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Predicting negative health outcomes in older general practice patients with chronic illness: rationale and development of the PROPERmed harmonized individual participant data database

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1 **TITLE**

2 Predicting negative health outcomes in older general practice patients with chronic illness: rationale
3 and development of the PROPERmed harmonized individual participant data database

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43 **ABSTRACT**

44 The prevalence of multimorbidity and polypharmacy increases significantly with age, and are
45 associated with negative health consequences. However, most current interventions to optimize
46 medication have failed to show significant effects on patient-relevant outcomes. This may be due to
47 ineffectiveness of interventions themselves, but may also reflect other factors: insufficient sample
48 sizes, heterogeneity of population. To address this issue, the international PROPERmed collaboration
49 was set up to obtain/synthesize individual participant data (IPD) from five cluster-randomized trials.
50 The trials took place in Germany and The Netherlands and aimed to optimize medication in older
51 general practice patients with chronic illness. PROPERmed is the first database of IPD to be drawn from
52 multiple trials in this patient population and setting. It offers the opportunity to derive prognostic
53 models with increased statistical power for prediction of patient-relevant outcomes resulting from the
54 interplay of multimorbidity and polypharmacy. This may help patients from this heterogeneous group
55 to be stratified according to risk and enable clinicians to identify patients that are likely to benefit most
56 from resource/time-intensive interventions. The aim of this manuscript is to describe the rationale
57 behind PROPERmed collaboration, characteristics of the included studies/participants, development
58 of the harmonized IPD database and challenges faced during this process.

59 **Registration**

60 PROSPERO ID: CRD42018088129

61 **Keywords** (max. 6)

62 Elderly, hospitalization, meta-analysis, multimorbidity, polypharmacy, prognosis, quality of life.

63

64 INTRODUCTION

65 Older people with multiple chronic diseases (multimorbidity) are the norm rather than the exception,
66 and up to 80% of consultations in general practice are devoted to helping them (1, 2). These patients
67 are frequently treated with multiple drugs (polypharmacy), which increases the risk of both
68 inappropriate prescriptions and medication underuse (3-7). Both multimorbidity and polypharmacy
69 are associated with a range of negative health outcomes such as falls, hospital admissions, reduced
70 health-related quality of life (HRQoL), decreased functionality and loss of autonomy (8-13).
71 Multimorbidity and polypharmacy have been recognized as major challenges facing health care
72 systems, as they not only worsen health outcomes in individuals, but lead to higher costs, e.g., for
73 health care utilization, treatment of adverse drug reactions (ADR), and home care (13-15).
74 To optimize the care and treatment of chronically ill patients, various interventions have been
75 developed and tested, of which most were complex and resource intensive. However, most cluster-
76 randomized controlled trials (cRCT) evaluating complex interventions associated with polypharmacy
77 and multimorbidity in general practice have failed to demonstrate significant effects on patient-
78 relevant outcomes (16). While positive effects have been shown on process parameters (e.g.,
79 outcomes related to prescribing quality), interventions have showed few and inconsistent effects on
80 clinical outcomes (e.g., falls), and no effect on well-being (e.g., quality of life) (17-21). Several factors
81 may be responsible for this. Firstly, the intervention may have been ineffective or of inadequate
82 intensity, or its implementation may have failed, perhaps because the follow-up period was too short
83 to allow for behavioural change in the prescribers. Secondly, the study design and the methodology
84 may have been flawed, possibly because cross-sectional data on frequently changing medication
85 regimens was not collected for long enough, or due to contamination. Thirdly, the Hawthorne effect
86 may have played a role, and the simple fact of participation in a trial may have resulted in an
87 improvement in patients' health (19-24). Furthermore, existing definitions of multimorbidity and
88 polypharmacy lead to heterogeneity in this patient group because they cover a broad range of patients,

89 ranging from the fit and active that are in a good state of health despite their diseases and
90 prescriptions, to those with a high disease and treatment burden and negative outcomes.
91 Heterogeneity in this patient population makes it particularly difficult to target the population that
92 may benefit most from interventions that are time- and resource-intensive and often complex (25).
93 The use of prognostic models can help predict the risk of specific future outcomes in individual patients
94 and may therefore help stratify risk and identify patients in need (26). A systematic review of existing
95 tools to predict risk found models aimed at identifying the risk of adverse events in patients with
96 multimorbidity, but none of them adequately considered polypharmacy-related risks and the
97 interrelation of multiple conditions and medication (27-30). In general, prognostic models that have
98 taken multimorbidity into account have shown only modest predictive accuracy. The authors of the
99 review identified three main limitations to implementing prognostic models in this setting - ethical and
100 data privacy issues, a lack of acceptance for such models among health professionals, and a lack of
101 evidence of their (cost-) effectiveness (31). Using risk assessment tools is felt to be beneficial for
102 initiating discussion, engaging patients in risk discussions, and guiding both health professionals and
103 patients around decision-making (32). However, the little effect has been found on patient attitudes
104 who express difficulties trying to understand the information provided with this type of tools (33).
105 To support the creation of prognostic models that address the problems mentioned above, a group of
106 international researchers that are active in the field of multimorbidity and polypharmacy in general
107 practice set up the PROPERmed collaboration and constructed the first major database of individual
108 patient information that was drawn from multiple trials in this population. As the approach offers both
109 statistical and clinical advantages, our aim was to provide a harmonized individual patient database to
110 support the development and validation of prognostic models, (34). In this manuscript we describe the
111 rationale behind the PROPERmed collaboration, the characteristics of the included studies and
112 patients, and the design, development and challenges of creating a harmonized individual participant
113 data (IPD) database.

