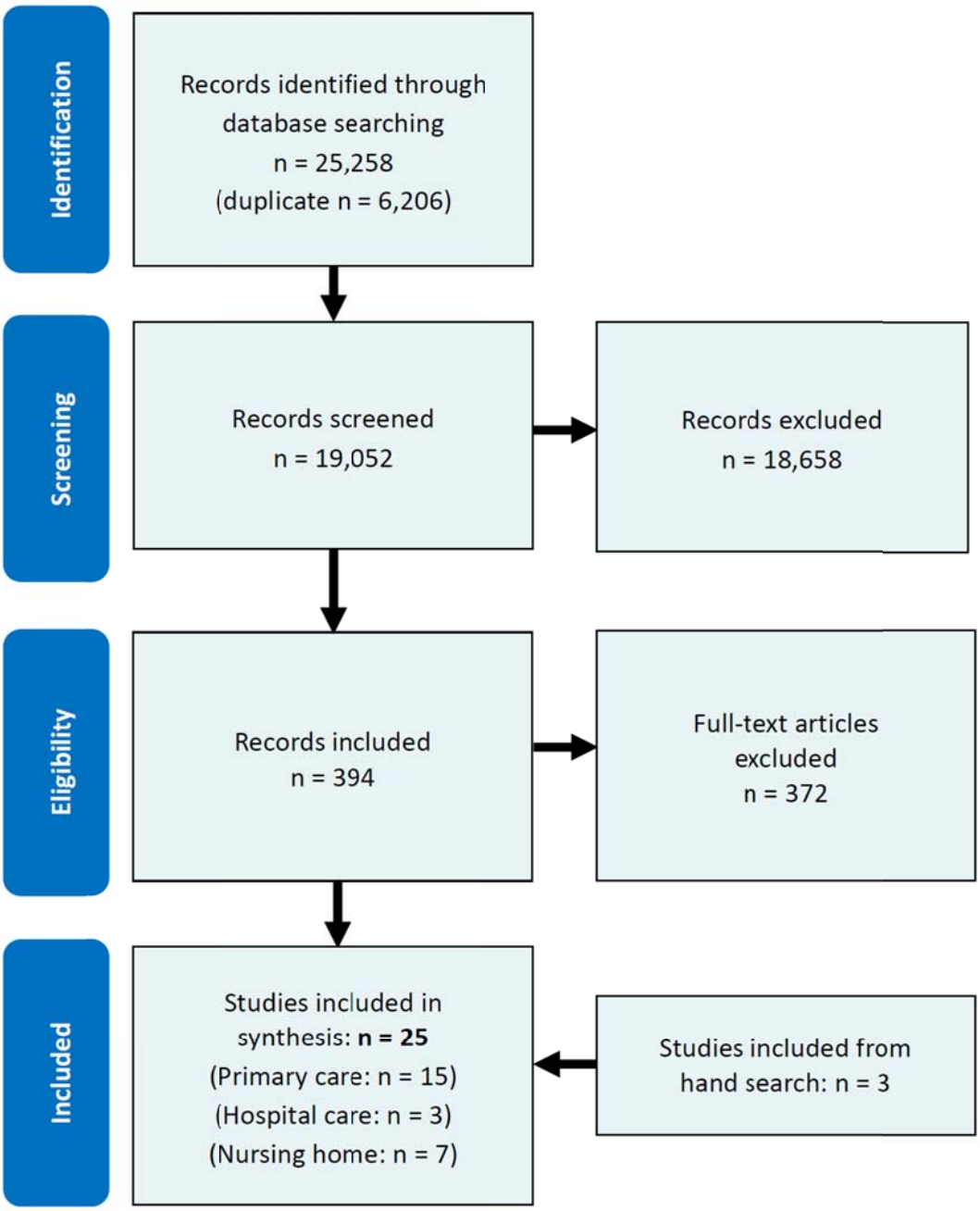
Table 2: Recommendations for a sample of 5 drug-indication pairs derives from the PRIMA-eDS systematic reviews

Recommendation	Strength of the recommendation/Quality of the evidence
Opioids/Pain	
It is suggested not to start transdermal fentanyl delivery system (TTS fentanyl) at a dose of 25 mcg/h or higher for non-malignant chronic pain, especially in older people, because benefits (lower pain, improvement in quality of life) are similar compared to starting with lower doses (12.5 mcg/h) and adverse events are higher.	Weak/Low
It is suggested to use the lowest possible dose of oral opioids for the management of chronic non-cancer pain because higher doses (e.g. >=40 mg/d of Morphine - the patient is using [here the eDS-tool automatically inserts the dose the patient is taking]/d) may increase the risk of fractures while there is less confidence of this risk for lower doses. However, adequate pain relief is a priority, and the minimum dose that effectively meets this goal should be used.	Weak/Low
It is suggested to discontinue codeine or codeine combinations because codeine may increase the risk of fractures (probably due to falls), cardiovascular outcomes, hospitalizations and all-cause mortality compared to other opioids or non-use of codeine.	Weak/Low
Non-steroidal anti-inflammatory drugs (NSAIDs)/Musculosceletal disorders	
It is recommended to discontinue the use of NSAIDs because it might increase the risk of cardiovascular events. If necessary, naproxen and the additional use of proton-pump inhibitors (PPI) might be considered if the gastrointestinal risk is high (e.g. history of peptic ulcer, upper gastrointestinal bleeding). If PPIs are used in addition to NSAID, it is recommended to discontinue also PPI after 2 weeks when discontinuing NSAID.	Strong/low
Thiazides/Hypertension	
It is suggested to reduce high doses of thiazides for the management of hypertension because high doses (50 to 90 mg/day hydrochlorothiazide or equivalent) may be less effective in reducing mortality and coronary artery disease and may be associated with higher risk of gout compared to other antihypertensive medication including low thiazide doses. If the patient has also heart failure, please take the symptoms of heart failure additionally into account.	Weak/Low
It is suggested to discontinue both drugs belonging to the combination of hydrochlorothiazide and triamterene in older adults over the age of 80 because the benefits of this treatment may not be established in this age group when compared with placebo and because it may be associated with the development of gouty arthritis, especially in men with high serum uric acid and creatinine levels.	Weak/Low

Six of the systematic reviews and the methodology have been published in a peer reviewed journal.

An additional systematic review explored the effectiveness and impact of strategies to reduce polypharmacy (≥4 drugs) on health outcomes, processes of care, health resources, cost-effectiveness, as well as user and patient satisfaction/acceptance in older (≥65 years) patients, with the aim, to optimize the PRIMA-eDS-tool regarding efficacy. A PICOS-framework (population, intervention, control, outcome and study design) was used in order to specify the research questions and their elements used as study selection criteria. We used the GRADE Pro assessment tool to assess the quality of studies reporting on mortality and hospitalization (critical endpoints). In total 25 studies were included in this systematic review (Figure 1: PRISMA Flow Diagram). We identified three main categories of different types of interventions (pharmacist led interventions, physician led interventions and multidisciplinary team led interventions) and three main categories of settings where the interventions were implemented (primary care setting, nursing home setting, hospital setting). Participants' (appropriate) medication use was reviewed using different methods (tools and instruments), whereof we identified four main methods: checklists (e.g. MAI, the Beers list), drug-drug interactions tools (e.g. software, lists), reconciliation methods and expert opinion. Performance of medication review and the decision criteria were not always described in detail in the included studies. The included studies provide limited evidence due to small sample sizes, poor quality, risk of bias, and short follow-up periods.

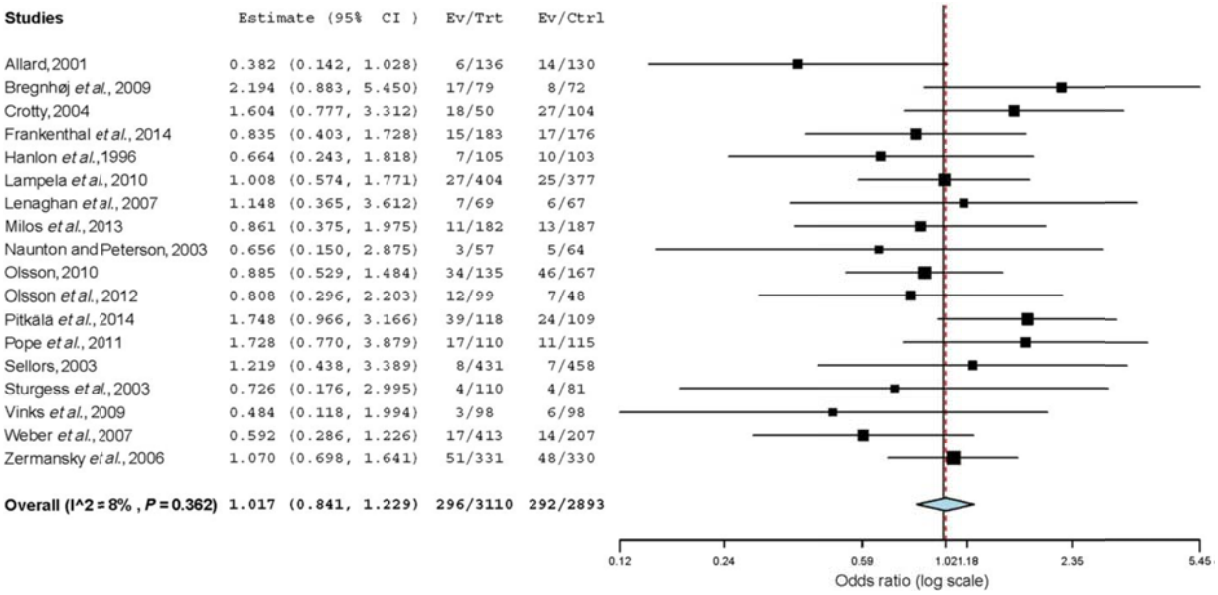
Figure 1: PRISMA-Flow-Diagram of the systematic review on strategies to reduce polypharmacy



Remarkable heterogeneity was found between studies. On the one hand, there was clinical heterogeneity in terms of populations, intensity and duration of interventions, outcomes, and follow-up times. On the other hand, there was also methodological heterogeneity such as differences in trial design (17 RCTs, 4 cluster-RCTs and 4 non-randomized controlled trials) and quality. Due to these inequalities a consistent interpretation of the results was seriously limited.

Overall the interventions had very limited effect regarding our outcomes of interest. Neither any single study nor our meta-analysis of effects on all-cause mortality during the study period showed any significant effect in favour of the intervention group (OR: 1.02, 95 % CI 0.84 to 1.23) (see fig. 2).

Figure 2: Metaanalysis of the primary endpoint (mortality) of the systematic review on strategies to reduce polypharmacy



Only single studies found improvements in hospitalization in favour of the intervention group. The weighted mean including all prescribed drugs at baseline was in both groups 7.4 drugs per patient. At follow-up the weighted mean of drugs was reduced (-0.2) in the intervention group while it increased (+0.2) in controls but the difference did not reach significance. Further 12 outcome measures of interest were analysed in this SR but only single studies revealed significant differences between intervention and control (probably due to multiple testing and chance).

The evidence regarding effectiveness of interventions in the included studies is rather weak. It is unclear how to ideally organize and implement interventions (pharmacist led, physician led or led by a multidisciplinary team) in order to achieve clinically significant improvements in multimorbid older patients with polypharmacy. There is a great need of large long-term RCTs exploring the effect of strategies to reduce polypharmacy on clinically relevant patient outcome measures such as mortality and hospitalization. Thus the PRIMA-eDS trial is well justified. The harms of polypharmacy are well documented in the scientific literature, but it is not proven yet that interventions to reduce polypharmacy have a positive effect on patients' outcome. Furthermore best practice models to reduce polypharmacy are still lacking. Due to the demographic development, the burden of chronic diseases and polypharmacy will increase. Polypharmacy is an emergent problem and a societal and economic challenge for most health care systems.

1.3.1.2 Building up the PRIMA-eDS-tool

In addition to the evidence derived from the systematic reviews carried out within the PRIMA-eDS-project, existing evidence was used to build the PRIMA-eDS-tool. DMP produced a list of recommendations which were relevant to older people under polypharmacy developed from the existing EbMeDS data base. Researchers with medical background from UWH gave feedback to this list of recommendations and an agreement was reached about important recommendations for older people. Thus, DMP identified a total of 1638 evidence summaries from EBM Guidelines (www.ebm-guidelines.com or www.ebm-guidelines.at) that were relevant for pharmacotherapy in

older individuals. Selected evidence summaries were used as a basis of recommendations along with the results of the systematic reviews.

A total of 147 individual rules were included in the eDS tool, containing more than 200 different messages. 42 recommendations (messages from the rules) were developed on the basis of the systematic reviews. A general rule reminding that a drug is on the European PIM list was developed. Specific rules for several of the drugs on the PIM list were developed to guide the use of the drugs more accurately. The rest of the included rules were derived and (if necessary) modified from the existing rule set of EBMeDS. Descriptions of the rules and their evidence-base are available at http://www.ebmeds.org/web/guest/scripts?query=prima-eds+&lang=en.

We then incorporated the databases of indications, contraindications, dosing, drug interactions (SFINX®), renal dosing (Renbase®), and adverse effects (PHARAO®) in the PRIMA-eDS-tool. Each of these has a rule that enables the use of the database as part of the eDS tool. SFINX®, Renbase®, PHARAO® are developed and maintained by Medbase Ltd. (www.medbase.fi). Before use in the eDS, modifications were made to the databases by inactivating alerts on drug interactions of low significance, and renal dosing alerts in mild renal dysfunction for drugs. Specific rules were developed for several classes of drugs in Renbase® and in SFINX® to guide decision making more accurately than standard drug database alerts.

The total numbers of different feedback messages from the drug databases included in the eDS tool is 30171 (Table 3) which is about 30% more than anticipated in the project plan. All the messages are available in English, German and Italian.

Table 3: Messages in drug databases included in the eDS tool

Drug – drug Interactions	14565
Drug and Renal Malfunction	5024
Drug Contraindications	3144
Drug Indications	4141
Dosage Warnings	3297
Total	**30171**

A database of laboratory test results relevant for medications was developed on the basis of EBM Guidelines. The database contains reference values of tests related to medications, and recommended follow-up intervals of tests in safety monitoring of drug therapy.

Rule descriptions, rule logic, and executable rules were then developed using the EBMeDS content authoring tool. The testing environment of the EBMeDS content authoring tool was used to test each rule with varying test patient data by a minimum of three people independently of each other before publishing.

Feedback from pilot physicians participating in the study as well as from Finnish users of the eDS tool were analyzed and changes were made to some rules. Of the drug databases, the most extensive changes were made to the indications database where a number of coded indications were added, mostly because missing ICD-10 codes and variable use of the codes by the participating physicians.

The frailty scale on the eCRF was used as input variable to guide some decisions suggested by the rules.

1.3.1.3 Electronic case report form (eCRF) and interfaces

With the aim to make the tool accessible to physicians and to gather data for the PRIMA-eDS randomized trial, we developed an electronic case report form (eCRF) in cooperation with Avain Technologies ltd. The forms application of Avain Technologies Ltd. that is used as the platform for the eCRF is conformant with the Medical Device Directive (class 1 software product).

Search engines for drugs (ATC codes) and diagnoses (ICD-10 codes) were developed, and updated on the basis of user feedback during the first phase of (baseline) data entry of the study. The SF-12 form and the frailty scale were implemented as parts of the eCRF. The functions for outcome data entry require the data to be checked and reported at baseline and at every scheduled visit by asking the users to enter the data and tick a box that the data has been updated.

The functionality of the eCRF form was finalized for the study. Several changes to the original version were made on the basis of the pilot testing. Data export from the eCRF was performed and tested by the statistical team of the consortium.

A screenshot of the first page of the eCRF is shown in figure 3 (German version, the eCRF was alos available in English and Italian for the respective study centres. A print out of an eCRF containing patient data of a test-patient is depicted in figure 4.

