Online Appendix

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Table 1a: Per-protocol analysis, results for primary and key secondary outcomes

	Control group		Decision support tool group		Adjusted comparison†	p-value†
	n	Estimate*	n	Estimate*	Co-eff (95% CI)	
Primary outcome						
Death or first NEH	1712	873 (51.0%)	1682	774 (46.0%)	OR: 0.82 (0.68, 0.98)	0.026
- Sensitivity, time to death or first NEH	1712	0.51 (0.01) ‡	1682	0.46 (0.01) ‡	HR: 0.88 (0.78, 1.00)	0.049
Key secondary outcome						
Last recorded number of drugs	1712	10.59 (2.96)	1682	10.11 (3.04)	IRR: 0.95 (0.93, 0.97)	<0.001
- Sensitivity, change in drugs from baseline	1712	0.09 (2.10)	1682	-0.45 (2.20)	MD: -0.50 (-0.71, -0.29)	<0.001

*Mean (standard deviation) or number (%) unless otherwise indicated
†P-value based on the primary analysis
‡Estimated proportion (SE) reaching endpoint by 24 months, from survivor function.
NEH=Non-elective hospitalization. OR=Odds-ratio. HR=Hazard-ratio. IRR=Incidence-rate ratio. MD=Mean difference.

Table 2a: Number of recommendations elicited by the tool

Recommendation type	**Control group (n=1519)**		**Decision support tool group (n=1509)**	
Number of	Mean/patient	SD	Mean/patient	SD
Contraindicated drugs at T0	0.47	0.90	0.47	0.90
Contraindicated drugs at T3	0.30	0.76	0.29	0.75
Reduction of contraindicated drugs T0-T3	0.17	0.75	0.18	0.77
Indications not provided at T0	2.92	2.12	2.93	2.22
Indications not provided at T3	2.79	2.20	2.20	2.27
Reduction in indications not provided T0-T3	0.13	1.58	0.73	1.92
Interactions T0	0.10	0.36	0.13	0.41
Interactions T3	0.03	0.20	0.04	0.24
Reduction of interactions T0-T3	0.07	0.35	0.09	0.37
Recommendations based on best available evidence T0	3.65	1.90	3.53	1.84
Recommendations based on best available evidence T3	1.87	2.34	1.44	2.00
Reduction of recommendations based on best available evidence T0-T3	1.78	2.52	2.09	2.31
Renal-dosing-reminders T0	0.58	1.39	0.59	1.42
Renal-dosing-reminders T3	0.32	1.06	0.31	1.07
Reduction of renal-dosing-reminders T0-T3	0.26	1.42	0.28	1.39
Total reminders T0	7.77	3.75	7.71	3.70
Total reminders T3	5.35	3.69	4.33	4.20
Reduction of total reminders T0-T3	-2.43	3.98	-3.38	4.06

T0=baseline visit. T3=final visit.

Table 3a: Number of drugs and top 25 substances discontinued during the study

Control group (n=1519)				Decision support tool group (n=1509)			
Drug	**Number of prescriptions at T0**	**Number of prescriptions at T3**	**Reduction in number of prescriptions from T0 to T3**	**Drug**	**Number of prescriptions at T0**	**Number of prescriptions at T3**	**Reduction in number of prescriptions from T0 to T3**
Total	12761*	11283*	1478	Total	13514*	10747*	2767
Hydrochlorothiazide	538	420	118	Hydrochlorothiazide	493	331	162
Acetylsalicylic acid	671	554	117	Acetylsalicylic acid	618	468	150
Simvastatin	667	554	113	Simvastatin	608	464	144
Amlodipine	478	409	69	Ramipril	420	333	87
Ramipril	415	365	50	Allopurinol	328	248	80
Metformin	341	297	44	Metformin	320	245	75
Phenprocoumon	209	171	38	Pantoprazole	411	344	67
Allopurinol	299	262	37	Amlodipine	408	343	65
Metoprolol	259	236	23	Furosemide	303	244	59
Enalapril	97	74	23	Lansoprazole	178	135	43
Digitoxin	82	65	17	Phenprocoumon	214	181	33
Alendronate	99	82	17	Calcium carbonate	163	132	31
Lisinopril	110	94	16	Metoprolol	262	231	31
Pantoprazol	453	438	15	Doxazosin	92	62	30
Bendroflumethiazide	48	33	15	Amiodaron	60	31	29
Salmeterol	62	47	15	Omeprazol	253	225	28
Glimepirid	62	48	14	Warfarin	129	101	28
Clopidogrel	113	99	14	Diclofenac	67	39	28
Doxazosin	109	95	14	Clopidogrel	127	100	27
Candesartan	138	124	14	Atenolol	73	46	27
Paracetamol	216	202	14	Tramadol	80	53	27
Omeprazol	215	202	13	Codeine	90	65	25
Isosorbiddinitrat	58	46	12	Bisoprolol	470	446	24
Bisoprolol	454	442	12	Nebivolol	83	60	23
Diclofenac	48	37	11	Lisinopril	105	82	23