114

115 **THE PROPERMED COLLABORATION**

116 The PROPERmed collaboration included trialists from five study centers in Germany and The
117 Netherlands that shared strong links due to pursuing a common interest in multimorbidity and
118 polypharmacy research: i) Goethe University Frankfurt/Main (Germany), ii) Amsterdam University
119 Medical Center (The Netherlands), iii) Maastricht University (The Netherlands), iv) Leiden University
120 Medical Center (The Netherlands), and v) Ruhr University Bochum (Germany). A collaborative
121 approach was used in preference to a systematic approach (35) because this was the first time a meta-
122 analysis of data from this population had been conducted, and the ability to confront unknown
123 difficulties required the expertise of a group of researchers with an established common interest. All
124 the trials had been registered and approved by the respective Medical Ethics Committees. The
125 PROPERmed collaboration further involved German experts from Heidelberg University Hospital and
126 the University of Freiburg (Cochrane Germany), as well as an international scientific advisory board
127 that included experts from Bond University, Gold Coast (Australia), as well as the University of Oxford
128 and the Centre for Prognosis Research, Keele University (UK). Key barriers of successfully implementing
129 prognostic models not only include a lack of acceptance among health professionals (31), but also a
130 lack of support by leading stakeholders in the field of application as well as patients' acceptance .
131 Furthermore, a timely application of prognostic models in routine care seems to facilitate
132 implementation (26). Therefore, to ensure the stakeholder perspective was not neglected, the
133 Techniker Krankenkasse (TK) statutory health insurance fund was also involved in the collaboration. By
134 collaborating with the TK, we will be able to gain relevant insights with regard to the potential
135 implementation of our model considering the macro, meso and micro level: i) Macro: German
136 statutory health insurances are represented in the Federal Joint Committee (G-BA). The G-BA consists
137 of umbrella organizations of the self-governing healthcare system including patient representatives
138 and is responsible for the definition of healthcare services to be paid by statutory health insurances,

139 and quality assurance of care; ii) Meso: Depending on the model, the included variables and defined
140 outcomes, the potential application of the prognostic model to data from routine care provided by
141 statutory health insurances will be discussed; iii) Micro: As not all variables included in the final model
142 may be available in routine data from statutory health insurances, additional possibilities of data
143 collection including patients will be discussed (e.g., via patient apps) in order to complement available
144 data from routine care.

145

146 **SOURCE OF DATA – CHARACTERISTICS OF THE PROPERmed STUDIES**

147 The PROPERmed study included IPD from five cRCTs: PRIMUM (24), Opti-Med (36, 37), PIL (Netherlands
148 Trial Register, NTR2154) (38), ISCOPE (39) and RIME (Deutsches Register Klinischer Studien-ID,
149 DRKS00003610). The cRCTs were conducted from 2009 onwards in general practices from The
150 Netherlands (ISCOPE, Opti-Med, and PIL) and Germany (PRIMUM and RIME) and evaluated complex
151 interventions aimed at optimizing (pharmacological) treatment in older patients with chronic disease.
152 Practices served as the unit of randomization in all the trials. Four of the five cRCTs used a pragmatic
153 parallel-group design and one used a stepped-wedge design (PIL). All the trials compared a structured
154 medication review (complex intervention) with usual care except one (ISCOPE), which compared usual
155 care with an integrated care plan that used a functional geriatric approach. Table 1 provides an
156 overview of the characteristics of the included trials.

157 [About here: Table 1 on Main characteristics of the included trials].

158

159 **DEFINITION OF THE CORE DATA SET**

160 At a kick-off meeting in May 2017, we and the other collaborators decided upon the data to be
161 collected for the IPD-MA based on the availability of relevant data in the trials. We agreed upon overall
162 inclusion and exclusion criteria for practices and patients, as well as a core data set covering a variety

163 of candidate prognostic factors and patient-relevant outcomes to be predicted in the subsequent
164 modelling approach.

165 **Participants**

166 *Practices*

167 To be included in the trials, general practices had to provide primary care within the framework of the
168 German or Dutch statutory health insurance systems. In one study (PRIMUM), practices specializing in
169 unconventional treatments or special conditions (e.g., HIV) were excluded. No additional exclusion
170 criteria were applied to practices in the other trials.

171 *Patients*

172 Based on the inclusion criteria in the trials, we included patients in PROPERmed that were aged 60
173 years and older, had been diagnosed with at least one chronic condition, and had at least one chronic
174 prescription at study baseline. We defined chronic conditions in accordance with O'Halloran et al. (40),
175 and defined chronic prescriptions in the same way as the trials (two weeks in PRIMUM, two months in
176 ISCOPE, and three months in Opti-Med, PIL and RIME).

177 In accordance with the exclusion criteria used in the trials, critically ill patients with a limited life
178 expectancy were not included. Additional inclusion and exclusion criteria were specified in individual
179 trials, such as abuse of alcohol or illegal drugs, which was an exclusion criterion in PRIMUM and PIL.
180 Between-trial heterogeneity resulting from the impact of trial-specific criteria was considered to be
181 acceptable.

182 **Outcomes and candidate prognostic variables**

183 For the planned prediction models, we agreed upon outcomes signifying deterioration in health-
184 related quality of life (dHRQoL) and all-cause hospital admissions at six-month follow up. Following a
185 discussion with the co-authors, the outcomes of interest were selected based on their relevance and
186 availability across the included trials. We also selected a full range of candidate prognostic variables
187 for the models, including data on socio-demographics and lifestyle, patient morbidity, medication,

188 functional status and well-being (HRQoL, physical and cognitive components), and whether patients
189 had been hospitalized in the 12 months previous to study enrolment.

190

191 **DATA COLLECTION AND HARMONIZATION**

192 Regardless of format, IPD for all five included cRCTs, the lists of variables, and information on data
193 collection, were gathered and stored in a secure data repository. As the measuring instruments used
194 in the studies varied, ex-post data harmonization procedures were conducted before model
195 development. As data harmonization aimed to preserve as much information as possible, missing data,
196 inconsistencies, and errors that occurred during data preparation were queried and discussed with the
197 original authors. Variables from the original trials were also harmonized using different techniques,
198 which included the recoding of categories and labels, and the clinical harmonization of variables (e.g.,
199 see ‘morbidity-related candidate prognostic variables’). Whenever necessary, new variables were
200 created from other available information by, for example, using cut-offs (see ‘depressive symptoms’).
201 If specific trials used psychometric instruments based on differing constructs to measure the same
202 outcome (see ‘functional status and well-being’), the underlying psychometrical constructs were
203 preserved and standardized mean differences used to render them comparable. Table 2 provides more
204 detailed information on the data harmonization process.

205 [About here: Table 2 on Data harmonization].