Figure 3: Screenshot of the eCRF

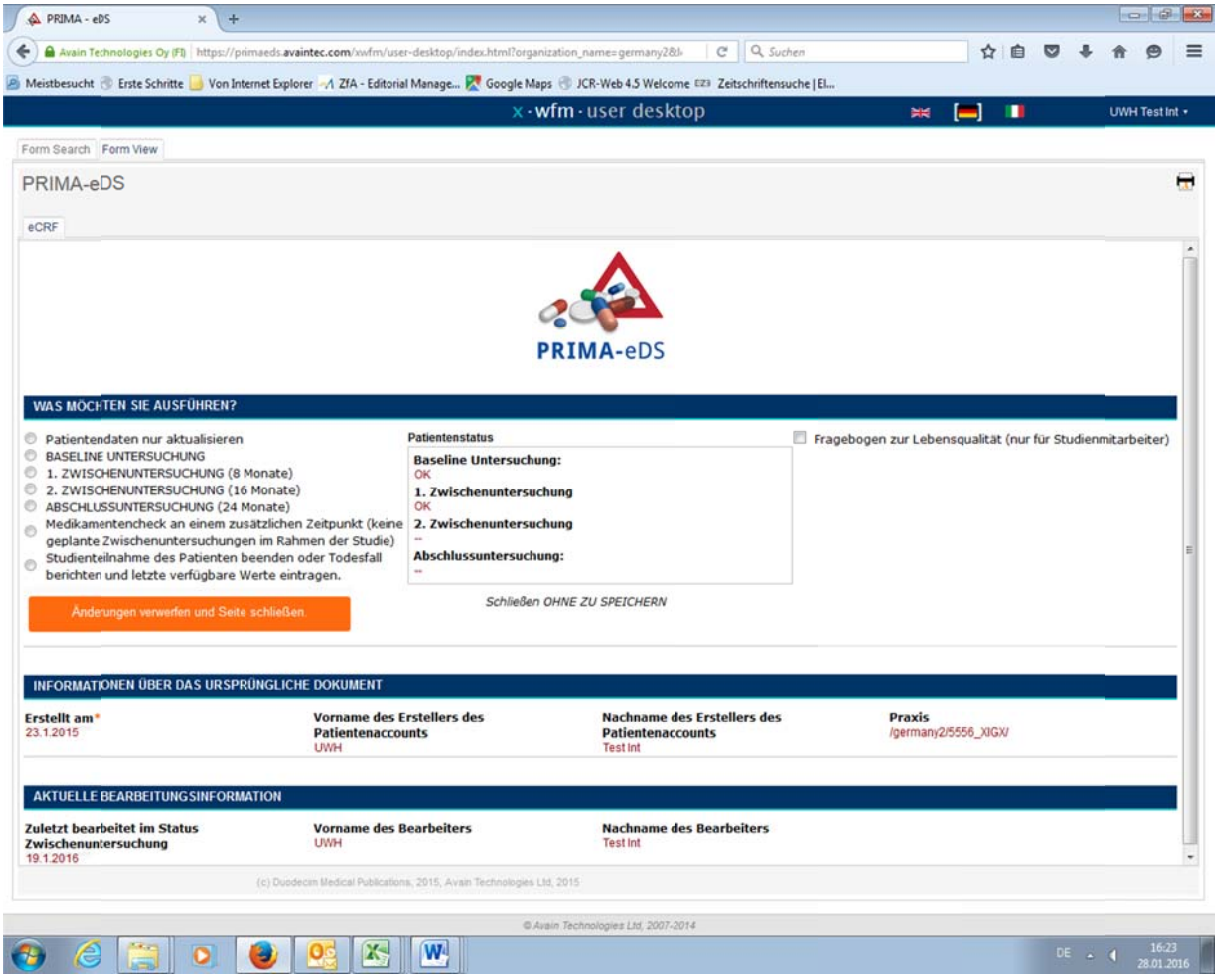


Figure 4a: Printout of the eCRF, part 1

CHOOSE AN OPERATION

* SCHEDULED STUDY visit (0 months)	[ ]6-CIT	[ ]SF-12

PATIENT IDENTITY

Internal Study ID	Patient Identifier *	Born *	Gender *
PID544	99999999	19.1.1927	Male

CURRENT MEDICATION

Generic name	Dosage		Start date		End date
hydrocortisone ** ANTIINFLAMMATORY AGENTS ** OPHTHALMOLOGICALS	Frequency * daily	Adm. route * Topical	Year Older	Month (if known) 1	Date
	Total dose * 1	Unit * g	Reason for discontinuation		
enalapril ** ACE INHIBITORS, PLAIN ** AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	Frequency * daily	Adm. route * Oral	Year Older	Month (if known) 1	Date
	Total dose * 3000	Unit * mg	Reason for discontinuation		
warfarin ** ANTITHROMBOTIC AGENTS ** ANTITHROMBOTIC AGENTS	Frequency * other	Adm. route * Oral	Year 2014	Month (if known) 3	Date
	Total dose * 5	Unit * mg	Reason for discontinuation		
hydrochlorothiazide ** LOW-CEILING DIURETICS, THIAZIDES ** DIURETICS	Frequency * daily	Adm. route * Oral	Year Older	Month (if known) 1	Date
	Total dose * 25	Unit * mg	Reason for discontinuation		
acetylsalicylic acid ** ANTITHROMBOTIC AGENTS ** ANTITHROMBOTIC AGENTS	Frequency * daily	Adm. route * Oral	Year Older	Month (if known) 1	Date
	Total dose * 100	Unit * mg	Reason for discontinuation		
metformin ** BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS ** DRUGS USED IN DIABETES	Frequency * daily	Adm. route * Oral	Year Older	Month (if known) 1	Date
	Total dose * 3000	Unit * mg	Reason for discontinuation		
valsartan ** ANGIOTENSIN II ANTAGONISTS, PLAIN ** AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	Frequency * daily	Adm. route * Oral	Year Older	Month (if known) 1	Date
	Total dose * 40	Unit * mg	Reason for discontinuation		

DIAGNOSES

Primary hypertension (I10) Type 2 diabetes (E11) Chronic heart failure (I50) Stroke or TIA (I64) Renal insufficiency is automatically calculated from the GFR.	Depression (F32) Arthrosis (M19)

OTHER DIAGNOSES RELEVANT TO THE MEDICATION

Code	Name	Start	End
M35.3	Polymyalgia rheumatica	20.7.1994	
I48X	Atrial fibrillation and flutter	21.7.2014	

MEDICATION SUSPECTED OF CAUSING ADVERSE DRUG EVENTS

Generic name	Leading symptom	Severity
acetylsalicylic acid ** ANTITHROMBOTIC AGENTS ** ANTITHROMBOTIC AGENTS	Dyspnea	[ ]Severe

SYMPTOMS WITHIN ONE MONTH (PROBABLY) NOT RELATED TO THE MEDICATION

Please provide all currently present symptoms within the time frame of the previous month by ticking the appropriate box.

Figure 4b: Printout of the eCRF, part 2

Symptom	Severe	Symptom	Severe
Constipation Fatigue		Dyspnea Leg swelling Other	

HOSPITALISATIONS

	Reason	Date	Length (nights)

FRACTURES

Please provide all fractures occurred during the course of the study.

Date *	Type of fracture
15.7.2014	Fracture of lumbar spine and pelvis

FALLS

Please provide the date and the severity of injury of all falls of this patient during the course of the study.

Date *	Severity *		
8.7.2014	Serious injury		

MEASUREMENTS AND PROCEDURES

Please provide anthropometric measurements, blood pressure, frailty scale, smoking status and creatinine. Please carry out if not available in your records.
All other lab results are only to be provided if they are available on your records. Otherwise please leave blank as we want to avoid additional laboratory analyses.
Frailty: Read more about frailty scale [http://www.ebmeds.org/cmr/Annex_II_Frailty_scale.pdf]

Measurements

	Value	Unit	Date
Height	* 174	* cm	
Weight	* 67	* kg	* 7.7.2014
BP	* 150 / * 78	mmHg	* 7.7.2014
Frailty scale	* 6 - Moderately frail		
Smoking status	* smoker		
Creatinine	167	µmol/l	30.6.2014
Total Cholesterol	6.8	mmol/l	1.7.2014
HDL Cholesterol	0.78	mmol/l	8.7.2014
Triglycerides	1.7	mmol/l	17.7.2013
LDL Cholesterol			
Fasting Glucose	6.9	mmol/l	7.7.2014
HbA1c	8.9	%	8.6.2011
INR	4.2	-	10.6.2014
B-Hb	109	g/l	21.7.2014
Platelet count	90	10E9/l	15.7.2014
ALT	180	U/l	14.7.2014
Potassium	5.4	mmol/l	29.6.2014
Sodium	124	mmol/l	21.7.2014
Proteinuria	[ ]Yes		

Procedures

Value	Date
[ ]Drug Eluting Stent (DES)	
[ ]Transcatheter Aortic Valve Replacement (TAVI)	
[ ]Heart Valve Replacement mechanical	

INITIAL DOCUMENT INFORMATION

Date *	Creator Firstname	Creator Lastname	HC Unit
22.7.2014	Test	Doctor	/neverland/NVL_HC1_XIGX/

LAST EDIT INFORMATION

Date *	Editor Firstname	Editor Lastname

The eCRF was then connected to the eDS-tool via a specific interface. The interface between the eCRF and eDS has been developed in cooperation with Avain Technologies Ltd. and is based on XML messaging. When data entry on the form has been completed, and the user clicks the "perform medication review" button, the form creates an XML message that is received by the eDS service and analysed using the rules and data tables created for the purpose. The response time of the eDS service is well under 2 seconds. eDS returns an XML message containing suggestions to modify the patient's medications or to improve care by monitoring of potential adverse effects of the medication. The suggestions are then shown in the user interface of the eCMR. A screenshot of the eCMR is shown in fig. 5. The CMR could also be saved in pdf-format and printed if necessary or desired.

Figure 5a: User interface of the eDS tool – part 1.

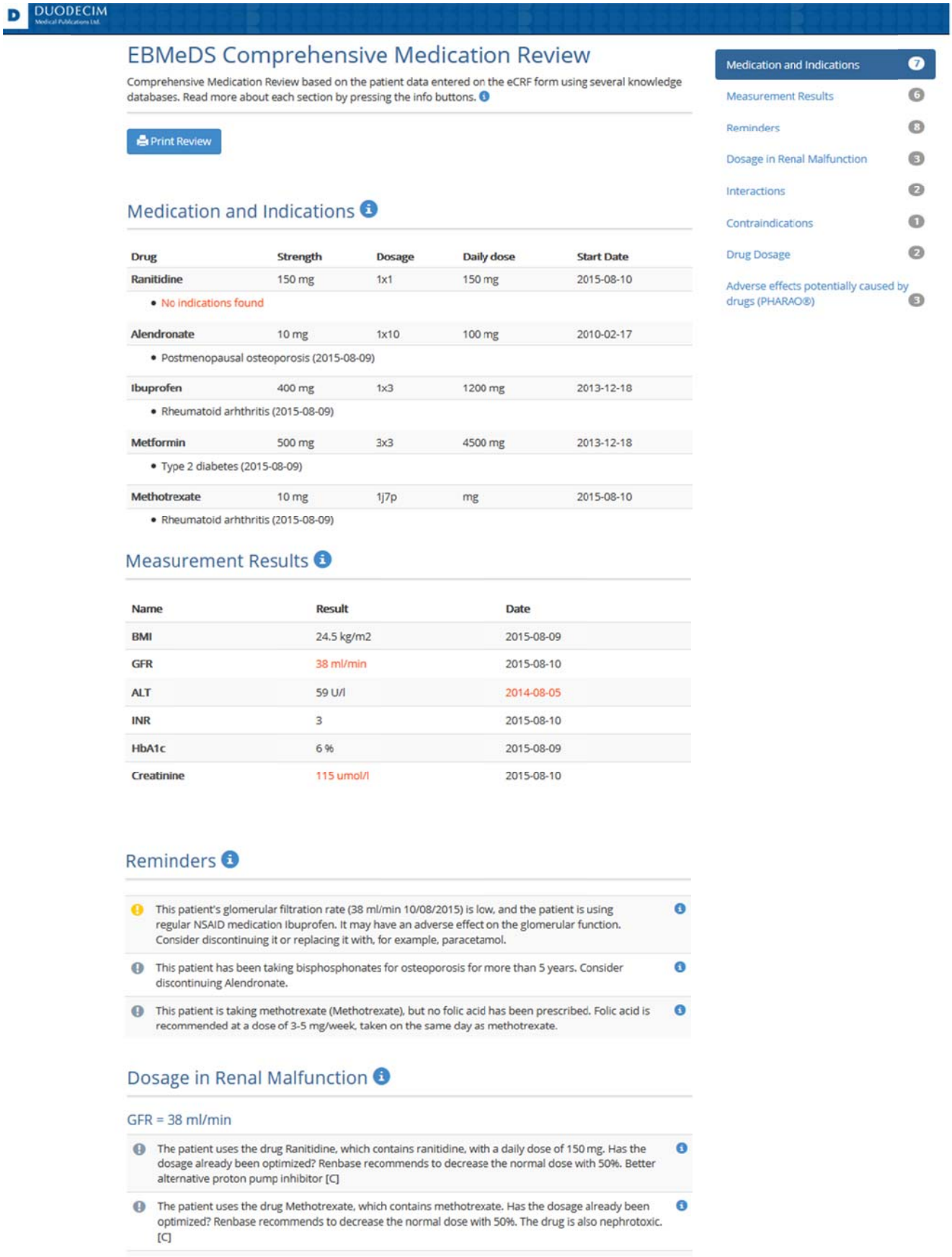
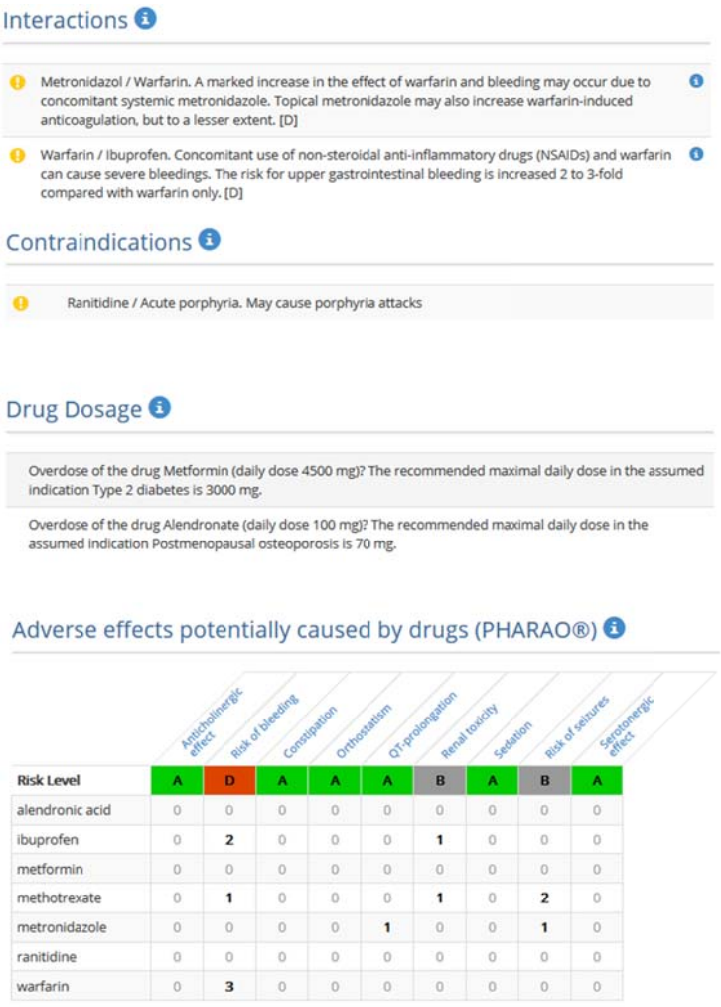


Figure 5b: User interface of the eDS tool – part 2.



All transactions between the eCRF and the EBMeDS (eDS) service were stored in a log file for further analysis. For the control group, the recommendations of the eDS tool were recorded in the log file, but were not shown to the clinician.

Each time the form was updated by the clinician, it was stored on a dedicated server hosted in Finland. When the patient came for a follow-up visit, the form containing previously entered data was collected from the server. The user updated the data and entered the results of the patient assessment. The updated version of the eCRF was then stored on the server.

The data and backup copies of the data (with patient study identification codes created at baseline) were stored on the safe servers of Avain Technologies. Anonymous data for analyses were exported and delivered to be analysed by the statistical team of the consortium.

eCRF and data storage on a central server were protected by special security measures provided by Avain Technologies Ltd. Only authorized users (the clinicians participating in the study and researchers monitoring the study) were able to access the data on the forms. User rights administration by Avain assured that any GP was only able to access data of his own patients. Because confidentiality and safe transfer of the patient data on the form was an absolute requirement, an independent external information security audit has been performed, and an archives certificate has been awarded for Avain Technologies (Certificate number 6692-04, by Inspecta).

1.3.1.4 Pilot study and usability studies

Before starting the PRIMA-eDS-trial, a pilot study was carried out to test and optimize the functionality of the eCRF and the eDS-tool. The main subject identified was the expenditure of time needed for entering patient data into the eCRF. The eCRF form was also perceived as too complex and not simple and intuitive enough to use, especially for those users who do not have much technical experience. Study assistants reported a list of minor bugs and errors back to the DMP team so that they could be corrected as soon as possible. Despite the difficulties encountered when using the study tools, most GPs that have taken part in the pilot study expressed their desire to use the CMR in their practice. Several changes to facilitate data entry were suggested and implemented. For instance, the eCRF was adapted to account for faster data entry and better operability. The CMR output page was adapted and optimized several times to offer compact and fast information to the physician. Usability of the tool have been evaluated in qualitative and quantitative studies, and the results have been incorporated in the tool and the eCRF.

1.3.2 Evaluation of the PRIMA-eDS-tool in a randomized controlled trial

1.3.2.1 Study protocol, ethics approval and trial registration

In parallel to the development of the tool, the PRIMA-eDS randomized controlled trial was planned and initiated. The study protocol has been finalized including final sample size calculation. In 2016 the study protocol was published in a peer reviewed journal. Ethics approval for the coordinating study centre (UWH) was granted on December 3rd, 2013. The study has been approved unconditionally by the ethics committee of Salzburg on the 8th of April 2014 for PMU. The study was approved by the Ethics Committee of the Rostock University Medical Centre on February 14th, 2014 (Approval-No. A 2014-0020). Ethics approval for SAGP was granted on the 19th of June 2013 by the Ethics Committee of Belluno. Ethics approval for UNIMAN was obtained on the 6th of June 2014 at the Ethics Committee of NRES Committee North West - Greater Manchester East. Due to extension of the study to other research networks because of recruiting problems we had to obtain additional ethics approvals of local authorities in the UK and of the Bavarian Chamber of Physicians (Bayerische

Ärztekammer) which were granted before the start of the trial. Trial registration was performed July 31, 2014 with Current Controlled Trials ltd (http://www.controlled-trials.com/ISRCTN10137559).

1.3.2.2 Physician recruitment

Due to regional differences regarding the health system and organisational differences in primary healthcare, each study centre had to develop its own standard operating procedures regarding recruitment. To account for these differences in the trial and to avoid bias due to the existing differences between countries, randomisation was stratified by country. The procedures of GP recruitment were as follows:

UWH

Recruitment of GP practices took place in three waves. We obtained lists of all practicing GPs under statutory health insurance of the Westfalen-Lippe region and adjacent regions from the "Kassenärztliche Vereinigung Westfalen-Lippe" and the "Kassenärztliche Vereinigung Nordrhein". We informed the GPs in writing about the PRIMA-eDS trial and asked for a response by fax expressing interest to participate. In total we contacted 1192 physicians. The overall first response rate expressing interest was approximately 10 %, finally 76 GPs recruited patients (response rate 6.4%).

UMR

At the Rostock study centre, recruitment of GPs via mail started in February 2014. In May 2014 a total of 74 GPs decided to enroll for the study. Unfortunately, between June 2014 and April 2015 18 of these GPs changed their mind and withdrew from the study. Reasons included e.g. a loss of interest, or too long waiting time until the start of the trial. Rostock study centre therefore decided to further recruit in the area of Mecklenburg-Western Pomerania as well as in Berlin. Over the entire recruitment period a total of 1.730 GPs from the regions Mecklenburg Western-Pomerania (1.120 GPs), Schleswig-Holstein (50 GPs) and Berlin (560 GPs) have been contacted over seven waves. Positive feedback and interest in the study was declared by 175 GPs. After telephone contact a total of 87 GPs (5.0%) finally took part in the trial.

SAGP

SAGP recruited GPs in the neighboring region of Veneto, Italy. The local collaboration partner of SAGP was SVeMG (Scuola Veneta di Medicina Generale = School of General Practice in Veneto), which has extensive history and experience with the performance of scientific projects in the primary care setting. SVeMG supported SAGP in all aspects of recruitment of GPs and later in the recruitment of patients for PRIMAeDS. Italian GPs for PRIMAeDS were recruited within the Primary Care Health Research Network of Veneto " MilleInRete". All GPs of the network were invited by email to participate in the project. The invitation contained information about the project, requirements for participation and an attached participation form, which GPs were asked to sign in case of interest. Seventy GPs replied and declared to be interested in participating in PRIMAeDS by sending us the signed participating form. Finally, 72 Italian GPs signed the informed consent and received eCRF training.

PMU

The recruitment strategy of PMU was planned stepwise and manifold due to the fact that we knew from previous experiences that recruitment of study practices in the area is a demanding challenge. We informed GPs via letter, via mail and via fax in different regions (Austria, Bavaria) in several waves through different providers such as the PMU, general practitioners federation in Bavaria, laboratory

community, general practitioners society in Salzburg (SAGAM). Written information was followed by phone calls. Common reasons for not participating were lack of time, not treating enough polypharmacy patients, and software (medical health record) in the surgery was not suitable for patient identification (e.g. lack of filter function). The PRIMA-eDS study including participation information was published in a regional journal of the Physician's chamber of Salzburg (Medium 11/2013, circulation of 3.600); and in a national journal, ÖGAM News (06/2015). Several face-to-face presentations at different occasions were held: e.g. project information event at Paracelsus Medical University, Salzburg (10/2013), external GP meetings "Bezirksärzte-Fortbildung Salzburg" (03/2014). An additional effort was an advertisement of the study via the Chamber of Physicians (Ärztekammer) Salzburg homepage (07/2014). Several personal, phone and mail contacts were performed to recruit GPs via "snow-ball strategy". In summary, all efforts during the whole recruitment period resulted in about 80 GPs interested in the study. Eventually sixty-seven GPs signed the contract to participate; however eight withdrew their consent before randomization, and thus only 59 GPs finally participated. PMU recruitment strategy was presented at the annual meeting of the German College of General Practitioners and Family Medicine 2015.

UNIMAN

UNIMAN collaborated with five National Institute for Health Research (NIHR) Clinical Research Networks (CRN). The five CRNs were Eastern, North Eastern, Wales, North West Coast and Greater Manchester. The CRNs are widely spread across four different UK regions, the North West, North East, Wales, and the South East. From these, 76 practices provided expressions of interest from which 67 signed up for the trial and recruited patients.

1.3.2.3 Physician instruction

Just like physician recruitment, GP instruction for the trial had to beorganized by each study centre separately due to differences in local conditions.

UWH

Instruction of GPs was carried out using several approaches to reach a maximum effectiveness. It differed between intervention and control group. All GPs were offered general information about the RCT in writing and by phone, Instruction on using the eCRF via personal visit of the practice by a study nurse, and by providing a manual on eCRF-usage as well as a video on eCRF-usage. Both the manual and the video were made available on the PRIMA-eDS-website in English, German and Italian for all GPs of the PRIMA-eDS-trial in all study centres. We also provided continuing instruction via a telephone hotline which was implemented specifically for the study.

In addition, all GPs of the intervention group received instruction on the use of the PRIMAS-eDS-tool and on the shared decision making process of reducing polypharmacy in collaboration with the patients. We provided a manual and a video on PRIMA-eDS-tool usage and shared decision making. The manual and the video were made available in English, German and Italian for all GPs of the intervention group of the PRIMA-eDS-trial in all study centres. Furthermore, all GPs of the intervention group were offered participation in a webinar explaining and detailing eDS-tool usage and shared decision making (duration approximately 45 min. The webinar was offered to all German speaking GPs of the intervention group, also in the other study centres). Personal visits by a study nurse to explain the eDS-tool were offered but not widely made use off. A telephone hotline during regular office hours was implemented to provide continuous support on eDS-tool usage and shared decision making.

UMR

Instructions on proper use of the eCRF were provided by the study personnel during the initial visits of the GPs. After randomization, GPs of the intervention group received a tutorial for proper use of the eDS-Tool (DVD) and written information. In addition, via telephone a physician was ready to answer all questions of the GPs. The manuals, webinars and videos described under “UWH” were also offered to the GPs.

SAGP

eCRF training: The research personnel of SAGP trained all Italian PRIMAeDS GPs in using the eCRF. eDS training: eDS training meetings were held for GPs of the intervention group. Individual eDS training was provided for GPs not being able to participate in the training meetings. All PRIMA-eDS meetings (regarding information, recruitment, eCRF-and eDS- training and feedback) with the participating GPs were held in collaboration with SVeMG at its headquarters in Caselle di Selvazzano, PD. The manuals and videos described under “UWH” were also offered to the GPs.

PMU

Training in the usage of eCRF and eDS was adapted to the regional setting. Because of regional characteristics (e.g. GP practices are foremost organized as single handed offices), workload and limited time resources, participating GPs refused to attend group training sessions in a centralized location. Project staff delivered the training face-to face within each practice in a two to four-hour session covering identification of eligible participants and entering data in the eCRF. As the eCRF was not ready for use when we started the GP recruitment the first GP visits focused on identification of eligible participants only. Patient identification was started as soon as possible as the procedure had to be performed via manual search by the project staff due to limited software options in regional GP offices. After randomization GPs in the intervention group were trained on how to use eDS and eCRF within a second visit by project staff in the respective offices. GPs in the control groups were instructed via telephone, and the eCRF manual mentioned above was sent to the GP. To support the participating GPs, we installed a telephone hotline for PRIMA-eDS GPs.

UNIMAN

Training in the eCRF and eDS was adapted to the UK context. Because UK GPs are only undertaking Medication Reviews, not the non-Medication Review tasks required for the trial (approaching and consenting patients, completing patient questionnaires and completion of the eCRF), the GP recruitment process included negotiating whether CRN, practice or research team staff would complete the non-Medication-Review tasks, as agreed in the original CRN negotiations. Therefore some parts of the training given to GPs in other countries, in the UK was delivered to other staff groups (mainly nurses). In the Eastern and North Eastern CRN areas peripatetic Research Nurses employed by the CRNs cascaded training to GPs and carried out the non-Medication Review tasks themselves. The study team provided training days in Cambridge and Newcastle for the teams of Research Nurses there, with hands-on training in both non-Medication-Review tasks and Medication Reviews for Intervention practices and only non-Medication-Review tasks for Control practices. In Wales, North West Coast and Greater Manchester all training was delivered by the study team to practices directly. Face-to-face non-Medication-Review training was completed with the CRN/practice personnel identified when the practices were recruited, and timed to facilitate patient recruitment. Medication Review training was undertaken post-Randomisation, initially face-to-face, then by teleconference for speed only for the intervention practices.

1.3.2.4 Patient recruitment

Like GP- recruitment, patient recruitment hat to be organized locally due to different local conditions.

UWH

GPs were instructed to perform searches in their electronic health records to identify eligible patients (patients ≥75 years of age taking ≥8 drugs). Eligible patients were informed about the study by the GP in writing or personally when entering the practice at the discretion of the GP. If more than 15 eligible patients were willing to participate in the study, GPs were asked to randomly select patients or recruit a random sample by continuous recruitment of patients coming to the practice. GPs were asked to recruit at least eight and no more than 15 patients to assure uniformity of cluster size, but GPs with less than 8 or more than 15 patients were not excluded. After signing informed consent, baseline data of the patients were entered into the eCR. SF-12 was performed on paper, and the filled out forms were sent to the UWH study centre for data entry. After completing recruitment, GPs were asked to inform the study centre. To assure concealment of allocation during recruitment, GPs were randomized after the completion of recruitment. After randomization GPs could not include additional patients in the study. Recruitment ended September 30, 2015, and all GPs not randomized yet were randomized on Oct 5, 2015, no matter how many patients they had recruited. In total, 742 patients were recruited by 76 GPs for the UWH study centre.

UMR

Based on standard operating procedures eligible patients were selected from the electronic health record of the GP practices. The list was presented to the GP and he/she was asked to exclude patients not suitable for the study (exclusion criteria). A random sample of a maximum of 30 patients was then selected from the remaining list. These patients received an invitation letter to participate in the study. Patients interested in participating contacted their GP and made an appointment to receive further information, to sign informed consent and to record baseline data. In total, at Rostock study centre 987 patients have been included by 87 GPs.

SAGP

Patients were selected from the electronic health records of the GP surgeries through two special software querys, according to the inclusion criteria of PRIMA-eDS. This was feasible, because all members of the research network, in which we recruited GPs, use the same practice software *MilleWin*, which is able to extract the patients according to the PRIMAeDS inclusion criteria. For the selected patients, GPs had to apply exclusion criteria one by one. The remaining patients were put in random order by blinded research-personnel of SAGP. The first 30 patients of this random list of eligible patients were invited by letter to take part in the study. All GPs were asked to recruit 11 patients. In total, 70 GPs recruited 905 patients for the PRIMA-eDS-trial with a maximum of 15 patients and a minimum of 8 patients per GP.

PMU

All eligible patients were selected by an electronic search of the electronic health records in the respective GP practice. The list of all eligible patients was numbered serially and brought in random order. Following the random list, the first 30 patients fulfilling inclusion criteria were identified by manual search. Invitation letters for the selected patients were prepared by project staff during the first visit at the GP surgery. In the invitation letter patients were informed about the project and asked to make an appointment at their GP-practice for further information and to sign informed

consent. The GP decided whether to use the invitation letters or personally contact patients or both. Baseline data was obtained for the eCRF after informed consent was signed by the patient. As soon as the last patient consented to participate, the respective GP sent a confirmation fax. The project team checked whether all patients met inclusion criteria and submitted a randomization request for the respective practice to the randomization centre. In total, 587 patients were recruited by 59 GPs.

UNIMAN

A total of 702 patients have been recruited from across 67 practices. Four of these patients were subsequently found to be ineligible for the trial, leaving a total eligible sample of 698; very close to the target of 735 patients from 67 practices. Patients were recruited via practices, who posted an invitation pack (letter on practice stationery, study information, reply slip and prepaid envelope) to selected patients identified from the practice list. Interested patients met with a CRN/practice nurse/university researcher who explained the study further, gave the opportunity to ask questions and to consider participation further. Patients who were still interested in the study signed the informed consent form and with this permission could then complete the patient questionnaires and have their data entered into the eCRF.

1.3.2.5 Randomization

A statistician created lists for blockwise randomization stratified by study centre. GP practices were then allocated to either the intervention group or the control group when they had completed patient recruitment. Cluster randomization was performed by the Department of Medical Informatics, Biometry and Epidemiology of the Ruhr-University Bochum (AMIB) starting January 10, 2015 and ending October 5, 2015. Weekly randomization reports were provided by AMIB.

1.3.2.6 Blinding

To minimize bias and confounding, all patients were blinded, i.e. patients were not informed explicitly whether their doctor was part of the intervention group or the control group. Inherent to the study protocol general practitioners could not be blinded. Also, it was not possible to blind all research-personnel. As research-personnel did not interact directly with patients or GPs, the risk of bias due to the lack of blinding appears to be negligible. The statistician performing final analysis of the trial was blinded regarding GPs belonging to the intervention or the control group.

1.3.2.7 Carrying out the trial

Intervention

After completion of recruitment and randomization, the GPs of the intervention group were instructed to perform the medication review with their patients using the PRIMA-eDS-tool. GP-instruction was carried out via face-to-face-instruction by study personnel as well as video-instruction provided via the PRIMA-eDS website (www.prima-eds.eu) and webinars held by study personnel. A hotline was available throughout the study, if GPs encountered technical or medical problems using the tool. In the instruction, special emphasis was put on a shared decision making process to come to an agreement with the patient regarding discontinuation of inappropriate medication. The GPs of the control group received instructions and continuous support on the use of the eCRF, and were advised to prescribe medication to their patients as usual according to current guidelines.

Recording outcome measures and assessment of data

GPs performed the baseline visit and documented patient data in the electronic case report form (eCRF) after recruitment and informed consent, but before randomization to assure concealment of allocation. All GPs were instructed to complete any baseline data still missing after randomization. The medication review was then carried out using the PRIMA-eDS-tool in the intervention group while the control group checked patient medication as usual. GPs were reimbursed for recruitment and baseline data acquisition after completing all their baseline examinations. For the follow up examinations scheduled after 8, 16 and 24 months, GPs were reminded to prepare/perform these follow-ups and document all patient data as required by the eCRF. Letters and faxes were sent to the GPs and followed up by telephone calls if necessary. We allowed a time frame from 4 to 12 months after randomization for follow up 1 (FU1), from 12 to 20 months for follow up 2 (FU2), and from 20 to 28 months for follow up 3 (FU3).

The project team continuously supported GPs to assure the conduction of the intervention (e.g. GP instructions on how to use eCRF/eDS correctly, data collection and data entry of SF-12, baseline and first follow-up examination) in the intervention group and to assure correct completion of the eCRF in the control group.

Data management and statistical analysis

All data were stared securely by Avain Technologies ltd. Anonymized data files were transferred to AMIB on a weekly basis for data cleaning and quality check. Any deviations and errors in data recordings were reported to the monitors who in turn contacted the respective GP for data correction or clarification.

A statistical analysis plan was developed by AMIB in cooperation with UWH and UNIMAN.

Monitoring, quality assurance, and Safety and Data Monitoring Committee (SDMC)

To ensure safety of all patients throughout the study, an independent data and safety monitoring board (SDMC) was set up. The SDMC met periodically throughout the study. The members reviewed and discussed the current data (at baseline and at the various follow-up visits. The SDMC was informed about dropouts, deaths, hospitalisations, and any other relevant safety issue if applicable. The main focus of the interim analyses presented to the SDMC was, to detect discrepancies in relevant safety parameters and their effects on the (non-) achievement of the outcome parameters. All interim analyses were kept blind regarding events in the intervention or the control group. The SDMC received a blinded descriptive synopsis of the most important variables (especially primary outcomes such as deaths, hospitalizations, reported symptoms related to changes in medication, dropouts, monitoring results etc.) in preparation for their regular conferences. The SDMS checked the monitoring of the study and approved of the continuation of the study. The SDMC at no point had any concerns about patient safety throughout the trial, and a discontinuation of the trial was never recommended.

The designated site monitors at each study site performed the local monitoring activities and reported their results to the coordinating monitor at UMR. Throughout the study, site monitors established and maintained contact to general practitioners and practice teams of the respective study site, clarified issues and difficulties during the monitoring contact and prepared status reports on completed on- and offsite visits. All monitoring activities were coordinated and reviewed by UMR including the distribution of relevant information and the review of all monitoring reports provided by the site monitors.

Overall, vivid and frequent communication as well as sharing of experiences between site monitors and coordinating monitors were carried out, mainly via individual phone calls, monthly phone conferences, e-mail, and at steering-committee- and project meetings. In order to facilitate a transparent and quick communication, the online-forum freedcamp.com was used by all monitoring personnel, not only to forward and share documents and information, but also to explicitly exchange experiences between site monitors of all study sites. Additionally, the coordinating monitors regularly reported on the current monitoring trends and results to the consortium via oral presentations held at the project meetings or telephone conferences.