206 **Health-related quality of life (HRQoL)**

207 At baseline and after the six-month follow-up, all trials used the EQ-5D-3L index score (41) to measure
208 generic HRQoL in the dimensions mobility, self-care, usual activities, pain/discomfort, and
209 anxiety/depression. In two of the Dutch trials (PIL and ISCOPE), the translated question on “mobility”
210 had to undergo slight linguistic adaptation because the original item in the standardized questionnaire
211 frequently resulted in missing values in older populations (42). We calculated EQ-5D-3L index scores
212 based on time trade-off norm values (43) and defined the binary outcome dHRQoL as a decrease in

213 the EQ-5D-3L index score of at least five percent between baseline and six-month follow-up. We
214 considered this cut-off to be clinically relevant because it was derived from observations of the minimal
215 important difference (MID) in HRQoL deterioration that is perceived by patients. This is a rather
216 conservative assumption, as MIDs in the populations under investigation varied depending on disease
217 severity and age (44, 45).

218 **All-cause hospital admissions**

219 We defined hospital admission as the moment when a patient receives inpatient services in a hospital
220 for any reason between baseline and six-month follow-up. As some trials provided no precise
221 information on reasons for admission and length of stay, hospitalizations included emergency
222 admissions and planned admissions from waiting lists, both day and night. Trials either used patient-
223 reported data from questionnaires (Opti-Med, PIL, ISCOPE and RIME) or physician-reported case report
224 forms (PRIMUM) to collect information on hospital admissions. All trials except Opti-Med collected
225 baseline information on previous hospitalizations, with PRIMUM, ISCOPE and RIME providing
226 information on the number of admissions in the twelve-month period before baseline. With respect
227 to follow-up information, admissions between baseline and six-month follow-up were recorded in
228 PRIMUM, Opti-Med and RIME, and between baseline and 12-month follow-up in PIL and ISCOPE. The
229 number of admissions at baseline was considered to be a continuous variable, while the number of
230 follow-up admissions was operationalized as a binary outcome, as it resulted in fewer missing values.

231 **Sociodemographic and lifestyle-related variables**

232 All trials collected sociodemographic and lifestyle-related variables at baseline using self-administered
233 questionnaires (PRIMUM, Opti-Med, PIL and ISCOPE), or patient interviews (RIME). Trials recorded the
234 age of the patient when recruited, and gender. We categorized living situation as “living at home” or
235 “institutionalized living”. We categorized educational level according to the aggregated levels of the
236 International Standard Classification of Education (ISCED) issued by the United Nations Educational,
237 Scientific and Cultural Organization (UNESCO) (46). The UNESCO recognizes seven levels of education

238 in ISCED, from Level 0 (pre-primary education) to Level 6 (second stage of tertiary education), which
239 can be collapsed into three aggregated levels: low, medium and high. Three trials (PRIMUM, PIL, and
240 RIME) gathered information on the smoking status of their patients. We classified smoking status as
241 current smoker, ex-smoker, or non-smoker.

242 **Morbidity-related candidate prognostic variables**

243 Information on diagnoses was collected at baseline in all trials except PIL, which reported it at the start
244 of the intervention. Three studies collected morbidity data using international classifications: Two
245 studies provided GP-reported data (PRIMUM using ICD-10 codes (47) and PIL using ICPC-1 codes (48)).
246 ISCOPE took patients' chronic diagnoses from electronic medical records (EMR), defined them
247 according to O'Halloran et al. (40), and coded them based on the second version of the International
248 Classification of Primary Care (ICPC-2) (49). The remaining two trials used a limited list of conditions,
249 which were either taken from EMR (Opti-Med, 26 conditions) or during patient interviews (RIME, 28
250 conditions). In PROPERmed, we clinically harmonized the data on medication and used the ICPC-2 to
251 describe chronic conditions: ICPC-1 (PIL) and ICD-10 (PRIMUM) codes were thus converted into the
252 corresponding ICPC-2 codes, and the respective codes were assigned to the list of non-coded chronic
253 conditions described in Opti-Med and RIME.

254 Multimorbidity can be expressed in terms of a disease count, based on multimorbidity scores or
255 multidimensional assessment methods. Before using these instruments in PROPERmed, they had to be
256 modified according to the common chronic conditions that were assessed in all the trials. See Table 3
257 for more detailed information on proxies for multimorbidity instruments.

258 [About here: Table 3 on Proxies for multimorbidity instruments]

259 *Modified Diederichs disease count*

260 The Diederichs list (50) contains 17 chronic conditions, which, according to a systematic review, are
261 considered in 39 different multimorbidity indexes. Our modified Diederichs list contains 12 (71 %) of
262 the 17 conditions in the original instrument.

263 *Modified Physical Component Summary score (PCS) and Mental Component Summary score (MCS)*
264 The recently published Health-related Quality of life Comorbidity Index (HRQoL-CI) consists of two
265 independent subscales (51-53). The comorbidity subscale for physical HRQoL (PCS) considers 20 groups
266 of chronic conditions, while the subscale for mental HRQoL (MCS) consists of 15 groups of conditions.
267 We derived modified PCS and MCS scores (51, 52) depending on the chronic conditions considered in
268 all five cRCTs. The modified PCS score included 12, and the MCS 6 groups of chronic conditions (60 %
269 and 40 % respectively of the total count in the original instrument).

270 *Modified Charlson Comorbidity Index*

271 The Charlson Comorbidity Index (CCI) (54) is the most commonly used scale to measure multimorbidity
272 in hospital admission predicting models (31). The CCI assesses the comorbidity level by considering
273 both the number and severity of 19 pre-defined comorbid conditions. It provides a weighted score of
274 a patient's morbidities, which can be used to predict such short- and long-term outcomes as functional
275 status, length of stay in hospital, and mortality rates. In general, 0-1 points indicates the absence of
276 any comorbidity, 2 points indicates mild comorbidity and a score of ≥ 3 indicates severe comorbidity.
277 We considered the sum-scores of the CCI provided in two of the trials (PRIMUM and RIME). The CCI
278 modified for use in the PROPERmed predicting models did not include dementia, as only one trial
279 (ISCOPE) included patients with this diagnosis.