To assure correct and standardized monitoring as well as data quality, a monitoring manual was developed and updated during the study. The monitoring manual and its updates were delivered to every cooperating trial site and all beneficiaries via e-mail. The monitoring manual served as a quality plan that complies with Good Clinical Practice (GCP) guidelines. Additionally, monitoring documentation forms (checklists, report forms, log- & communication-sheets, etc.) and standard operation procedures (SOPs) to support site monitors performing standardized local monitoring activities were developed and adapted throughout the study. Before monitoring started, two online monitoring trainings were conducted to prepare site monitors for the onsite- and offsite-visits at Baseline- (T0) and FU1-(T1) Monitoring. Site monitors and the coordinating monitors discussed all arising questions. Baseline monitoring was performed from April 2015 until April 2016. Altogether, site monitors conducted onsite-visits in 51 of 359 randomized practices and checked 3,919 out of 3,919 Informed Consent Forms during baseline-monitoring. 15 patients had to be excluded due to a lack of a signed informed consent form or withdrawal of consent before randomization, leaving 3904 patients in the intention-to-treat study-population. The most time-consuming aspects mentioned by the site monitors were the search for source data due to huge differences in the quality of documentation within the normal practice routine. Written documentation in practices often lacked information, especially regarding medication, symptoms, start & stop dates, dosage and diagnoses.

FU1-(T1)-monitoring was conducted from March to October 2016. In total, site monitors performed offsite-visits in 80 of 348 included practices at T1. For two random samples of 10% each of the practices, site monitors checked 558 out of 3,904 included patients at T1. Additionally, 100% of all dropouts were monitored. All conspicuous cases detected were reported by using the respective monitoring forms.

The final monitoring of FU3 (T3) was conducted from October 2016 to November 2017. Overall, 3,210 patients in 342 practices were monitored for primary endpoints during the offsite-visits at T3. Moreover, 656 reported dropouts were monitored regarding the primary endpoints (hospitalization, death). Additionally, further items (e. g. medication) were checked for three patients each in 10% of all monitored practices. The majority of GPs and practice personnel were cooperative during monitoring, but some complained about the time needed. For 694 patients of the intention-to-treat-population, monitoring could not be completed or performed at all due to refusal of the GP, drop out, lost-to-follow-up or other reasons. These patients were included in the intention-to-treat analysis with their respective known time-under-risk (date of last available data on hospitalization or death). All detected discrepancies were documented in the respective monitoring documents and discussed with the coordinating monitor.

1.3.3 Main results of the PRIMA-eDS-trial

Baseline characteristics of the study sample are presented in tables 4-7. On average, participants were taking 10.5 substances (±2.4) and had 9.5 diagnoses (±4.9). HMG CoA reductase inhibitors were the most commonly used drug, followed by proton pump inhibitors, selective beta blocking agents,

platelet aggregation inhibitors, ACE inhibitors, loop diuretics, and dihydropyridine derivatives. Essential (primary) hypertension was the most common diagnosis, followed by disorders of lipoprotein metabolism, diabetes mellitus type 2, and arthrosis.

Table 4 Demographic and clinical characteristics of the study population

Characteristics	All subjects (n=3904)		Control group (n=1951)		Intervention group (n=1953)	
	N		N		N	
Sociodemographic data						
Age						
<85 (n, %)	3036	77.8	1511	77.5	1525	78.1
≥85 (n, %)	868	22.2	440	22.6	428	21.9
mean ±SD (years)	3904	81.5 ±4.4	1951	81.5 ±4.5	1953	81.5 ±4.4
Female, n (%)	2240	57.4	1137	58.3	1103	56.5
Male, n (%)	1664	42.6	814	41.7	850	43.5
Educational level, n (%)*						
Low	1536	39.3	748	38.3	788	40.4
Medium	1465	37.5	726	37.2	739	37.8
High	577	14.8	292	15.0	285	14.6
Health-related factors						
Smokers, n (%)*	154	3.9	88	4.5	66	3.4
BMI, n (%)*						
BMI <18.5	34	0.9	19	1.0	15	0.8
BMI 18.5-24	957	24.5	474	24.3	483	24.7
BMI 25-29	1606	41.1	790	40.5	816	41.8
BMI ≥30	1307	33.5	668	34.2	639	32.7
Frailty level, n (%)*						
Managing well	1643	42.1	771	39.5	872	44.6
Vulnerable	868	22.2	442	22.7	426	21.8
Mildly frail	660	16.9	362	18.6	298	15.3
Moderately frail	505	13.0	250	12.8	255	13.1
Severely frail	97	2.5	53	2.7	44	2.3
Very severely frail	8	0.2	5	0.3	3	0.2
Physical health composite score, median	3484	36.6	1710	36.6	1774	36.7
Mental health composite score, median	3483	48.7	1710	48.7	1773	48.7
Study centre, n (%)						
PMU	587	15.0	295	15.1	292	15.0
UMR	981	25.1	506	25.9	475	24.3
UWH	742	19.0	369	18.9	373	19.1

SAGP	901	23.1	450	23.1	451	23.1
UNIMAN	693	17.8	331	17.0	362	18.5
Substances, n (mean ±SD)	3904	10.5 ±2.4	1951	10.5 ±2.4	1953	10.6 ±2.5
Diagnoses, n (mean ±SD)	3904	9.5 ±4.9	1951	9.7 ±5.4	1953	9.3 ±4.4

Legend: SD= Standard deviation, BMI= Body Mass Index, N= number; CG= control group, IG= intervention group, * the total n given above does not correspond to the n within this variable due to missing data.

Table 5 Percentage of the population using substances (ATC level 4)

Substances		All subjects		Control group		Intervention group	
		N	(%)	N	(%)	N	(%)
C10AA	HMG CoA reductase inhibitors	2479	63.5	1254	64.3	1225	62.7
A02BC	Proton pump inhibitors	2328	59.6	1152	59.1	1176	60.2
C07AB	Beta blocking agents, selective	2240	57.4	1088	55.8	1152	59.0
B01AC	Platelet aggregation inhibitors excl. heparin	1952	50.0	977	50.1	975	49.9
C09AA	ACE inhibitors, plain	1751	44.9	860	44.1	891	45.6
C03CA	Loop diuretics	1715	43.9	838	43.0	877	44.9
C08CA	Dihydropyridine derivates	1611	41.3	836	42.9	775	39.7
C09CA	Angiotensin II antagonists, plain	1355	34.7	707	36.2	648	33.2
C03AA	Thiazides, plain	1354	34.7	716	36.7	638	32.7
A11CC	Vitamin D and analogues	1120	28.7	548	28.1	572	29.3

Legend: CG= control group, IG= intervention group

Table 6 Most common diagnoses of the study population

Diagnoses		All subjects					
		N	(%)	N	(%)	N	(%)
I10	Essential (primary) hypertension	3428	87.8	1708	87.6	1720	88.1
E78	Disorders of lipoprotein metabolism	2078	53.2	1060	54.3	1018	52.1
E11	Diabetes mellitus type 2	1850	47.4	925	47.4	925	47.4
M19	Osteoarthritis	1752	44.9	821	42.1	931	47.7
I25	Chronic ischaemic heart disease	1473	37.7	719	36.9	754	38.6
M54	Dorsalgia	1442	36.9	715	36.7	727	37.2
I48	Atrial fibrillation and flutter	1172	30.0	580	29.7	592	30.3
I50	Heart failure	1142	29.3	536	27.5	606	31.0
K21	Gastro-oesophageal reflux disease	982	25.2	497	25.5	485	24.8

F32	Depressive episode	853	21.9	416	21.3	437	22.4

Legend: CG= control group, IG= intervention group

Table 7 Demographic and clinical characteristics per study centre

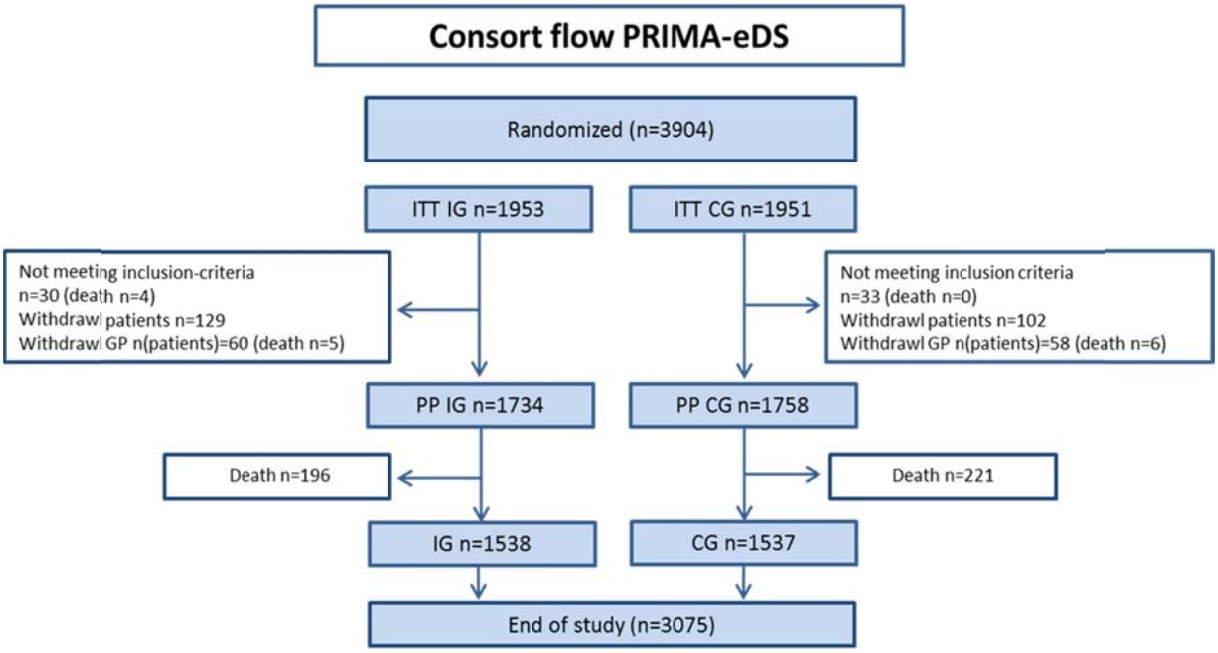
Characteristics	**PMU**		**UMR**		**UWH**		**SAGP**		**UNIMAN**	
	N		**N**		**N**		**N**		**N**	
Sociodemo-graphic data										
Age										
<85 (n, %)	42	73.1	771	78.6	568	76.5	712	79.0	556	80.2
≥85 (n, %)	15	26.9	210	21.4	174	23.5	189	21.0	137	19.8
mean ±SD (y)	58	82.2 ±4.6	981	81.5 ±4.3	742	81.6 ±4.5	901	81.3 ±4.4	693	81.1 ±4.4
Female, n (%)	36	61.7	606	61.8	415	55.9	521	57.8	336	48.5
Male, n (%)	22	38.3	375	38.2	327	44.1	380	42.2	357	51.5
Educational level, n (%)*										
Low	23	39.2	152	15.5	245	33.0	598	66.4	311	44.9
Medium	22	37.8	608	62.0	346	46.6	92	10.2	197	28.4
High	5	10.0	217	22.1	132	17.8	21	2.3	148	21.4
Health-related factors										
Smokers, n (%)*	1	1.9	45	4.6	23	3.1	44	4.9	31	4.5
BMI, n (%)*										
BMI <18.5		0.8	8	0.8	8	1.0	7	0.8	6	0.9
BMI 18.524	17	29.6	195	19.9	157	21.2	255	28.3	176	25.4
BMI 25-29	22	38.2	384	39.1	316	42.6	385	42.7	297	42.8
BMI ≥30	18	31.4	394	40.2	261	35.2	254	28.2	214	30.9
Frailty level, n (%)*										
Managing well	24	41.7	415	42.3	255	34.4	376	41.7	352	50.8
Vulnerable	12	21.1	229	23.3	178	24.0	170	18.9	167	24.1
Mildly frail	9	15.5	158	16.1	125	16.8	171	19.0	115	16.6

Moderately frail	8	14.3	139	14.2	144	19.4	92	10.2	46	6.6
Severely frail	2	3.6	28	2.9	19	2.6	23	2.5	6	0.9
Very severely frail		0.3		0.2	4	0.5	0	0.0	0	0.00
Physical health composite score,	50	36.7 (13-62)	948	35.9 (12-63)	713	35.0 (11-62)	675	38.7 (11-68)	639	37.5 (10-60)
Mental health composite	50	47.6 (16-74)	946	48.6 (12-72)	715	47.5 (17-76)	676	46.8 (14-72)	640	53.5 (16-74)
Substances										
<8	25	44.1	351	35.8	334	45.0	439	48.7	261	37.7
≥10	32	55.9	630	64.2	408	55.0	462	51.3	432	62.3
n (mean ±SD)	58	10.4 ±2.3	981	10.9 ±2.7	742	10.4 ±2.4	901	10.0 ±2.0	693	10.9 ±2.7
Diagnoses, n (mean ±SD)	58	8.5±3.5	981	12.9 ±6.2	742	10.4 ±4.5	901	7.6 ±2.7	693	6.8 ±3.5

Legend: N= Number SD= Standard deviation, BMI= Body Mass Index, * the total n given above does not correspond to the n within this variable due to missing data.

Figure 6 depicts details of the consort flow chart. 3904 patients were randomized and considered for the ITT analysis. 3492 patients were included in the per-protocol analysis.

Figure 6: Consort-Flow Chart Intention to treat analysis and per-protocol analyses



Abbrevations: ITT= intention to treat; PP= per protocol, IG= intervention group, CG= control group

In the intention-to-treat analysis at follow-up 3 (after 24 months), the hazard ratio (HR) for the combined endpoint for all study centers was 0.92 (95% CI 0.82-1.04) thus just missing significance (see table 8). The time-to-even-graph (survival-plot) of the composite primary endpoint shows a clear trend in favor of the intervention (see fig. 4). When the combined endpoint was stratified by research center, PMU had a significantly lower hazard ratio between intervention group and control group in favor of the intervention [0.68 (95% CI 0.50-0.94) than UWH, SAGP, UNIMAN, and UMR (see table 9). The HR for death was 0.92 (95% CI 0.74-1.14), and for the first hospitalization 0.93 (95% CI 0.82-1.06). Table 10 presents a descriptive analysis of the number of events (death/first hospitalization, death, and hospitalization) according to research center.

Table 8 Cox regression analysis of the composite primary endpoint (death/first unplanned hospitalization), and the secondary endpoints all cause death, and first unplanned hospitalization in ITT analysis

Outcome	Treatment	Hazard ratio (95% CI)	p
Composite endpoint death/first unlanned hospitalization	IG vs CG	0.92 (0.82-1.04)	0.19
All cause death	IG vs CG	0.92 (0.74-1.14)	0.43
First unplanned hospitalization	IG vs CG	0.93 (0.82-1.06)	0.28

Table 9 Cox regression analysis of the composite primary endpoint (death/first unplanned hospitalization) stratified by research center in ITT analysis

Research center	Treatment	Hazard ratio (95% CI)	P
SAGP	IG vs CG	0.97 (0.76-1.24)	0.79
UNIMAN	IG vs CG	0.94 (0.73-1.20)	0.61
UMR	IG vs CG	0.99 (0.75-1.31)	0.93
PMU	IG vs CG	0.68 (0.50-0.94)	0.02
UWH	IG vs CG	1.05 (0.82-1.33)	0.72

Table 10 Number of events (death/first unplanned hospitalization, death, and hospitalization) according to research center

		Death and/or hospitalisation				Death				Hospitalisation			
		No		Yes		No		Yes		No		Yes	
Research Center	**Treatment**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
SAGP	CG	296	65.8	154	34.2	390	86.7	60	13.3	312	69.3	138	30.7
	IG	300	66.5	151	33.5	411	91.1	40	8.9	310	68.7	141	31.3
	Total	596	66.1	305	33.9	801	88.9	100	11.1	622	69.0	279	31.0
UNIMAN	CG	207	62.5	124	37.5	304	91.8	27	8.2	217	65.6	114	34.4
	IG	237	65.5	125	34.5	339	93.6	23	6.4	244	67.4	118	32.6
	Total	444	64.1	249	35.9	643	92.8	50	7.2	461	66.5	232	33.5
UMR	CG	255	50.4	251	49.6	465	91.9	41	8.1	265	52.4	241	47.6
	IG	251	52.8	224	47.2	428	90.1	47	9.9	262	55.2	213	44.8
	Total	506	51.6	475	48.4	893	91.0	88	9.0	527	53.7	454	46.3
PMU	CG	103	34.9	192	65.1	248	84.1	47	15.9	119	40.3	176	59.7
	IG	142	48.6	150	51.4	256	87.7	36	12.3	153	52.4	139	47.6
	Total	245	41.7	342	58.3	504	85.9	83	14.1	272	46.3	315	53.7
UWH	CG	146	39.6	223	60.4	317	85.9	52	14.1	159	43.1	210	56.9
	IG	152	40.8	221	59.2	314	84.2	59	15.8	165	44.2	208	55.8
	Total	298	40.2	444	59.8	631	85.0	111	15.0	324	43.7	418	56.3
Total	**CG**	1007	51,6	944	48,4	1724	89,7	197	10,3	1072	54,9	879	45,1
	IG	1082	55,4	871	44,6	1748	89,5	205	10,5	1134	58,1	819	41,9
	Total	2089	53.5	1815	46.5	3472	88.9	432	11.1	2206	56.5	1698	43.5

Legend: CG: control group, IG: intervention group

Figure 7: Survival plot combined endpoint (ITT Analysis)

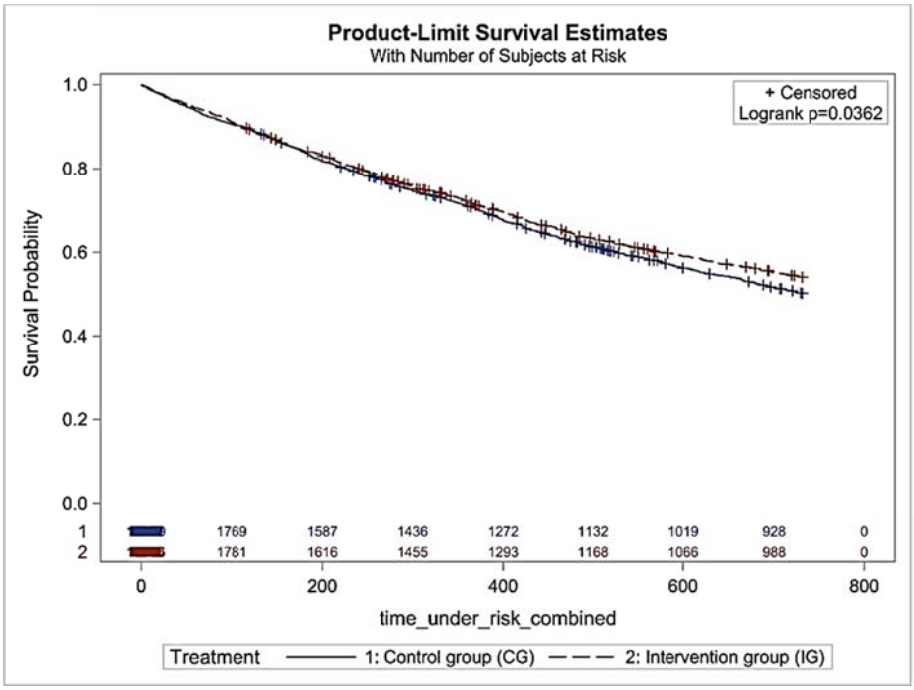


Table 11 describes the number of drugs at baseline, at the end of the study and the change between the two points according to study centre.