280 **Medication-related candidate prognostic variables**

281 All trials obtained medication data as patient-reported data at baseline except PIL and ISCOPE, in which
282 the general practitioner reported the medications at baseline (ISCOPE), or at the start of the
283 intervention (PIL).

284 *Potentially inappropriate medications (PIM) and potential prescribing omissions (PPOs)*

285 Medication inappropriateness and omissions were assessed using several instruments: the EU-PIM list
286 (55), STOPP-START criteria (56), the Dreischulte high-risk prescribing list (57), the Anticholinergic Drug
287 Scale (ADS) (58, 59), the Drug Burden Index (DBI) (60-62) and the Anticholinergic Drug Burden

288 according to Duran et al (63). From those lists, we measured: 1) any PIM or PPO (yes/no); 2) number
289 of PIMs or PPOs prescribed per patient; 3) individual scores measured by the instruments, when
290 applicable. Instruments included in PROPERmed were modified, as missing information in (some of)
291 the trials, such as daily doses, duration of use, and information on severity of disease, meant they did
292 not represent the full range of PIMs and PPOs considered in the original instruments.

293 **Functional status and well-being**

294 *Functional status*

295 All trials used patient questionnaires to obtain patient-reported data on functional status at baseline.
296 Two trials (ISCOPE and PIL) measured functional status using the Katz-15 (combination of KATZ-6 and
297 Lawton IADL) questionnaire (64), two trials (PRIMUM and RIME) used the 13-item vulnerable elderly
298 survey (VES-13) (65) and one trial (Opti-Med) measured functional status using the Geriatric Giants
299 VAS (GGV) scale (0-10) (66) for mobility problems, which was created *ad hoc*. We standardized the
300 original instruments' scales statistically, thus enabling the information to be included in analysis
301 models, irrespective of differences in the underlying constructs of the instruments.

302 *Pain*

303 Using different approaches, pain was assessed at baseline in all trials. One trial (PRIMUM) measured
304 pain using the von Korff index (67), one trial (Opti-Med) used a VAS scale that had been elaborated *ad*
305 *hoc* (from 0 to 10), another (ISCOPE) used a single question (pain yes or no), two trials (Opti-Med and
306 RIME) used the pain-related question from SF-12 (68, 69) and one (PIL) used the pain-related question
307 from SF-36 (70). We constructed categorical variables for pain by clinically harmonizing the different
308 instruments used across trials as follows: a) Pain intensity was classified as “no pain”, “low intensity
309 pain” and “high intensity pain”, based on data from PRIMUM (67), Opti-Med and PIL (68); b) Pain
310 disability was categorized as “no disability from pain”, “disability of low intensity” and “disability of
311 high intensity” based on data from PRIMUM (67), Opti-Med, RIME (68) and PIL (70); c) Binary
312 classification of pain (i.e. pain vs. no pain) was based on data from PRIMUM (67), Opti-Med, PIL,

313 ISCOPE and RIME (68); and d) Pain according to SF surveys was based on data from Opti-Med, RIME
314 (68) and PIL (70) and did not require harmonization.

315 *Depressive symptoms*

316 All trials used several questionnaires at baseline to assess depressive symptoms. Three trials used the
317 Geriatric Depression Scale (GDS) to assess symptoms of depression (PRIMUM and ISCOPE used the
318 GDS with 15 items (71), and RIME used it with 5 items (72)). Two trials (Opti-Med and RIME) used the
319 depressive symptoms-related question on SF-12 (68), and PIL used the depressive symptoms-related
320 question on SF-36 (70). In addition to standardized forms of the various instruments, we also derived
321 categorical variables by considering the cut-offs of the original instruments as follows: a) A binary
322 classification of depressive symptoms (i.e. depressive symptoms vs. no depressive symptoms) was
323 carried out using data from PRIMUM and ISCOPE (GDS-15 cut-off of ≥ 5 for depressive symptoms) (71,
324 73) and RIME (GDS-5 cut-off of ≥ 2 for depressive symptoms) (72); b) The binary classification of
325 depressive symptoms was also performed for Opti-Med and RIME (SF-12 cut-off of < 42 for depressive
326 symptoms) (74) and for PIL (SF-36 cut-off of < 50.2 for depressive symptoms) (75).

327

328 **RISK OF BIAS ASSESSMENT**

329 A risk of bias assessment (RoB) was conducted for each included trial in order to assess possible
330 differences in the definitions and measuring methods of outcomes and variables across all five cRCTs.
331 The RoB was determined using PROBAST (Prediction model Risk of Bias Assessment Tool), which is a
332 qualitative assessment tool developed for evaluating both RoB and the applicability of prognostic
333 prediction models (76). It includes the following domains: 1. participant selection, 2. predictors, 3.
334 outcomes, 4. sample size and participant flow, and 5. analysis. Since not all domains were relevant to
335 the included cRCTs, the robustness of evidence was assessed for the relevant ones by one researcher
336 (DKDG) and checked by another (AIGG). Any inconsistency was resolved by discussion.

337 Based on PROBAST, the overall RoB assessment of the included trials was “unclear”, mainly due to
338 uncertainty about the definition and assessment method of possible predictor variables reported in
339 the studies. However, differences in definitions and measurement methods were also considered and
340 accounted for during the data harmonization process. Since the PROPERmed dataset was designed on
341 the basis of the available data from the trials, the applicability of the data from the cRCTs in the
342 prognostic models was automatically rated as of “low concern”.

343 See Table 4 for more detailed information about the RoB assessment.

344 [About here: Table 4 on Risk of bias assessment with the PROBAST tool].

345

346 **CHARACTERISTICS OF THE PROPERMED STUDY POPULATION**

347 In total, 6,139 patients were potentially eligible for inclusion in the PROPERmed IPD-MA dataset. Two
348 hundred and eighteen patients did not meet the inclusion criteria and 1,360 patients did not provide
349 relevant data at baseline. After excluding these patients from the IPD-MA, we finally included 4,561
350 patients from 307 general practices. See Figure 1 for more detailed information about the selection
351 and maintenance of PROPERmed participants.

352 [About here: Figure 1 on Selection and maintenance of PROPERmed participants]

353 The median age of the PROPERmed population was 78 years and ranged from 60 to 102 years. Women
354 represented 58% of patients in the IPD-MA. Most participants (95%) lived at home, had a low or
355 medium educational level (89%) and had smoked (49%), or were current smokers (43%).