Table 11: Number of drugs per patient and study centre

	Research center	N	Mean	SD	Median	Min	Max	Lower quartile	Upper quartile
Number of drugs at Baseline	**SAGP (Italy)**	901	10.00	1.95	10.0	6	25	9.0	11.0
	UNIMAN (UK)	693	10.86	2.72	10.0	5	24	9.0	12.0
	UMR (Germany1)	981	10.89	2.68	10.0	5	26	9.0	12.0
	PMU (Austria)	587	10.43	2.31	10.0	7	21	9.0	12.0
	UWH (Germany2)	742	10.35	2.33	10.0	6	23	9.0	12.0
	Overall	3904	10.51	2.44	10.0	5	26	9.0	12.0
Number of drugs (total) End of study	**SAGP (Italy)**	901	9.20	2.54	9.0	1	18	8.0	11.0
	UNIMAN (UK)	693	9.95	3.19	10.0	0	26	8.0	12.0
	UMR (Germany1)	981	10.56	3.26	10.0	0	26	8.0	12.0
	PMU (Austria)	587	9.73	3.04	9.0	0	21	8.0	12.0
	UMR (Germany2)	742	10.01	3.03	10.0	0	26	8.0	12.0
	Overall	3904	9.91	3.05	10.0	0	26	8.0	12.0
Change number of drugs (total) End-Baseline	**SAGP (Italy)**	901	-0.80	2.05	0.0	-13	6	-2.0	0.0
	UNIMAN (UK)	693	-0.92	2.45	-1.0	-16	7	-2.0	0.0
	UMR (Germany1)	981	-0.33	2.45	0.0	-14	11	-1.0	1.0

	PMU (Austria)	587	-0.70	2.44	0.0	-15	7	-2.0	1.0
	UWH (Germany2)	742	-0.34	2.30	0.0	-14	10	-1.0	1.0
	Overall	3904	-0.60	2.35	0.0	-16	11	-2.0	1.0

Table 12 depicts the number of drugs at baseline, at the end of the study, and the change between the two points of measurement according to treatment group. Overall, the number of drugs per patient were reduced by a mean of -0.599 drugs per patient. The mean reduction was -0.841 in the intervention group, compared to -0.356 in the control group.

Table 12: Number of drugs per patient and treatment group

	Treatment	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Lower quartile**	**Upper quartile**
Number of drugs at Baseline	**Control group (CG)**	1951	10.46	2.41	10.0	5	23	9.0	12.0
	Intervention group (IG)	1953	10.55	2.48	10.0	5	26	9.0	12.0
	Overall	3904	10.5	2.44	10.0	5	26	9.0	12.0
Number of drugs (total) End of study	**Control group (CG)**	1951	10.11	3.01	10.0	0	26	8.0	12.0
	Intervention group (IG)	1953	9.71	3.09	9.0	0	26	8.0	11.0
	Overall	3904	9.91	3.05	10.0	0	26	8.0	12.0
Change number of drugs (total) End-Baseline	**Control group (CG)**	1951	-0.36	2.29	0.0	-16	11	-1.0	1.0
	Intervention group (IG)	1953	-0.84	2.38	0.0	-15	9	-2.0	0.0
	Overall	3904	-0.60	2.35	0.0	-16	11	-2.0	1.0

Table 13 depicts the mean number of drugs at baseline, at the end of the study, and the change between baseline and the end of the study according to research centre and treatment group. The largest reduction in the number of drugs in the intervention group was achieved in Italy (SAGP), with a reduction of 1.26 drugs per patient. The smallest reduction was seen in Germany 2 (UWH) with a reduction of only 0.5 drugs per patient. Interestingly, the reduction of drugs in the UK was larger in the control group than in the intervention group.

Table 13: Number of drugs per patient, research center and treatment

	Study centre	**Treatment group**	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Lower quartile**	**Upper quartile**
Number of drugs at Baseline	**SAGP (Italy)**	**Control group (CG)**	450	9.96	1.93	9.0	6	17	8.0	11.0
		Intervention group (IG)	451	10.03	1.97	10.0	7	25	9.0	11.0
	UNIMAN (UK)	**Control group (CG)**	331	10.80	2.69	10.0	5	21	9.0	12.0
		Intervention group (IG)	362	10.92	2.75	10.0	5	24	9.0	12.0
	UMR (Germany1)	**Control group (CG)**	506	10.83	2.50	10.0	5	23	9.0	12.0

		Intervention group (IG)	475	10.95	2.87	10.0	5	26	9.0	12.0
	PMU (Austria)	**Control group (CG)**	295	10.33	2.39	10.0	8	21	8.0	12.0
		Intervention group (IG)	292	10.54	2.22	10.0	7	17	9.0	12.0
	UWH (Germany2)	**Control group (CG)**	369	10.39	2.41	10.0	6	19	9.0	12.0
		Intervention group (IG)	373	10.31	2.26	10.0	7	23	9.0	11.0
Number of drugs (total) End of study	**SAGP (Italy)**	**Control group (CG)**	450	9.63	2.45	9.0	3	18	8.0	11.0
		Intervention group (IG)	451	8.77	2.56	9.0	1	18	7.0	10.0
	UNIMAN (UK)	**Control group (CG)**	331	9.80	3.11	10.0	0	20	8.0	12.0
		Intervention group (IG)	362	10.08	3.26	10.0	3	26	8.0	12.0
	UMR (Germany1)	**Control group (CG)**	506	10.78	3.05	10.0	0	21	9.0	12.0
		Intervention group (IG)	475	10.33	3.46	10.0	0	26	8.0	12.0
	PMU (Austria)	**Control group (CG)**	295	9.93	3.24	10.0	0	21	8.0	12.0
		Intervention group (IG)	292	9.54	2.82	9.0	0	19	8.0	11.0
	UWH (Germany2)	**Control group (CG)**	369	10.21	3.12	10.0	1	26	8.0	12.0
		Intervention group (IG)	373	9.81	2.93	10.0	0	22	8.0	11.0
Change number of drugs (total) End-Baseline	**SAGP (Italy)**	**Control group (CG)**	450	-0.34	1.89	0.0	-13	6	-1.0	0.0
		Intervention group (IG)	451	-1.26	2.10	-1.0	-10	4	-3.0	0.0
	UNIMAN (UK)	**Control group (CG)**	331	-1.01	2.61	-1.0	-16	7	-2.0	0.0
		Intervention group (IG)	362	-0.84	2.29	-1.0	-9	5	-2.0	0.0
	UMR (Germany 1)	**Control group (CG)**	506	-0.05	2.22	0.0	-12	11	-1.0	1.0
		Intervention group (IG)	475	-0.62	2.65	0.0	-14	9	-2.0	1.0
	PMU (Austria)	**Control group (CG)**	295	-0.40	2.39	0.0	-13	7	-1.0	1.0
		Intervention group (IG)	292	-1.00	2.46	-1.0	-15	5	-2.0	0.0
	UWH (Germany 2)	**Control group (CG)**	369	-0.18	2.34	0.0	-14	10	-1.0	1.0
		Intervention group (IG)	373	-0.50	2.26	0.0	-11	6	-1.0	0.0

The treatment effect on the number of drugs at the end of the study was tested in a multi level analysis of covariance with “numbers of drugs at baseline” as a co-variate. The cluster factors “research centre”, the interaction between “research centre” and “treatment” and the random GP

practice effect were all showing significant effects (see table 14). There also was a significant treatment effect between the control and the intervention group (p >0.0003).

Table 14: Ancova-table of treatment effect on the number of medications

Effect	p
Number of drugs at baseline	<.0001
Treatment	0.0003
Research center	0.0006
Research center *treatment	0.0398

In the per-protocol analysis for the combined endpoint (first hospitalization/death) the HR was 0.880 (95% CI 0.779-0.994), p=0.040, and thus statistical significance was reached. Figure 8 depicts the survival plot of the primary composite endpoint. Table 15 depicts the events of the endpoints death, hospitalization, and the combined endpoint according to research centre.

Figure 8: Survival Plot of the per-protocol analysis regarding the primary endpoint

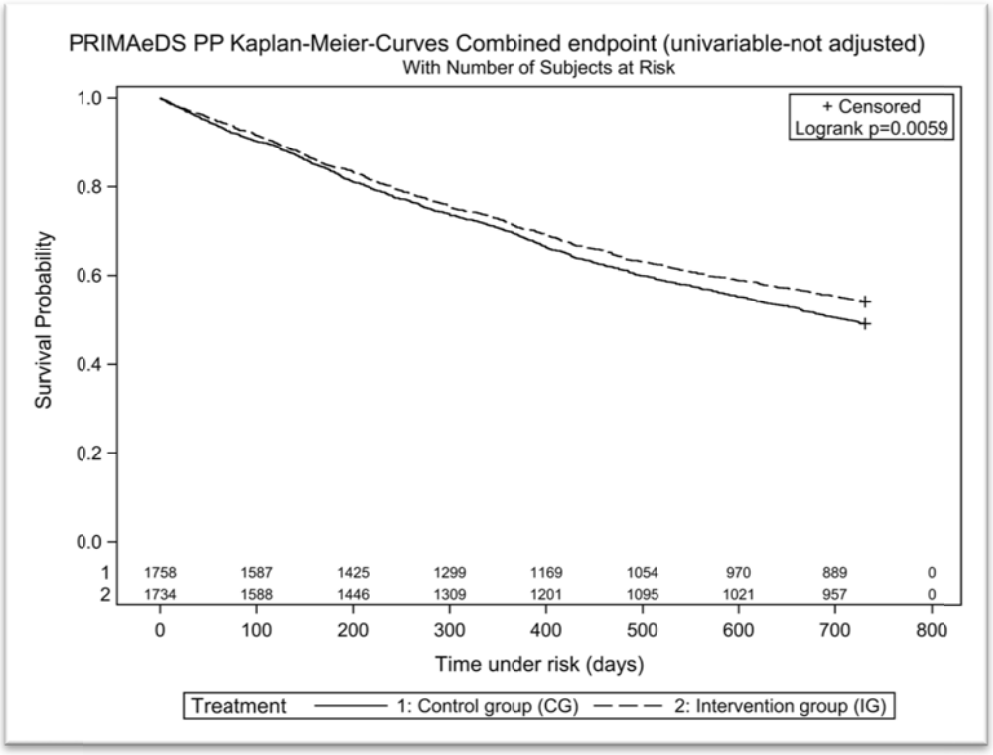


Table 15: Per-protocol analysis of primary composite endpoint

Research center	Treatment	Death and/or hospital stay				Death				Hospital stay			
		No		Yes		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%	N	%	N	%
SAGP (Italy)	Control group (CG)	262	63.1	153	36.9	355	85.5	60	14.5	278	67.0	137	33.0
	Intervention group (IG)	280	65.9	145	34.1	385	90.6	40	9.4	290	68.2	135	31.8
	Total	542	64.5	298	35.5	740	88.1	100	11.9	568	67.6	272	32.4
UNIMAN (UK)	Control group (CG)	184	60.5	120	39.5	277	91.1	27	8.9	194	63.8	110	36.2
	Intervention group (IG)	194	63.2	113	36.8	286	93.2	21	6.8	201	65.5	106	34.5
	Total	378	61.9	233	38.1	563	92.1	48	7.9	395	64.6	216	35.4
UMR (Germany)	Control group (CG)	203	47.1	228	52.9	394	91.4	37	8.6	211	49.0	220	51.0
	Intervention group (IG)	194	49.7	196	50.3	349	89.5	41	10.5	200	51.3	190	48.7
	Total	397	48.4	424	51.6	743	90.5	78	9.5	411	50.1	410	49.9
PMU (Austria)	Control group (CG)	92	32.6	190	67.4	235	83.3	47	16.7	108	38.3	174	61.7
	Intervention group (IG)	135	48.9	141	51.1	240	87.0	36	13.0	146	52.9	130	47.1
	Total	227	40.7	331	59.3	475	85.1	83	14.9	254	45.5	304	54.5
UWH (Germany)	Control group (CG)	123	37.7	203	62.3	276	84.7	50	15.3	135	41.4	191	58.6
	Intervention group (IG)	135	40.2	201	59.8	278	82.7	58	17.3	148	44.0	188	56.0
	Total	258	39.0	404	61.0	554	83.7	108	16.3	283	42.7	379	57.3
Total	Control group (CG)	864	49.1	894	50.9	1537	87.4	221	12.6	926	52.7	832	47.3
	Intervention group (IG)	938	54.1	796	45.9	1538	88.7	196	11.3	985	56.8	749	43.2
	Total	1802	51.6	1690	48.4	3075	88.1	417	11.9	1911	54.7	1581	45.3

Overall, the effectiveness of the PRIMA-eDS tool regarding the reduction of polypharmacy could be shown in our trial. The primary endpoint – the composite of death and first unplanned hospitalisation could be shown to be significant in per protocol analysis only. This result points to the fact that the tool has not been used as extensively as anticipated. The survey carried out to examine the usability of the tool also revealed that not all GPs in the intervention group made use of the tool as they were instructed to do, due to several barriers. One of the most important barriers turned out

to be the lack of integration of the tool in the electronic health record used in the practices. This required extra time and effort of the GPs having to enter patients' medication and other data already present in the EHR once again in the eCRF. Further analyses are ongoing to take a more detailed look at which drugs have been discontinued, and to check whether there are any correlations between usage of the tool according to the answers in the usability survey and the actual discontinuation of drugs by the respective GP in the trial.

1.4 Potential Impact, Main Dissemination Activities and Exploitation of Results

1.4.1 Impact of PRIMA-eDS on population health and health expenditure

Although the PRIMA-eDS intervention could not be shown to have an impact on the primary endpoint of the PRIMA-eDS-trial in the intention-to-treat population, quite an important impact on population health may be expected, as per-protocol-analysis revealed a significant reduction in hospitalization and death. In absolute numbers, the risk for the primary endpoint event was 45.9% in the intervention group and 50.9% in the control group, accounting for an absolute risk reduction of 5% in an observation period of two years. This means that one hospitalisation or death is avoided per year for one out of 40 patients cared for with the PRIMA-eDS-tool used decision support for avoiding inappropriate medication.

Roughly it can be estimated that there are more than 4.4 Million patients with polypharmacy in Germany (approximately 25% of all persons over 65 years). Thus, a nation wide implementation and usage of the PRIMA-eDS-tool would help to avoid 110,000 hospital stays or deaths per year. Extrapolating these numbers to the EU with about 500 Million people would lead to a tremendous impact on health and healthcare. European statistics estimate that 19.2% (96 Million) of the European population are older than 65 years (48). Even a conservative estimate of a polypharmacy rate of only 15% (14.4 Million) would result in avoiding 360,000 hospitalisations or deaths.

The second important result of the PRIMA-eDS trial revealed discontinuation of approximately 0.8 drugs per patient in the intervention group. When estimating average annual costs of only 100 €/drug, the discontinuation of 0.8 drugs/patient corresponds to health expenditure savings of 80 €/year/patient when using the PRIMA-eDS-tool. Using the population estimates from above this would correspond to annual savings of (14.4 Million x 80 €) 1.152 Million €.