356 The median number of chronic diseases according to the modified Diederichs list (50) was three and
357 ranged from zero to ten chronic diseases per patient. The most prevalent chronic conditions were
358 hypertension (67%), diabetes (36%), coronary heart disease (34%), osteoarthritis (34%), and vision
359 problems (32%).

360 The median number of drugs per patient was seven and ranged from one to 28. According to the EU-
361 PIM list (55), 2,624 (58%) of 4,561 patients were taking at least one inappropriate medication, with a

362 median of one per patient and ranging from zero to seven. The number of patients with at least one
363 PIM according to the STOPP criteria (56), and one PPO according to START criteria (56) was 3,899 (86%)
364 and 2,634 (58%) patients respectively. Regarding anticholinergic medication, 1,311 (29%), 1,646 (36%)
365 and 2,269 (50%) patients were respectively taking at least one drug included on the ADB (63), DBI (60-
366 62) and ADS score (58, 59) lists. The most prevalent ATC codes (3-digit level) representing chronic
367 prescriptions were B01 – Antithrombotic agents (64%), C09 - Agents acting on the renin-angiotensin
368 system (63%), C10 - Lipid modifying agents (53%), C07 – Beta blocking agents (53%) and C03 – Diuretics
369 (41%).

370 Of the included patients, 68% experienced some pain, and 15% / 21% had symptoms suggesting
371 depression according to GDS (71) / SF-12 (68, 69) and SF-36 (70), respectively.

372 Table 5 provides a detailed description of patient characteristics based on variables related to
373 candidate prognostic variables and outcomes.

374 The mean EQ-5D-3L index at baseline and six-month follow-up was 0.73 (0.25) in the PROPERmed
375 population. The number of patients that had been admitted to hospital at least once during the six-
376 month follow-up period was 404 of the 3,296 patients (21%) that participated in PRIMUM, ISCOPE
377 and RIME.

378 [About here: Table 5 on Descriptives of outcomes and candidate prognostic variables].

379

380 **DISCUSSION**

381 PROPERmed is the first study to combine the data of older patients with multiple conditions and
382 chronic medication prescriptions from five cRCTs. Increasing case-mix variability is generally
383 considered to raise the performance of prognostic models. However, systematic between-study
384 heterogeneity resulting from different time frames and health care policies may be a problem. Thus,
385 it is certainly a major advantage that the PROPERmed dataset includes trials completed after the year
386 2009 in The Netherlands and Germany. The reduction to two countries of origin within a reasonable

387 time frame reduces variation between drug markets and ensures that the prescribing preferences and
388 patterns of GPs vary little and are at low risk of being biased by, for example, differences in the
389 availability of medicines (77-80). On the other hand, the generalizability of the results from the
390 PROPERmed prognostic models may be affected by similarities in the inclusion and exclusion criteria
391 across the cRCTs. External validation in another population from another setting or in another
392 timeframe is therefore important.

393 In IPD-based research, data harmonization is absolutely essential to subsequent analyses. This
394 required enormous effort but resulted in comprehensive data, which is essential if data is to be used
395 in prognostic models. Furthermore, data harmonization minimizes the potential RoB of individual
396 studies. In order to generate comparable morbidity counts or indexes, PIM or PPO lists, and scores
397 across all the trials, we had to modify some of the validated instruments. In this particular example,
398 limited information on morbidity (Opti-Med and RIME) and medication (doses, duration of use, and
399 severity of diseases) were significant obstacles and had to be overcome. We met the challenge of the
400 use of different scales to measure functional status and depressive symptoms by standardizing the
401 original instruments. The use of standardized measures means it will be slightly more difficult to
402 interpret the results. Furthermore, the measures will have to be back translated to the original
403 instruments for straightforward clinical interpretation.

404 In projecting the future success of any analysis, a lack of information on specific reasons for
405 hospitalization may well be significant. Unfortunately, the available information prevents us from
406 predicting unplanned hospitalizations, although this is highly relevant and would lead to better
407 performing models. Instead we will only be able to predict emergency admissions and planned
408 admissions simultaneously, and will not be able to distinguish between day- and night-time
409 admissions. This may be seen as a limitation to the further use of our model.

410 Other research collaborations have been confronted with the challenges of data harmonization. The
411 European Project on Osteoarthritis (EPOSA) (81), which focuses on personal and societal burden and

412 the determinants of osteoarthritis, merged the data from cohort studies in five European countries.
413 They described the entire harmonization processes in a harmonization guideline and highlighted the
414 difficulties that arose from differences in wording and categories, and in the classifications and absence
415 of data. They also stressed how important it is to make the original data accessible to ensure the ex-
416 post harmonized data is easy to interpret (81). As in PROPERmed, the design of the International
417 Mission for Prognosis and Clinical Trial (IMPACT) database (82) prioritized the extraction of a key set
418 of variables that existed in the included trials. The harmonization process was also described as labor
419 intensive and requiring considerable clinical insight. Establishing a consistent set of categories with
420 which to code each variable, while adhering to the guiding principle of never discarding information,
421 was a major issue in the IMPACT harmonization process, as in our own. Data harmonization requires
422 solving all problems on an ongoing basis and sharing updates to the database with trialists and other
423 project collaborators.

424 Developing and validating the PROPERmed models using datasets that were originally designed and
425 conducted for many different purposes was challenging, as we were neither able to control what kind
426 of data was collected, nor how it was accomplished. However, this concern was more than offset by
427 the superior quality of the collected data, as well as the low number of missing values that is typical of
428 controlled trials.

429 In future trials on multimorbidity and polypharmacy, data collection should be standardized to a
430 greater degree, e.g., by including the agreed core outcome set proposed by Smith et al. (83). Moreover,
431 potential studies may benefit from such advance planning, as it would ensure data analyses are of high
432 quality.

433

434 **CONCLUSIONS**

435 In summary, the present manuscript presents the PROPERmed collaboration. It describes the
436 development of a database for the first IPD-MA-based prognostic model for older patients with chronic

437 conditions and chronic prescriptions in general practice that aims to identify patients at risk of
438 undesirable health-outcomes. IPD-MA are becoming increasingly popular, as they have large sample
439 sizes and employ high-quality data. However, they also require data harmonization, which is a great
440 deal of work and may result in the loss of information.