1.4.2 Main dissemination activities

Ther PRIMA-eDS project has been made well known by the consortium already during the time of the project. Eleven peer-reviewed journal articles have been published (10–17,46,49,50). Two peer-reviewed articles are currently under review. Several further articles are being prepared, among others the main publication of the trial results. The project has been presented at numerous national and international conferences (see section 2).

1.4.3 Exploitation of results

The PRIMA-eDS-tool has been continuously updated and optimized during the trial by Duodecim and the PRIMA-eDS-consortium. It has been incorporated by Duodecim in its EbMeDS environment thus making the PRIMA-eDS tool available for further use in the Finnish health care system as

"Comprehensive Medication Review". Information about the availability of this "Comprehensive Medication" Reviews has been translated into English and German, and DMP and UWH are currently seeking possibilities to implement the tool in the electronic health records of the participating countries. Contacts with EHR-vendors have been made, and contacts with policy-makers are planned. The information on the "Comprehensive Medication Review" provided by DMP is attached as appendix 1.

1.5 Project Public Website

We established, and are maintaining a PRIMA-eDS-website (www.prima-eds.eu) giving relevant information about the project and the project achievements for the public. The website (www.prima-eds.eu) has been installed during the first months of the project and has been updated regularly since. The website has been used both for publishing of the PRIMA-eDS-project and for internal communication of the consortium. It has also been used as an entrance gateway for the GPs to access the eCRF forms, and it served as an online resource for the GPs regarding instruction on eCRF- and eDS-tool-usage. This service has now been discontinued as the main PRIMA-eDS-trial has been completed.

The website will be updated with the upcoming publications. The main results are withheld at the moment to avoid public availability of main results before the acceptance of the main manuscript by a peer-reviewed journal.

2 Use and Dissemination of Foreground

The following publication plan has been established:

Publication	**Status**
Title: Polypharmacy in chronic diseases–Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS): study protocol for a randomized controlled Trial Authors: Andreas Sönnichsen, Ulrike S. Trampisch, Anja Rieckert, Giuliano Piccoliori, Anna Vögele, Maria Flamm, Tim Johansson, Aneez Esmail, David Reeves, Christin Löffler, Jennifer Höck, Renate Klaassen-Mielke, Hans Joachim Trampisch, Ilkka Kunnamo Journal: Trials Language: English	Published
Title/ concept: Polypharmacy in chronic diseases– Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS): a cross-sectional analysis of factors predisposing for excessive polypharmacy Authors: Anja Rieckert, Ulrike Trampisch, Renate Klaasen-Mielke, Eva Drewelow, Annez Esmail, Tim Johansson, Sophie Keller, Ilkka Kunnamo, Christin Löffler, Joonas Mäkinen, Giuliano Piccoliori, Anna Vögele, Andreas Sönnichsen Data: Baseline data Journal: BMC Family Practice	Submitted (Peer-review)

Language: English	
Title/ concept: Polypharmacy in chronic diseases– Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS): a survey of GPs experiences Authors: Anja Rieckert, Anne-Lisa Teichmann, Eva Drewelow, Celine Kriechmayr, Giuliano Piccoliori, Adrine Woodham, Andreas Sönnichsen Data: Survey Journal: Language: English	Drafted, expected to be submitted end of March
Title/concept: Publication of our primary and secondary endpoints Authors: Anja Rieckert, (to be determined), Ulrike Trampisch, Sabine Weissbach, Andreas Sönnichsen Data: primary endpoint: composite endpoint of first non-elective hospital admission or death during the observation period measured as a binary outcome. Secondary endpoint: all-cause mortality, nonselective hospital admission (number of episodes and duration), falls (number and severity), fractures, quality of life (SF-12v2), the number and types of drugs (total number, number discontinued, number not discontinued despite the recommendation to discontinue, number re-administered for symptom control), adverse event rate, and medication costs over the observation period Journal: to be determined Language: English	Currently drafted, analyses not finished yet
Title/concept: Predictors of GP ratings of patient frailty. This will be an analysis of the baseline dataset to identify patient variables that predict GP ratings of patient frailty. Variables include diagnoses, polypharmacy, BMI, falls, SF12, etc. The paper may include construction of a “frailty index” from the data in the eCRF and correlating this with the GP assessment. Authors: David Reeves, (to be determined) Data: Baseline Data Journal: Language: English	Not started
Title/concept: GP ratings of patient frailty as a predictor of patient outcomes. This will make use of the full dataset (i.e. all two years), to explore whether GP frailty ratings predict future patient outcomes, including death, hospitalisations, falls, QoL, etc, both with and without control for other baseline factors. It may also compare frailty ratings with other baseline predictors of outcomes for predictive ability, including polypharmacy and a frailty index constructed from the eCRF data. It will also explore whether frailty ratings moderate the association between polypharmacy and outcomes.	Not started

Authors: David Reeves, (to be determined) Data: full dataset Journal: Language: English	
Title/concept: Barriers for implementing electronic decision support tools, Qualitative synthesis Authors: Malin Wörster, (to be determined), Andreas Sönnichsen Data: pilot study & literature search Journal: Language:	Conducting the search
Title/concept: Validation of the Pharao table. Correlation of symptoms with Pharao table. Authors: (to be determined), Andreas Sönnichsen Data: Baseline Data+ CMR (Pharao) Journal: to be determined Language: English	Developing an analysable database/development of concept
Title/concept: What is the potential of the tool? Analysis of the recommendations. Which drugs recommends the tool to discontinue? Authors: Anja Rieckert (?) (to be determined), Andreas Sönnichsen Giuliano is interested in contribution. Experience with PRIMA Italy (based on experts evaluations). Data: CMR data Journal: to be determined Language: English	Developing an analysable database
Title/ concept: Analysis of what did the tool recommend to discontinue and what was actually discontinued. Data: CMR+ 1st follow-up Journal: to be determined Language: English	Developing an analysable database
Title/concept: Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis Authors: Tim Johansson, Muna E. Abuzahra, Sophie Keller, Eva Mann, Barbara Faller, Christina Sommerauer, Jennifer Höck, Christin Löffler,	Published

Anna Köchling, Jochen Schuler, Maria Flamm and Andreas Sönnichsen Data: SR strategies to reduce polypharmacy Journal: Br J Clin Pharmacol Language: English	
Title/ concept: Interventions to reduce inappropriate polypharmacy: Implications for research and practice. Authors: Tim Johansson, Maria Flamm, Andreas Sönnichsen Data: Journal: Elsevier Maturitas Language: English	Published
Title/ concept: Letter to the editor. Reply to 'Endpoints in strategies to reduce polypharmacy'. Authors: Tim Johansson, Maria Flamm, Andreas Sönnichsen, Jochen Schuler Data: Journal: British Journal of Clinical Pharmacology Language: English	Published
Title/ concept: A set of systematic reviews to help reduce inappropriate prescribing to older people: study protocol Authors: Yolanda V Martinez, Anna Renom-Guiteras, David Reeves, R Erandie Ediriweera de Silva, Aneez Esmail, Ilkka Kunnamo, Anja Rieckert, Christina Sommerauer, Andreas Sönnichsen Data: Journal: BMC Geriatrics Language: English	Published
Title/concept: Effectiveness and safety of Dipeptidyl peptidase 4 inhibitors in the management of type 2 diabetes in older adults: a systematic review and the development of recommendations to reduce inappropriate prescribing Authors: Gisela Schott, Yolanda V Martinez, Erandie Ediriweera de Silva, Anna Renom-Guiteras, Anna Vögele, David Reeves, Ilkka Kunnamo, Minna Marttila-Vaara, Andreas Sönnichsen Data: SR gliptins/diabetes Journal: BMC Geriatrics Language: English	Published
Title/concept: Effectiveness and safety of beta blockers in the	Published

management of hypertension in older adults: a systematic review to help reduce inappropriate prescribing Authors: Anna Vögele, Tim Johansson, Yolanda V Martinez, Lisa Schlender, Anna Renom-Guiteras, Anja Rieckert, Anne-Lisa Teichmann, Andreas Sönnichsen Data: SR ß-Blocker/Hypertension Journal: BMC Geriatrics Language: English	
Title/concept: Thiazides in the management of hypertension in older adults – a systematic review Authors: Christina Sommerauer, Neha Kaushik, Adrine Woodham, Anna Renom-Guiteras, Yolanda V Martinez, David Reeves, Ilkka Kunnamo, Steffen Hübner, Andreas Sönnichsen Data: SR Thiazides/Hypertension Journal: BMC Geriatrics Language: English	Published
Title/concept: Efficacy and Patient safety with Vitamin-K-antagonists and new anticoagulants in the Treatment/Prevention of Thromboembolism in Atrial Fibrillation in older adults – an overview of reviews Authors: Christina Sommerauer, Lisa Schlender, Marc Krause, Sabine Weißbach, Anja Rieckert, Yolanda V Martinez, Anna Renom-Guiteras, Ilkka Kunnamo, Andreas Sönnichsen Data: SR VKA/NOACs atrial fibrillation Journal: BMC Geriatrics Language: English	Published
Title/concept: Efficacy and Patient safety with platelet aggregation inhibitors in the management of cerebral infarction, transient ischaemic attacks, peripheral artery occlusive disease and coronary disease in older adults – a systematic review Authors: Maren Meinshausen, Anja Rieckert, Anna Renom-Guiteras, Moritz Kröger, Christina Sommerauer, Ilkka Kunnamo, Yolanda V Martinez, Aneez Esmail, Andreas Sönnichsen Data: SR PAI Journal: BMC Geriatrics Language: English	Published
Title/concept: Efficacy and safety of metformin in the management of type 2 Diabetes mellitus in older adults: a systematic review for the development of recommendations to reduce inappropriate prescriptions Authors: Lisa Schlender, Yolanda V Martinez, Charles, David Reeves, Barbara Faller, Christina Sommerauer, Ilkka Kunnamo, Andreas	published

Sönnichsen, Anna Renom-Guiteras Data: SR Metformin Journal: BMC Geriatrics Language: English	
Title/concept: Efficacy and patient safety with NSAIDs in the management of musculoskeletal disorders in older adults – a systematic review Authors: Anja Rieckert, Barbara Faller, Christina Sommerauer, Lisa Schlender, Anne-Lisa Teichmann, Erandie Ediriweera de Silva, Sabine Weißbach, Anna Renom-Guiteras, Thekraiat Al'Quaran, Ilkka Kunnamo, Andreas Sönnichsen Data: SR NSAIDs Journal: to be determined Language: English	1,4000 hits were screened 14 included; update completed
Title/concept: Insulin –SR Authors: Raniah El-Jezawi, (more to be determined), Lisa Lechterbeck, Andreas Sönnichsen Data: SR Insulin Journal: to be determined Language: English	Study selection 1,2, 3a completed; comprehensive search needs to be conducted 10,000 hits are currently screened
Title/concept: Insulin – Protocol Authors: Lisa Schlender, Raniah El-Jezawi, Andreas Sönnichsen Data: SR Insulin Journal: to be determined Language: English	Draft ready
Title/concept: Statins SR of SRs Authors: Thekraiat Al'Quaran, Moritz Kröger (joint first authorship), Anja Rieckert, Anna Renom-Guiteras, David Reeves, Ilkka Kunnamo, Yolanda Martinez, Andreas Sönnichsen Data: SR Statins Journal: to be determined Language: English	Update completed; currently Search 3a+3b
Title/concept: Using the electronic decision support tool PRIMA-eDS to optimize medication in primary care – a qualitative study for practical implementation	Re-submitted (mid-March)

Authors: Anja Rieckert, Christina Sommerauer, Anja Krumeich, Andreas Sönnichsen Data: Interviews with GPs from Witten Journal: BMC Family Practice Language: English	
Working title/concept: Validation of the tool. Comparison with recommendations from Dara Koper. Authors: Ann-Kathrin Bücherl, (to be determined), Andreas Sönnichsen Data: Kopers patients are entered into the PRIMA-eDS tool. Recommendations by the PRIMA-eDS tool are compared to recommendations provided by the study of Dara Koper Journal: (to be determined) Language: English	Database will be ready by mid-April
Title/concept: Recruitment of general practitioners for research - Experiences from a multicentre cluster-randomized controlled trial (PRIMA-eDS) Authors: Sophie Keller, Tim Johansson, Eva Drewelow, Christin Löffler, Anja Rieckert, Ulrike Trampisch, Maria Flamm Data: Questionnaires Journal: BMC Medical Research Methodology Language: English	Determination of new Journal after being rejected
Title/concept: On which quality are our clinical decisions based on? Quality of studies & systematic review – Interrater Reliability Authors: Lisa Schlender, , Andreas Sönnichsen Data: Search and data extraction documents Journal: to be determined Language: English	Analysis started
Title/concept: Validation of the PRIMA-eDS tool – comparison with data from the PRIMA study Italy Authors: Giuliano Piccoliori, Anna Vögele Data: Journal: Language:	CMR database needed

2.1 Section A: Dissemination Measures and Publications

Dissemination measures of the PRIMA-eDS-project are shown in tables 16 (A1) and 17 (A2). Table 16 (A1) depicts peer-reviewed journal articles already published. Table 17 (A2) shows other dissemination activities.

Table 16 (A1): List of scientific (peer reviewed) publications (starting with the most important ones)

No.	Title	Main author	Title of journal	Issue, date	Publisher	Place of Publication	Year of publication	Pages	link or doi	open access (y/n)
1	Polypharmacy in chronic diseases–Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS): study protocol for a randomized controlled Trial	Sönnichsen	BMC Trials	17:57 29 Jan 2016	Biomed Central	UK	2016	1-9	https://doi.org/10.1186/s13063-016-1177-8	y
2	Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis.	Johansson	Br J Clin Pharmacol.	Aug;82(2):	Wiley	UK	2016	532-48	10.1111/bcp.12959	n
3	A set of systematic reviews to help reduce inappropriate prescribing to older people: study protocol	Martinez; Renom-Guiteras	BMC Geriatrics	17. Oct. 2017	Biomed Central	UK	2017	1-9	10.1186/s12877-017-0570-9	y
4	Interventions to reduce inappropriate polypharmacy: Implications for research and practice.	Johansson	Maturitas.	97	Elsevier	UK	2017	66-68.	https://doi.org/10.1016/j.maturitas.2016.12.007	n
5	User perspectives on an electronic decision-support tool performing comprehensive medication reviews - a focus group study with physicians and nurses	Koskela	BMC Medical Informatics and Decision Making	16	Biomed Central	UK	2015	1-6	http://www.biomedcentral.com/1472-6947/16/6	y
6	Thiazides in the management of hypertension in older adults – a systematic review	Sommerauer	BMC Geriatrics	17, Oct. 2017	Biomed Central	UK	2017	145-157	10.1186/s12877-017-0576-3	y
7	Effectiveness and safety of beta blockers in the management of hypertension in older adults: a systematic review to help reduce inappropriate prescribing	Vögele	BMC Geriatrics	17, Oct. 2017	Biomed Central	UK	2017	119 - 143	10.1186/s12877-017-0575-4	y
8	Efficacy and safety of metformin in the management of type 2 diabetes mellitus in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing	Schlender; Martinez	BMC Geriatrics	17. Oct. 2017	Biomed Central	UK	2017	99-117	10.1186/s12877-017-0574-5	y

9	Effectiveness and safety of vitamin K antagonists and new anticoagulants in the prevention of thromboembolism in atrial fibrillation in older adults – a systematic review of reviews and the development of recommendations to reduce inappropriate prescribing	Sommerauer; Schlender	BMC Geriatrics	17. Oct. 2017	Biomed Central	UK	2017	73-98	10.1186/s12877-017-0573-6	Y
10	Effectiveness and patient safety of platelet aggregation inhibitors in the prevention of cardiovascular disease and ischemic stroke in older adults – a systematic review	Meinshausen; Rieckert	BMC Geriatrics	17. Oct. 2017	Biomed Central	UK	2017	41-71	10.1186/s12877-017-0572-7	y
11	Effectiveness and safety of Dipeptidyl peptidase 4 inhibitors in the management of type 2 diabetes in older adults: a systematic review and the development of recommendations to reduce inappropriate prescribing	Schott, Martinez	BMC Geriatrics	17. Oct. 2017	Biomed Central	UK	2017	11-39	10.1186/s12877-017-0571-8	Y
12	Reply to "Endpoints in strategies to reduce polypharmacy".	Johansson	Br J Clin Pharmacol.	83(2)	Wiley	UK	2017	434	DOI: 10.1111/bcp.13125	n

Table 17 (A2): List of Dissemination Activities (e.g. Conferences)