441

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458 **Author contributors**

459 JWB, MvdA, UT, WEH, HJT, PJME, GK, JJM, DKdG, RP, PG and CM contributed to the design of the
460 PROPERmed study. CM is the guarantor. AIG and TN wrote the first draft of the manuscript. JWB,
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465 study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The
466 corresponding author attests that all listed authors meet the authorship criteria and that no others
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468 **Competing interests**

469 All authors declare no support from any additional organizations for the submitted work, no financial
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471 three years, and no other relationships or activities that could appear to have influenced the submitted
472 work.

473 **Ethical approval**

474 The Ethics Commission of the Medical Faculty of the Johann Wolfgang Goethe University, Frankfurt /
475 Main confirmed that no extra vote was necessary for the anonymous use of data in the PROPERmed
476 IPD-MA (13/07/2017). All included trials were separately approved by their ethics commissions as
477 follows:

478 ISCOPE: The Medical Ethical Committee of Leiden University Medical Center approved the study (date:
479 30.06.2009, reference: P09.096).

480 Opti-Med: The Medical Ethics Committee of the VU University Medical Centre Amsterdam approved
481 the study (date: 12.01.2012, reference: 2011/408).

482 PIL: The Medical Ethics Review Board Atrium-Orbis-Zuyd approved the study (date: 15.12.2009,
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484 PRIMUM: The Ethics Commission of the Medical Faculty of the Johann Wolfgang Goethe University,
485 Frankfurt / Main approved the study (date: 20/05/2010, reference: E 46/10).

486 RIME: The Ethics Commission of the University Witten / Herdecke approved the study (date:
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Figure 1. Selection and maintenance of PROPERmed participants

HA = Hospital Admissions; IPD = Individual Participant Data; m = months; NA = Not Available

Table 1. Main characteristics of the included trials

	PRIMUM	Opti-Med	PIL	ISCOPE	RIME
Title	PRioritizing MUltimedication in Multimorbidity	Optimized clinical Medication reviews in older people	Polypharmacy intervention in Limburg	Integrated C Care for Older People	Reduction of potentially inadequate Medication in the Elderly
Study region	Hesse, Germany	Amsterdam, The Netherlands	Southern Limburg, The Netherlands	Leiden, The Netherlands	Witten and Hanover, Germany
Start/End	2010-2012	2013-2015	2010-2014	2009-2011	2012-2014
Design	2-arm parallel cRCT	2-arm parallel cRCT	2-arm parallel cRCT, stepped wedge	2-arm parallel cRCT	2-arm parallel cRCT
Setting	General practices (n=72)	General practices (n=22)	General practices (n=24)	General practices (n=51)	General practices (n=139)
Study population	N=502 ≥60 years ≥5 chronic prescriptions ≥3 chronic conditions	N=518 ≥65 years ≥1 chronic prescription Geriatric giant	N=727 ≥60 years ≥5 chronic prescription	N=1,617 ≥75 years complex problems on ≥3 domains	N=1,197 ≥6 chronic prescriptions
Exclusion criteria	Life expectancy of ≤12 months Abuse of alcohol or illegal drugs Inability to fill in questionnaires and to participate in telephone interviews Dementia	Life expectancy of ≤6 months Severe psychiatric illness or other reasons why GP regards patient as unable to participate Recent medication review (last 6 months) Dementia	Life expectancy of ≤12 months Abuse of alcohol or illegal drugs Dementia	Life expectancy of ≤3 months or terminal illness Dementia	Life expectancy of ≤6 months as assessed by the treating GP Dementia
Intervention	Structured medication review including several intervention components (complex intervention)	Structured medication review including several intervention components (complex intervention)	Structured medication review including several intervention components (complex intervention)	Integrated care plan using a functional geriatric approach	Structured medication review including several intervention components (complex intervention)
Data collection (study visits)	0, 6, 9 months	0, 3, 6 months	0, 3, 6, 12 months	0, 6, 12 months	0, 6, 12 months
Data collection (method)	CRF, patient questionnaire, telephone interview	CRF, patient questionnaire	CRF, patient questionnaire, home visit	Patient questionnaire, home visit	CRF, patient questionnaire, telephone interview

cRCT = cluster-randomized controlled trial; CRF = Case Report Form; GP = General Practitioner.

Table 2. Data harmonization

Type of variable	Variable	Harmonization	PRIMUM	Opti-Med	PIL	ISCOPE	RIME
<i>Sociodemographic and lifestyle-related</i>	Age	No need of harmonization	-	-	-	-	-
	Sex	Recoding of labels	-	-	-	-	+
	Living situation	Recoding of categories and labels	+	+	+	+	+
	Educational level	Recoding of categories and labels	-	-	+	+	+
	Smoking status	Recoding of categories and labels	+	x	+	x	+
<i>Morbidity-related</i>	Single conditions	Clinical harmonization	+	+	+	+	+
	Disease count ^a	Creation of new variable	+	+	+	+	+
	Multimorbidity index ^b	No need of harmonization	-	x	x	x	-
<i>Medication-related</i>	Medication inappropriateness and omissions ^c	Creation of new variable	+	+	+	+	+
<i>Functional status- and well-being-related</i>	Depressive symptoms	Dichotomization based on cut-offs	+	+	+	+	+
	Functional status	Standardized mean differences	+	+	+	+	+
	Quality of life (EQ-5D-3L index)	No need of harmonization	-	-	-	-	-
	Health-related quality of life comorbidity index	Creation of new variable	+	+	+	+	+
	Hospital admissions	Recoding of categories and labels	+	+	x	x	+

Legend: + data was harmonized; - no need to harmonized; x systematic missing

^a modified Diederichs list; ^b modified CCI; ^c modified EU-PIM list, STOPP-START criteria, Dreischulte high risk prescribing list, ADS, DBI, Anticholinergic Drug Burden

Table 3. Proxies for multimorbidity instruments

	Diederichs (50)	PCS (51-53)	MCS (51-53)	Charlson (54)
Cancer	X			X
Chronic obstructive pulmonary disease / asthma	X	X	X	X
Coronary heart disease	X ^a	X	X	X
Depression	X		X	
Diabetes	X	X	X	X
Degenerative neurological disorders (Parkinson)		X	X	
Hearing problems	X			
Heart failure	X		X	X
HIV infection /AIDS			X	X
Hypertension	X	X	X	
Osteoarthritis	X ^b	X	X	
Osteoporosis	X			
Rheumatoid/seropositive arthritis		X	X	
Cerebrovascular disease	X	X	X	X
Vision problems	X	X		
Total number of diagnoses included in the original list	17	20	15	17
Total number of diagnoses included in PROPERmed (% from the total number in the original list)	12 (71 %)	12 (60 %)	6 (40 %)	7 (41 %)

^a Includes heart disease, myocardial infarction and angina pectoris from the original list.