No	Type of activity	Main leader	Title	Date	Place	Type of audience	Size of audience	Countries addressed
1	Oral presentation	Johansson	17th annual meeting of the German Network for Evidencebased Medicine	3/3/2016	Cologne (GER)	Scientific community (higher education, research)	500	Austria, Germany, Italy
2	Oral presentation	Johansson & Vögele	51st congress for general practice and family medicine of German Association of General Medicine	21/9/2017	Düsseldorf (GER)	Scientific community (higher education, research)	600	Austria, Germany, Italy
3	Oral presentation	Johansson	50th congress for general practice and family medicine of German Association of General Medicine	29/9/2016	Frankfurt am Main (GER)	Scientific community (higher education, research)	600	Austria, Germany, Italy
4	Oral presentation	Keller	49th congress for general practice and family medicine of German Association of General Medicine	18/9/2015	Bolzano (ITA)	Scientific community (higher education, research)	600	Austria, Germany, Italy
5	Oral presentation	Johansson	48th congress for general practice and family medicine of German Association of General Medicine	19/9/2014	Hamburg (GER)	Scientific community (higher education, research)	600	Austria, Germany, Italy
6	Oral presentation	Johansson	15th annual meeting of the German Network for Evidence-based Medicine	13.3.2014	Halle, Saale (GER)	Scientific community (higher education, research)	500	Austria, Germany
7	Poster	Teichmann	51th congress for general practice and family medicine of German Association of General Medicine	21.09.17-23.09.2017	Düsseldorf (GER)	Scientific community (higher education, research)	600	Germany, Austria, Italy, UK
8	Poster	Schlender	51th congress for general practice and family medicine of German Association of General Medicine	21.09.17-23.09.2017	Düsseldorf, Germany	Scientific community (higher education,	600	Germany

						research)		
9	Poster	Faller	51th congress for general practice and family medicine of German Association of General Medicine	21.09.2017-23.09.2017	Düsseldorf, Germany	Scientific community (higher education, research)	600	Germany
10	Poster	Vögele	51th congress for general practice and family medicine of German Association of General Medicine	21.09.17-23.09.2017	Düsseldorf, Germany	Scientific community (higher education, research)	600	Italy, Austria, Germany
11	Oral presentation/ symposium	Renom-Guiteras	21st International Association of Gerontology and Geriatrics (IAGG) World Congress	23.07.2017-27.07.2017	San Francisco, California USA	Scientific community (higher education, research)		
12	Oral presentation	Rieckert	18 th annual meeting of the German Network for Evidence-based Medicine	09.03.2017 – 11.03.2017	Hamburg, Germany	Scientific community (higher education, research)	500	Germany, Austria, Italy, UK
13	Oral presentation	Rieckert	18 th annual meeting of the German Network for Evidence-based Medicine	09.03.2017 – 11.03.2017	Hamburg, Germany	Scientific community (higher education, research)	500	Germany
14	Oral presenation	Sönnichsen	18 th annual meeting of the German Network for Evidence-based Medicine	09.03.2017-11.03.2017	Hamburg, Germany	Scientific community (higher education, research)	500	Germany
15	Poster	Schlender	18 th annual meeting of the German Network for Evidence-based Medicine	09.03.2017 – 11.03.2017	Hamburg, Germany	Scientific community (higher education, research)	500	Germany
16	Oral presentation	Sönnichsen	Polypharmazie: ein Dilemma für Arzt und Patient. Ärztlicher Qualitätszirkel. Ärztlicher Qualitätszirkel	22/09/2016	Wetter a. d. Ruhr, Germany	Scientific community, Physicians		Germany
17	Oral presentation	Sönnichsen	15th german congress for healthcare research	05/10/2016-07/10/2016	Berlin, Germany	Scientific community (higher education, research)	600	Germany
18	Oral presentation	Sönnichsen	15th german congress for healthcare research	05/10/2016 – 07/10/2016	Berlin, Germany	Scientific community (higher education, research)	600	Germany
19	Poster	Rieckert	50 th congress for general practice and family medicine of German Association of General Medicine	29/09/2016-01/10/2016	Frankfurt am Main	Scientific community (higher education, research)	600	Germany, Austria, Italy, UK
20	Poster	Sommerauer	50 th congress for general practice and family medicine of German Association of General Medicine	29/09/2016-01/10/2016	Frankfurt am Main	Scientific community (higher education, research)	600	Germany
21	Poster	Schlager	WONCA SAR Conference 2016, Colombo, Sri Lanka	11/02/16-14/02/16	Colombo, Sri Lanka	Scientific community (higher education, research)		Germany, Austria, Italy
22	Poster	Rieckert	17th annual meeting of the German Network for Evidence-based Medicine	03/03/2016-05/03/2016	Köln, Germany	Scientific community (higher education, research)	500	Germany
23	Poster	Rieckert	1.Wittener research meeting	06.04.2016	Witten, Germany	Scientific community (higher education, research)		Germany
24	Poster	Celine Kriechmayr (PMU)	Einsatz der elektronischen Entscheidungshilfe zur Optimierung der Medikation in der hausärztlichen Versorgung – eine quantitative Untersuchung zur praktischen Umsetzung im Rahmen der cluster-randomisert kontrollierten Studie PRIMA-eDS 51st congress for general practice and family medicine of German Association of General Medicine	21/9/2017	Düsseldorf (GER)	Scientific community (higher education, research)	600	Austria, Germany, Italy
25	Poster	PMU/UWH/UMR/SAGP	Effektivität und Patientensicherheit von Betablockern bei älteren Menschen mit Hypertonie – Update einer systematischen Übersichtsarbeit 51st congress for general practice and family medicine of German Association of General Medicine	21/9/2017	Düsseldorf (GER)	Scientific community (higher education, research)	600	Austria, Germany, Italy
26	Poster	UWH	Einsatz der elektronischen Entscheidungshilfe PRIMA-eDS zur Optimierung der Mediation in der hausärztlichen Versorgung – eine quantitative Untersuchung zur	21.09.17-23.09.2017	Düsseldorf, Germany	Scientific community(higher education, research)	600	Germany, Austria, Italy, UK

			praktischen Umsetzung					
27	Poster	UWH	Ist Metformin immer noch die beste Option bei der Behandlung von älteren Typ-2 Diabetikern. Eine systematische Übersichtsarbeit.	21.09.17-23.09.2017	Düsseldorf, Germany	Scientific community (higher education, research)	600	Germany
28	Poster	UWH	Ein systematisches Review zum Einsatz nichtsteroidaler Antirheumatika (NSAR) in der Behandlung von muskuloskelettalen Erkrankungen bei älteren Menschen	21.09.2017-23.09.2017	Düsseldorf, Germany	Scientific community (higher education, research)	600	Germany
29	Oral presentation/ symposium	UWH	The PRIMA-eDS electronic decision support tool for polypharmacy – a multinational European project	23.07.2017-27.07.2017	San Francisco, California USA	Scientific community(higher education, research)		
30	Oral presentation	UWH	Welche Faktoren prädisponieren ältere Menschen für extreme Polypharmazie? Eine Querschnittsanalyse mit Daten aus der PRIMA-eDS-Studie 18. Jahrestagung Deutsches Netzwerk Evidenzbasierte Medizin	09.03.2017 – 11.03.2017	Hamburg, Germany	Scientific community(higher education, research)	500	Germany, Austria, Italy, UK
31	Oral presentation	UWH	Einsatz der elektronischen Entscheidungshilfe PRIMA-eDS zur Optimierung der Medikation in der hausärztlichen Versorgung – eine qualitative Untersuchung zur zukünftigen Implementierung 18. Jahrestagung Deutsches Netzwerk Evidenzbasierte Medizin	09.03.2017 – 11.03.2017	Hamburg, Germany	Scientific communit(higher education, research)y	500	Germany
32	Poster	UWH	Die Vorteile und Risiken von Metformin bei der Behandlung von älteren Typ-2 Diabetikern. Eine systematische Übersichtsarbeit	09.03.2017 – 11.03.2017	Hamburg, Germany	Scientific community(higher education, research)	500	Germany
33	Oral presentation	UWH	Diskrepante Ergebnisse bei Randomisiert kontrollierten Studien, Systematic Reviews und Metanalysen zu identischen Fragestellungen – Wie kann das sein? 18. Jahrestagung Deutsches Netzwerk Evidenzbasierte Medizin	09.03.2017 – 11.03.2017	Hamburg, Germany	Scientific community(higher education, research)	500	Germany
34	Journal article	PMU/UWH/	Interventions to reduce inappropriate polypharmacy: Implications for research and practice. Maturitas. 2017 Mar;97:66-68	3/2017		Scientific community (higher education, research)		All
35	Journal article,	PMU/UWH/	Reply to 'Endpoints in strategies to reduce polypharmacy'. Br J Clin Pharmacol. 2017 Feb;83(2):434	2/2017		Scientific community (higher education, research)		All
36	Oral presentation	UWH	Reduktion unangemessener Polypharmazie durch eine elektronische Entscheidungshilfe - das PRIMA-eDS-Projekt 15. Deutscher Kongress für Versorgungsforschung	05/10/2016-07/10/2016	Berlin, Germany	Scientific community(higher education, research)	600	Germany
37	Oral presentation	UWH	Reduktion von Polypharmazie-Risiken für ältere Patienten - eine Implementierungs-Studie mit einer komplexen Intervention 15. Deutscher Kongress für Versorgungsforschung	05/10/2016 - 07/10/2016	Berlin, Germany	Scientific community(higher education, research)	600	Germany
38	Poster	UWH	Welche Faktoren prädisponieren ältere Menschen für extreme Polypharmazie? Eine Querschnittsanalyse mit Daten aus der PRIMA-eDS-Studie		Poster	UWH		
39	Poster	UWH	Einsatz der elektronischen Entscheidungshilfe PRIMA-eDS zur Optimierung der Medikation in der hausärztlichen Versorgung - eine qualitative Untersuchung zur praktischen Umsetzung		Poster	UWH		
40	Poster	PMU/UMR/UWH	Die Effektivität von elektronischen und nicht-elektronischen Interventionen zur Reduktion von Polypharmazie hinsichtlich Morbidität, Lebensqualität und anderer Endpunkte – ´Update´ einer systematischen Übersichtsarbeit		Poster	PMU/UMR/UWH		
41	Poster	SAGP	Effektivität und Patientensicherheit von Betablockern bei älteren Menschen mit Hypertonie - eine systematische Übersichtsarbeit [Effectiveness and safety of beta blockers in the management of hypertension in older adults: a systematic review] 50th congress for general practice and family medicine of German Association of Family Medicine	29/09/2016 - 01/10/2016	Frankfurt, Germany	Scientific community(higher education, research)	600	Germany, Austria

42	Poster	PMU/UWH/UMR	Die Effektivität von elektronischen und nicht-elektronischen Interventionen zur Reduktion von Polypharmazie hinsichtlich Morbidität, Lebensqualität und anderer Endpunkte - 'Update' einer systematischen Übersichtarbeit 50th congress for general practice and family medicine of German Association of General Medicine	29/9/2016	Frankfurt am Main (GER)	Scientific community (higher education, research)	600	Austria, Germany, Italy
43	Journal article	PMU/UWH/UMR	Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis.Br J Clin Pharmacol. 2016 Aug;82(2):532-48	8/8/2016		Scientific community (higher education, research)		All
44	Poster	UWH	Einsatz der elektronischen Entscheidungshilfe PRIMA-eDS zur Optimierung der Medikation in der hausärztlichen Versorgung - eine qualitative Untersuchung zur praktischen Umsetzung 1.Wittener Forschertreffen	06.04.2016	Witten, Germany	Scientific community(higher education, research)	?	Germany
45	Oral presentation	Johansson (PMU)	Elektronische und nicht-elektronische Interventionen zur Reduktion von Polypharmazie – weiterhin fehlende Evidenz für einen Patientennutzen 17th annual meeting of the German Network for Evidencebased Medicine	03/03/2016	Köln (GER)	Scientific community (higher education, research)	500	Austria, Germany, Italy
46	Poster	UWH	Einsatz der elektronischen Entscheidungshilfe PRIMA-eDS zur Optimierung der Medikation in der hausärztlichen Versorgung - eine qualitative Untersuchung zur praktischen Umsetzung Rieckert et al 17th annual meeting of the German Network for Evidence-based Medicine	03/03/2016-05/03/2016	Köln, Germany	Scientific community(higher education, research)	500	Germany
47	Oral presentation	PMU/UMR/UWH	Elektronische und nicht-elektronische Interventionen zur Reduktion von Polypharmazie - weiterhin fehlende Evidenz für einen Patientennutzen Johansson et al. 17th annual meeting of the German Network for Evidence-based Medicine	03/03/2016-05/03/2016	Köln, Germany	Scientific community(higher education, research)	500	Austria, Germany
48	Poster	UWH	Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in elderly populations by electronic Decision Support (PRIMA-eDS) Schlager et al. WONCA SAR Conference 2016, Colombo, Sri Lanka	11/02/16-14/02/16	Colombo, Sri Lanka	Scientific community(higher education, research)	?	All
49	Presentation	DMP	Clinical Informatics Course	23/2/2016	Toronto, Canada	Physicians, medical students, clinical epidemiology students	35	Several, mostly Canadian
50	Presentation	DMP	WONCA International Classification Committee	14/9/2016	Helsinki, Finland	Physicians	25	Several
51	Presentation	DMP	Guidelines International Conference	29/9/2016	Philadelphia, USA	Physicians, guideline developers	20	Several
52	Presentation	DMP	ICT conference	7/6/2017	Khanty-Mansijsk, Russia	Physicians, IT professionals	50	Several (mainly Russian)
53	Presentation	DMP	Global Evidence Summit, Multimorbidity Working Group Workshop	14/9/2017	Cape Town, South Africa	Physicians	16	Several
54	Presentation	DMP	EBM Conference, Sechenov Medical University	23/10/2017	Moscow, Russia	Physicians, medical students	220	Russian
55	Presentation	DMP	PRIMA-eDS Conference	10/11/2017	Witten, Germany	Physicians	35	Several
56	Presentation	DMP	Nordic-German Health IT Symposium	30/11/2017	Hannover	Physicians, IT professionals, investors	28	German
57	seminar	UNIMAN	UK branch of PRIMA-eDS study David Reeves, Adrine Woodham, Yolanda Martinez	18/02/2014	Centre for Primary Care, University of Manchester	Scientific community	60	UK
58	presentation	DMP	WONCA World Congress, Prague: Reduction of polypharmacy in the elderly Ilkka Kunnamo	29.6.2013	Prague Congress Centre	Scientific community	65	Several
59	presentation	DMP	HIMSS Conference/Nordic Day, New Orleans: Medication and adverse drug events control with decision support	3.3.2013	New Orleans Congress Centre	Scientific community; Industry	100	Denmark, Finland, Norway,

			systems Ilkka Kunnamo					Sweden, Iceland, United States
60	presentation	DMP	Guidelines International Network Conference Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	19.8.2013	San Francisco	Scientific community	50	Several
61	presentation	DMP	Nordic Congress on General Practice Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	23.8.2013	Tampere	Scientific community	1000	Denmark, Finland, Norway, Sweden, Iceland, several
62	presentation	DMP	Cochrane Colloquium Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	20.9.2013	Quebec City	Scientific community	25	Several
63	presentation	DMP	WONCA International Classification Committee (webmeeting presentation) Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	20.9.2013	Johannesburg	Scientific community	50	Several
64	presentation	DMP	Kokkola Health Centre Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	20.12.2012	Kokkola, Finland	Civil society	20	Finland
65	presentation	DMP	Regional educational event for physicians Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	20.3.2013	Tampere, Finland	Civil society	600	Finland
66	presentation	DMP	Aalto University, Health Care Leadership programme Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	16.4.2013	Helsinki, Finland	Civil society, policy makers	25	Finlaned
67	presentation	DMP	Norbotten and Örebro health care authorities Reduction of polypharmacy by electronic decision support Peter Nyberg	18.4.2013	Örebro	Policy makers	10	Sweden
68	presentation	DMP	National institute for Health and Welfare Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	25.4.2013	Helsinki, Finlalnd	Policy makers, civil society	60	Finland, Denmark, Canada
69	presentation	DMP	National project on healthcare IT architecture Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	29.4.2013	Helsinki, Finland	Policy makers	30	Finland
70	presentation	DMP	WoHIT/eHealthWeek Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	14.5.2013	Dublin	Scientific community, Policy makers	80	Several
71	presentation	DMP	Tieto Healthcare Forum Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	29.8.2013	Helsinki, Finland	Policy makers, civil society	200	Finland
72	presentation	DMP	Health care management course for physicians in GP specialist training Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	26.9..2013	Helsinki, Finland	Civil society	65	Finland
73	presentation	DMP	National Guidelines Day Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	28.9.2013	Leuven, Belgium	Policy makers, civil society, scientific soviety	160	Belgium
74	presentation	DMP	Educational event for young doctors in Finland Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	25.10.2013	Helsinki, Finland	Civil society	500	Finland
75	presentation	DMP	Regional educational event for physicians Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	7.11.2013	Turku, Finland	Civil society	55	Finland
76	presentation	DMP	Physicianss' Association in Tampere Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	7.11.2013	Tampere, Finland	Civil society	45	Finland
77	presentation	DMP	Healh care leadership educational event Reduction of polypharmacy by electronic	8.11.2013	Helsinki, Finland	Civil society	80	Finland

			decision support Ilkka Kunnamo					
78	presentation	DMP	EQuiP meeting Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	15.11.2013	Bologna, Italy	Civil society, Scientific community	25	Several
79	presentation	DMP	Nokia Health Centre Reduction of polypharmacy by electronic decision support Peter Nyberg	14.12.2013	Nokia, Finland	Civil society	20	Finland
80	presentation	DMP	Regional educational event for physicians Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	10.1.2014	Helsinki, Finland	Civil society	25	Finland
81	presentation	DMP	Central Finland Physicians' Association Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	15.2.2014	Jyväskylä, Finland	Civil society	80	Finland
82	presentation	DMP	Ministry of Health, Finland Reduction of polypharmacy by electronic decision support Ilkka Kunnamo Timo Haikonen Peter Nyberg	6.3.2014	Helsinki, Finland	Policy makers	5	Finland
83	presentation	DMP	Health care leadership course, Finnish Medical Association Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	12.3.2014	Helsinki, Finland	Civil society	30	Finland
84	presentation	DMP	National institute for Health and Welfare Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	18.3.2014	Helsinki, Finland	Civil society	40	Finland
85	presentation	DMP	Finnish Innovation Fund (Sitra) Reduction of polypharmacy by electronic decision support Ilkka Kunnamo	6.5.2014	Helsinki, Finland	Industry, Civil society, Policy makers	170	Finland
86	journal article	UMR	Langer, C. (2014). Prima läuft der Arztbesuch. In: Studierendenschaft der Universität Rostock (Hrsg.). HEULER - Das Studentenmagazin der Uni Rostock auf Papier, No. 105; 04-2014, p.26.	Apr 2014	Rostock	civil society & scientific community	15.000	Germany
87	poster	UMR	Höck, J. et al. (2013). Polypharmazie bei Patienten mit chronischen Erkrankungen: Reduktion inadäquater Medikation und unerwünschter Arzneimittelwirkungen durch eine elektronische Entscheidungshilfe. Poster presented at F2-Forschung trifft Forschung-Forschungscamp, University of Rostock.	07. Nov 2013	Rostock	scientific community	150	Germany
88	presentation	PMU	PRIMA-eDS: Reduction of polypharmacy by electronic decision support Meeting of the regional association of general practitioners	26/03/2014	Salzburg (A)	scientific community	20	Austria
89	poster	PMU/UWH,UMR	A systematic review on strategies to reduce polypharmacy 15th annual meeting of the German Network for Evidence-based Medicine	13/03/2014	Halle (D)	scientific community	400	Germany, Austria
90	poster	PMU	A systematic review on strategies to reduce polypharmacy 47th congress for general practice and familiy medicine of German Association of General Medicine	12/09/2013	Munich (D)	scientific community	600	Germany, Austria
91	journal article	PMU	PRIMA-eDS: Reduction of polypharmacy by electronic decision support med.ium 11/2013 (a regional journal for physicians in Salzburg)	11/12/2013	Salzburg (A)	scientific community , civil society	3600	Austria
92	presentation	PMU	PRIMA-eDS: Reduction of polypharmacy by electronic decision support Information event at Paracelsus Medical University for physicians of the province of Salzburg	02/10/2013	Salzburg (A)	scientific community	30	Austria
93	poster	UWH and UNIMAN	Efficacy and safety of drugs commonly used in the management of chronic diseases in older adults: a compilation of systematic reviews for the development of an electronic decision support tool. Renom-Guiteras A, Martinez Y et al. 15th annual meeting of the German Network for Evidence-based Medicine	March 13th-15th, 2014	Halle, Germany	Scientific community	400	Germany, Austria
94	poster	UWH and SAGP	Wirksamkeit und Sicherheit von oralen Antidiabetika im Management von Diabetes mellitus Typ 2 bei älteren Erwachsenen – eine systematische	March 13th-15th, 2014	Halle, Germany	Scientific community	400	Germany, Austria

			Übersichtsarbeit [Efficacy and safety of oral antidiabetics in the management of type 2 Diabetes mellitus in older people – a systematic review]. Vögele A et al. 15th annual meeting of the German Network for Evidence-based Medicine					
95	poster	UWH	Efficacy and Patient Safety of Statins in the Prevention of Cardiovascular Events in Older Adults – a Systematic Review. Al Qur'An T et al. 15th annual meeting of the German Network for Evidence-based Medicine	March 13th-15th, 2014	Halle, Germany	Scientific community	400	Germany, Austria
96	poster	UWH	Wirksamkeit und Sicherheit von Antikoagulantien in der Prävention von Thromboembolien bei Vorhofflimmern bei älteren Erwachsenen - eine systematische Übersichtsarbeit. [Efficacy and safety of anticoagulants in the prevention of thromboembolism in atrial fibrillation in older adults – a systematic review]. Sommerauer C et al. 15th annual meeting of the German Network for Evidence-based Medicine	March 13th-15th, 2014	Halle, Germany	Scientific community	400	Germany, Austria
97	presentation	UWH	Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in elderly populations by electronic Decision Support. Sommerauer et al. 12th Annual Conference of the German network for health services research	October 23rd-25th, 2013	Berlin, Germany	Scientific community	700	Germany
98	presentation	UWH	Welche Medikamente sind evidenzbasiert bei multimorbiden älteren Patienten – eine systematische Literaturrecherche. [Which medications are evidence-based in older adults with comorbidity – compilation of systematic reviews]. Renom-Guiteras A et al. IZVF-Kolloquium at UWH	May 7th, 2014	Witten, Germany	Scientific community, policy makers	20	Germany
99	poster	UWH	Entwicklung einer elektronischen Entscheidungshilfe zur Reduktion von Polypharmazie: Das PRIMA-eDS Tool. [Development of an electronic decision tool for the reduction of polypharmacy: the PRIMA-eDS Tool]. Sommerauer et al. 13th Annual Conference of the German network for health services research	June 24-27th, 2014	Düsseldorf, Germany	Scientific community, policy makers	700	Germany
100	Workshop	DMP	Clinical decision support for professionals, at DECIDE Consortium meeting	3/6/2014	Edinburgh	Scientific community	13	UK, Italy, Norway, Netherl.
101	Demo	DMP	NHS Education Scotland	5/6/2014	Glasgow	Professionals	3	UK
102	Presentation	DMP	WONCA Europe, session on tools for chronic disease management	3/7/2014	Lisbon	Primary care physicians	More than 200	Several
103	Presentation	DMP	Clinical Decision support in guideline implementation, at Guidelines International Network conference	20/8/2014	Melbourne	Scientific community, guideline developers	43	Several
104	Presentation	DMP	Big data and decision support in health care. Symposium by the University of Eastern Finland	9/10/2014	Kuopio, Finland	Scientific community, IT develop.	160	Finland
105	Presentation	DMP	Comprehensive Medication Review, at Welfare ICT Forum by CGI Finland	10/10/2014	Tampere, Finland	Clinicians and IT developers	70	Finland
106	Presentation	DMP	Clinical decision support, at EBM postgraduate course	25/2/2015	Tartu, Estonia	Physicians	25	Estonia
107	Presentation	DMP	Experience of clinical decision support systems among Finnish doctors at Estonian Medical Convention	10/4/2015	Tallinn, Estonia	Physicians	60	Estonia
108	Presentation	DMP	Clinical decision support at Medical Faculty, University of Helsinki	21/5/2015	Helsinki, Finland	Medical students	100	Finland
109	Presentation	DMP	Clinical decision support at NIVA advanced course on occupational health	8/9/2015	Oslo, Norway	Physicians	19	Finland, Norway, Denmark, Taiwan
110	Presentations	DMP	Multimorbidity working group meeting, Guidelines International Network Conference	8/10/2015	Amsterdam, Netherlands	Physicians, guideline developers	20	Several
111	Face to face presentation	PMU/UWH	Die Effektivität von elektroni-schen und nicht-elektronischen Interventionen zur Reduktion von Polypharmazie – eine systema-tische Übersichtarbeit. 48th congress of the German Association of Family Medicine	19/09/2014	Hamburg (GER)	Scientific community	600	Austria, Germany, Italy
112	Poster	PMU	Ärzte für Studien gewinnen – Erfahrungen aus der Versor-gungsforschung. 49th congress of the	18/9/2015	Bolzano (ITA)	Scientific community (higher education,	600	Austria, Germany, Italy

			German Association of Family Medicine			research)		
113	Journal article	PMU	Polypharmazie im Praxisalltag bewältigen: das PRIMA-eDS-Tool ÖGAM News (Österreichische Gesellschaft für Allgemein und Familienmedizin – Mitglied der Wonca) Ausgabe 06/15	06/2015	AUT	Scientific community (higher education, research)	3600 + online	AUT
114	Oral presentation/ abstract publication	UNIMAN	Safely reducing inappropriate prescribing to the older adults with polypharmacy: the multinational PRIMA-eDS study (Awarded the prize of best oral paper at the conference)	20/11/2015	Annual Academic Sessions of the Sri Lanka Association of Geriatric Sessions (SLAGM), Waters Edge Hotel, Battaramulla, Sri Lanka	Scientific and clinician communities	400	Sri Lanka
115	Poster presentation	UNIMAN	Evidence-Based Recommendations for the Reduction of Polypharmacy in Older People with Multiple Chronic Conditions: A Set of Systematic Reviews.	15-16/6/2015	Academy Health - Annual Research Meeting. June 14-16, Minneapolis, Minnesota, U.S.	Scientific and clinician communities	1500	USA and International
116	Poster presentation	UNIMAN	Evidence-Based Recommendations for the Reduction of Polypharmacy in Older People with Multiple Chronic Conditions: A Set of Systematic Reviews.	9-10/7/2015	Annual Scientific Meeting of the Society for Academic Primary Care. University of Oxford, Oxford, U.K.	Scientific community	200	UK
117	poster	UWH	Tackling polypharmacy in older adults: A compilation of systematic reviews for the development of an electronic decision support tool Schlager et al. WONCA Europe Conference 2015	22/10/2015-25/10/2015	Istanbul, Turkey	Scientific community	3680	79 countries, 42 outside of Europe
118	poster	UWH	Behandlung der Hypertonie bei älteren Menschen Sommerauer et al. 49th congress for general practice and family medicine of German Association of General Medicine	17/09/2015-19/09/2015	Bozen, Italy	Scientific communitiy	600	Germany, Austria, Italy
119	poster	UWH	Effektivität und Sicherheit in der Behandlung von Schmerz bei älteren Menschen mit Opioiden und Nichtsteroidalen Antirheumatika - von der Evidenz zur Entwicklung von Empfehlun-gen. Schlager et al. 49th congress for general practice and family medicine of German Association of General Medicine	17/09/2015-19/09/2015	Bozen, Italy	Scientific communitiy	600	Germany, Austria, Italy
120	poster	UWH	Einsatz der elektronischen Entscheidungshilfe PRIMA-eDS zur Optimierung der Medikation in der hausärztlichen Versorgung - eine qualitative Untersuchung zur praktischen Umsetzung. Rieckert et al. 49th congress for general practice and family medicine of German Association of General Medicine	17/09/2015-19/09/2015	Bozen, Italy	Scientific communitiy	600	Germany, Austria, Italy
121	poster	UWH	Neue orale Antikoagulantien bei älteren Patienten. Sommerauer et al. 49th congress for general practice and family medicine of German Association of General Medicine	17/09/2015-19/09/2015	Bozen, Italy	Scientific communitiy	600	Germany, Austria, Italy
122	presentation	UWH	Polypharmacy in Chronic Diseases: Reduction of Inappropriate Medication and Adverse Drug Events in Older Populations by Electronic Decision Support (PRIMA-eDS). Renom et al. The International Association of Gerontology and Geriatrics	23/04/2015 – 26/04/2015	Dublin, Ireland	Scientific communitiy		
123	presentation	UWH	Entwicklung einer elektronischen Entscheidungshilfe zur Reduktion von Polypharmazie: Das PRIMA-eDS Tool. Sönnichsen et al. 16th annual meeting of the German Network for Evidence-based Medicine	13/03/2015-14/03/2015	Berlin, Germany	Scientific communitiy	400	Germany
124	poster	UWH	Effektivität und Patientensicherheit bei Protonenpumpeninhibitoren bei älteren Menschen - von der Evidenz zur Entwicklung von Empfehlungen Sommerauer et al.	13/03/2015-14/03/2015	Berlin, Germany	Scientific communitiy	400	Germany

			16th annual meeting of the German Network for Evidence-based Medicine					
125	poster	UWH	Effektivität und Sicherheit von Opioiden in der Behandlung von Schmerz und von Husten bei älteren Menschen - von der Evidenz zur Entwicklung von Empfehlungen Schlager et al. 16th annual meeting of the German Network for Evidence-based Medicine	13/03/2015-14/03/2015	Berlin, Germany	Scientific communitiy	400	Germany
126	poster	UWH	Efficacy and safety of drugs commonly used in the management of chronic diseases in older adults: a compilation of systematic reviews for the development of an electronic decision support tool Al Qur´an et al. 16th annual meeting of the German Network for Evidence-based Medicine	13/03/2015-14/03/2015	Berlin, Germany	Scientific communitiy	400	Germany
127	poster	UWH	Einsatz nichtsteroidaler Antirheumatika (NSAR) in der Behandlung von Erkrankungen des Stütz- und Bewegungsapparates bei älteren Menschen - von der Evidenz zur Entwicklung von Empfehlungen Reickert et al. 16th annual meeting of the German Network for Evidence-based Medicine	13/03/2015-14/03/2015	Berlin, Germany	Scientific communitiy	400	Germany
128	poster	UWH	Über die Einführung einer elektronischen Entscheidungshilfe zur Reduktion von Polypharmazie in der Hausarztpraxis - eine Pilotstudie. Wörster et al. 16th annual meeting of the German Network for Evidence-based Medicine	13/03/2015-14/03/2015	Berlin, Germany	Scientific communitiy	400	Germany
129	poster	UWH	Effektivität und Sicherheit von Antihypertensiva vier verschiedener Substanzklassen (Diuretika, ACE-Hemmer, Kalziumantagonisten, ß-Blocker) bei älteren Menschen – von der Evidenz zur Entwicklung von Empfehlungen Sommerauer et al. 48th congress for general practice and family medicine of German Association of Family Medicine	18/09/2015 – 20/09/2014	Hamburg, Germany	Scientific communitiy	600	Germany
130	poster	UWH	Effektivität und Sicherheit von Herzglykosiden in der Behandlung von Herzinsuffizienz und Vorhofflimmern bei älteren Menschen - von der Evidenz zur Entwicklung von Empfehlungen Schlager et al. 48th congress for general practice and family medicine of German Association of Family Medicine	18/09/2015 – 20/09/2014	Hamburg, Germany	Scientific communitiy	600	Germany
131	poster	UWH	Effektivität und Sicherheit von Thrombozytenaggregationshemmern (TAH) bei der Prävention und Behandlung von Herzkreislauferkrankungen älterer Menschen – von der Evidenz zur Entwicklung von Empfehlungen Meinshausen et al. 48th congress for general practice and family medicine of German Association of Family Medicine	18/09/2015 – 20/09/2014	Hamburg, Germany	Scientific communitiy	600	Germany
132	poster	UWH	Einsatz nichtsteroidaler Antirheumatika (NSAR) in der Behandlung von Erkrankungen des Stütz- und Bewegungsapparates bei älteren Menschen – von der Evidenz zur Entwicklung von Empfehlungen Rieckert et al. 48th congress for general practice and family medicine of German Association of Family Medicine	18/09/2015 – 20/09/2014	Hamburg, Germany	Scientific communitiy	600	Germany

2.2 Section B: Exploitable Foreground and Plans for Exploitation

Table 18 (B1): List of Applications for Patents, Trademarks, Registered Designs, etc.

Not applicable

Table 19 (B2): Exploitable Foreground

Type of exploitable foreground	Description of exploitable foreground	Confidential (y/n)	Foreseen embargo date	Exploitable product(s) or measure(s)	Sector(s) of application	Timetable, commercial or any other use	Patents or other IPR exploitation (licenses)	Owner & other beneficiaries involved
Computer programme	Comprehensive Medication Review	N	n/a	IT-programme	IT	Already commercially used	n/a	DMP

3 Report on Societal Implications

A General Information

Grant agreement number: 305388-2

Project acronym: PRIMA-eDS

Project full title: Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in elderly populations by electronic Decision SupportGrant Agreement Number:

Name and title of Coordinator: Prof. Dr. Andreas Sönnichsen

B Ethics

1. Did your project undergo an Ethics Review (and/or Screening)?	Yes	
If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? (Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 'Work Progress and Achievements')	Yes	
2. Please indicate whether your project involved any of the following issues		
RESEARCH ON HUMANS	Yes	
Did the project involve children?		No
Did the project involve patients?	Yes	
Did the project involve persons not able to give consent?		No
Did the project involve adult healthy volunteers?		No
Did the project involve Human genetic material?		No
Did the project involve Human biological samples?		No
Did the project involve Human data collection?	Yes	
RESEARCH ON HUMAN EMBRYO/FOETUS		No
Did the project involve Human Embryos?		No
Did the project involve Human Foetal Tissue / Cells?		No
Did the project involve Human Embryonic Stem Cells (hESCs)?		No
Did the project on human Embryonic Stem Cells involve cells in culture?		No
Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?		No
PRIVACY		

Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?		No
Did the project involve tracking the location or observation of people?		No
RESEARCH ON ANIMALS		
Did the project involve research on animals?		No
Were those animals transgenic small laboratory animals?		No
Were those animals transgenic farm animals?		No

C Workforce Statistics

Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Table 20: Personnel working in the PRIMA-eDS project

Type of Position	Number of Women	Number of Men
Scientific coordinator		1
Work package leaders	6	5
Experienced researchers (postdoc/PhD holders)	9	6
PhD students	11	4
Other	19	1

How many additional researchers were recruited specifically for this project? 33

4 Appendix

Appendix 1: Comprehensive Medication review offered commercially by DMP