^b Includes rheumatoid / seropositive arthritis.

Table 4. Risk of bias assessment using the PROBAST tool*

Domain Overall judgement	RoB Applicability	(a) Assessment for each trial					(b) Combined assessment of all trials
		PRIMUM	Opti-Med	PIL	ISCOPE	RIME	
Domain 1: Participant selection	RoB	Low	Unclear ^a	Low	Low	Low	Low ^e
	Applicability	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Domain 2: Predictors	RoB	Low	Low	Low	Low	Low	Unclear ^b
	Applicability	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Domain 3: Outcomes	RoB	Low	Low	Low	Low	Low	Low
	Applicability	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Domain 4: Sample size and participant flow	RoB	Not applicable to single studies, only overall judgement possible					Not available ^c
Domain 5: Analysis	RoB	Not applicable to single studies, only overall judgement possible					Not available ^c
Overall judgment ^d	RoB	Low	Unclear ^a	Low	Low	Low	Unclear
	Applicability	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern

RoB = Risk of Bias

^a Unclear because analyzed participants had a different state of health at baseline.

^b Unclear due to uncertainty about the definition and assessment method of potential predictor variables across included studies.

^c Data not available at the time the RoB assessment was performed.

* Adapted from PROBAST tool¹⁷ (Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann Intern Med* [Internet]. 2019;170(1):51)

Table 5. Descriptives of outcomes and candidate prognostic variables

Outcomes (six months follow-up)

	Variables	Categories	PRIMUM	Opti-Med	PIL	ISCOPE	RIME	PROPERmed
Outcomes	Quality of life: EQ-5D-3L, Index value – Mean (SD)		0.78 (0.24)	0.74 (0.21)	0.76 (0.22) ^a	0.69 (0.26) ^a	0.73 (0.25)	0.73 (0.25)
	Hospitalization (at least one) – Number (%)		79 (16.5%)	66 (16.3%)	NA ^b	NA ^b	259 (23.9%)	404 (20.5%)

Candidate prognostic variables – Sociodemographic and lifestyle-related (baseline)

	Variables	Categories	PRIMUM	Opti-Med	PIL	ISCOPE	RIME	PROPERmed
Sociodemographic and lifestyle-related	Age – Mean (SD)		72.18 (6.86)	77.24 (7.86)	73.18 (7.53)	81.83 (5.00)	76.90 (4.93)	77.56 (7.04)
	Sex (female) - Number (%)		262 (52.2%)	334 (65.0%)	356 (47.4%)	1,110 (68.9%)	599 (50.0%)	2,661 (58.2%)
	Living situation - Number (%)	Living at home	496 (98.8%)	486 (98.6%)	698 (95.0%)	1,471 (92.2%)	1,154 (96.4%)	4,305 (94.9%)
		Institutionalized living	1 (0.2%)	27 (1.4%)	37 (5.0%)	125 (7.8%)	43 (3.6%)	233 (5.1)
	Educational level - Number (%)	Low	311 (62.8%)	114 (23.6%)	526 (71.2%)	861 (53.3%)	219 (18.3%)	2,031 (44.9%)
		Medium	145 (29.3%)	225 (45.7%)	126 (17.1%)	616 (28.7%)	882 (73.7%)	1,994 (44.0%)
		High	39 (7.9%)	152 (30.7%)	87 (11.8%)	129 (8.0%)	96 (8.0%)	503 (11.1%)
	Smoking status - Number (%)	Smoker	248 (50.9%)	NA	146 (29.4%)	NA	543 (45.4%)	937 (43.0%)
		Ex-smoker	193 (39.6%)		284 (51.1%)		583 (48.7%)	1,060 (48.6%)
Non-smoker		46 (9.4%)		67 (13.5%)		71 (5.9%)	184 (8.4%)	

Candidate prognostic variables – Morbidity-related (baseline)

	Variables	Categories	PRIMUM	Opti-Med	PIL	ISCOPE	RIME	PROPERmed
Morbidity-related	Single conditions - Number (%)	Hypertension	422 (84.1%)	295 (57.4%)	441 (62.9%)	793 (49.7%)	1,054 (88.1%)	3,005 (66.6%)
		Diabetes	267 (53.2%)	115 (22.4%)	291 (41.5%)	398 (24.9%)	547 (45.7%)	1,618 (35.9%)
		Coronary heart disease	215 (42.8%)	127 (24.7%)	293 (41.8%)	388 (24.3%)	515 (43.0%)	1,538 (34.1%)
		Osteoarthritis	268 (53.4%)	160 (31.1%)	186 (26.5%)	366 (22.9%)	542 (45.3%)	1,522 (33.7%)
		Vision problems	72 (14.3%)	190 (37.0%)	215 (30.7%)	407 (25.5%)	573 (47.9%)	1,457 (32.3%)

	Chronic obstructive pulmonary disease	146 (29.1%)	109 (21.2%)	147 (21.0%)	285 (17.8%)	276 (23.1%)	963 (21.3%)
	Hearing problems	13 (2.6%)	47 (9.1%)	105 (15.0%)	249 (15.6%)	471 (39.3%)	885 (19.6%)
	Cancer	47 (9.4%)	137 (26.5%)	91 (13.0%)	311 (19.5%)	236 (19.7%)	822 (18.2%)
	Heart failure	86 (17.1%)	53 (10.3%)	61 (8.7%)	207 (13.0%)	403 (33.7%)	810 (18.0%)
	Cerebrovascular disease	98 (19.5%)	79 (15.4%)	111 (15.8%)	278 (17.4%)	165 (13.8%)	731 (16.2%)
	Osteoporosis	53 (10.6%)	98 (19.1%)	108 (15.4%)	167 (10.5%)	259 (21.6%)	685 (15.2%)
	Depression	85 (16.9%)	46 (8.9%)	53 (7.6%)	138 (8.6%)	143 (11.9%)	465 (10.3%)
	Rheumatoid arthritis	25 (5.0%)	15 (2.9%)	40 (5.7%)	64 (4.0%)	224 (18.7%)	368 (8.2%)
	Parkinsonism	7 (1.4%)	22 (4.3%)	6 (0.9%)	41 (2.6%)	26 (2.2%)	102 (2.3%)
	HIV/AIDS	0	1 (0.2%)	0	0	0	1 (0.02%)
	Disease count according to modified Diederichs – Median (IQR)	4 (1)	3 (2)	3 (2)	2 (2)	4 (2)	3 (2)
	Modified Charlson comorbidity index – Median (IQR)	3 (2)	NA	NA	NA	3 (3)	3 (3)

Candidate prognostic variables – Medication-related (baseline)

	Variables	Categories	PRIMUM	Opti-Med	PIL	ISCOPE	RIME	PROPERmed
Medication-related	No. of drugs [†] - Median (IQR)		9 (3)	5 (4)	7 (3)	5 (5)	9 (4)	7 (5)
	No. of Potentially Inappropriate Medications (PIM) according to the modified EU-PIM list - Median (IQR)		1 (1)	1 (1)	1 (2)	1 (1)	1 (2)	1 (1)
	STOPP criteria (modified) – Median (IQR)		2 (1)	1 (1)	1 (1)	1 (1)	2 (1)	1 (1)
	START criteria (modified) – Median (IQR)		1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)
	Dreischulte criteria (modified) – Median (IQR)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Drug Burden Index (DBI, modified) - Median (IQR)		0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)
	Anticholinergic Drug Burden (ADB) according to Duran - Median (IQR)		0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)
	Anticholinergic Drug Scale (ADS) according to Carnahan - Median (IQR)		0 (1)	0 (1)	1 (2)	1 (1)	1 (1)	1 (1)

Candidate prognostic variables – Functional status and well-being-related, plus hospital admissions (baseline)

	Variables	Categories	PRIMUM	Opti-Med	PIL	ISCOPE	RIME	PROPERmed
Functional status and well-being-related	Functional status and frailty – Mean (SD)		2.83 (2.81) ^c	5.04 (2.83) ^d	1.71 (2.44) ^e	3.13 (3.01) ^e	2.86 (2.57) ^c	
	Depressive symptoms (binary) – Number (%)	GDS 15/5	73 (14.8%) ^k	NA	NA	233 (15.2%) ^k	183 (15.3%) ^k	489 (15.2%)
		SF 12/36	NA	148 (30.9%) ^j	33 (4.9%) ^j	NA	298 (28.0%) ^j	479 (21.6%)
	Depression (Score) – Mean (SD)	GDS 15/5	2.39 (2.29) ^k	NA	NA	2.16 (2.50) ^k	0.73 (0.94) ^k	1.67 (2.17)
		SF 12/36	NA	63.87 (22.83) ^j	76.85 (17.85) ^j	NA	54.03 (9.50) ^j	63.21 (18.73)
	Pain (binary) – Number (%)		439 (87.5%) ^f	372 (75.0%) ^g	537 (77.8%) ^h	801 (50.3%) ⁱ	888 (74.9%) ^h	3,037 (68.0%)
	Pain Intensity – Mean (SD)		1.23 (0.65) ^f	1.15 (0.79) ^g	1.18 (0.77) ^h	NA	NA	1.19 (0.74)
	Pain Disability – Mean (SD)		0.60 (0.79) ^f	0.94 (0.61) ^j	0.78 (0.65) ^j	NA	1.07 (0.75) ^j	0.89 (0.73)
	Pain SF – Mean (SD)		NA	2.39 (1.05) ^j	2.18 (1.10) ^j	NA	2.74 (1.39) ^j	2.5 (1.27)
	Modified health-related quality of life comorbidity index, mental – Median (IQR)		2 (2)	1 (2)	1 (2)	1 (2)	2 (2)	1 (3)
	Modified health-related quality of life comorbidity index, physical – Median (IQR)		8 (4)	4 (4)	5 (4)	4 (4)	7 (5)	5 (5)
Quality of life: EQ-5D-3L, Index value (baseline) – Mean (SD)		0.79 (0.23)	0.74 (0.21)	0.77 (0.21) ^a	0.68 (0.27) ^a	0.73 (0.26)	0.73 (0.25)	
Hospital admissions	Hospitalization (at least once in past 12 months) – Number (%)		81 (16.1%)	NA	574 (78.1%)	412 (25.8%)	435 (36.4%)	1,502 (37.3%)

Legend: †No. of drugs refer to ATC codes (i.e., single active ingredients or fixed combinations as listed in ATC version 2012).

NA = not available.

^a EQ-5D was used in an experimental version in PIL and ISCOPE; ^b at 12 months from baseline; ^c VES-13; ^d Scale for Mobility problems; ^e Katz-15; ^f von Korff (cut-off ≥ 1 for categorical variable); ^g VAS (cut-off ≥ 1 for categorical variable); ^h PIL SF-36 and RIME SF-12; ⁱ single question; ^j Opti-Med and RIME MCS score SF-12 (cut-off < 50.2 for categorical variable), and PIL MCS score SF-36 (cut-off < 42 for categorical variable); ^k PRIMUM and ISCOPE GDS 15 (cut-off ≥ 5 for categorical variable), RIME GDS 5 (cut-off ≥ 2 for categorical variable).

Table 6. Knowledge gaps addressed by the PROPERmed collaboration

A harmonized individual participant data database of older patients with multimorbidity and polypharmacy in general practice
A prognostic model for deterioration in health-related quality of life in older patients with multimorbidity and polypharmacy in general practice
A prognostic model for hospital admissions in older patients with multimorbidity and polypharmacy in general practice