*only drugs with an equal or reduced number of prescriptions at T3

T0=baseline visit. T3=final visit.

Table 4a: Number of prescriptions and top 25 drugs eliciting reminders due to possible contraindications

	Control group at T0 (n=1519)		Decision support tool group at T0 (n=1509)		Control group at T3 (n=1519)		Decision support tool group at T3 (n=1509)	
drug	**Number of prescriptions**	**% of patients with drug**	**Number of prescriptions**	**% of patients with drug**	**Number of prescriptions**	**% of patients with drug**	**Number of prescriptions**	**% of patients with drug**
Total	718		716		455		437	
Acetylsalicylic acid	74	4.9	76	5.0	52	3.4	49	3.2
Hydrochlorothiazide	68	4.5	47	3.1	30	2.0	24	1.6
Amlodipine	58	3.8	43	2.8	30	2.0	33	2.2
Metformin	31	2.0	47	3.1	24	1.6	27	1.8
Lercanidipin	29	1.9	36	2.4	23	1.5	24	1.6
Glyceroltrinitrat	26	1.7	11	0.7	19	1.3	11	0.7
Diclofenac	20	1.3	21	1.4	9	0.6	10	0.7
Ibuprofen	20	1.3	23	1.5	9	0.6	9	0.6
Timolol	17	1.1	12	0.8	11	0.7	14	0.9
Bisoprolol	15	1.0	13	0.9	15	1.0	6	0.4
Etoricoxib	14	0.9	21	1.4	9	0.6	9	0.6
Oxycodon	14	0.9	14	0.9	13	0.9	7	0.5
Valsartan	11	0.7	9	0.6	5	0.3	10	0.7
Duloxetin	11	0.7	8	0.5	4	0.3	2	0.1
Furosemide	10	0.7	10	0.7	5	0.3	5	0.3
Diltiazem	10	0.7	6	0.4	5	0.3	1	0.1
Celecoxib	10	0.7	8	0.5	3	0.2	4	0.3
Metoprolol	9	0.6	10	0.7	8	0.5	9	0.6
Felodipin	8	0.5	3	0.2	6	0.4	1	0.1
Candesartan	8	0.5	11	0.7	4	0.3	6	0.4
Hydromorphon	8	0.5	2	0.1	5	0.3	1	0.1
Ursodesoxycholic acid	7	0.5	6	0.4	1	0.1	2	0.1
Nifedipin	7	0.5	14	0.9	6	0.4	5	0.3
Glimepirid	6	0.4	13	0.9	3	0.2	7	0.5
Sotalol	6	0.4	15	1.0	3	0.2	4	0.3

T0=baseline visit. T3=final visit.

Table 5a: Number of drugs and top 25 substances which elicited a reminder because no indication was provided

	Control group at T0 (n=1519)		Decision support tool group at T0 (n=1509)		Control group at T3 (n=1519)		Decision support tool group at T3 (n=1509)	
Drug	Number of drugs not indicated	% of patients with drug not indicated	Number of drugs not indicated	% of patients with drug not indicated	Number of drugs not indicated	% of patients with drug not indicated	Number of drugs not indicated	% of patients with drug not indicated
Total	4441		4427		4240		3321	
Pantoprazole	238	15.7	228	15.1	224	14.7	148	9.8
Metamizol	213	14.0	170	11.3	234	15.4	181	12.0
Cholecalciferol	168	11.1	188	12.5	190	12.5	156	10.3
Acetylsalicylic acid	167	11.0	147	9.7	142	9.3	102	6.8
Simvastatin	124	8.2	98	6.5	87	5.7	66	4.4
Omeprazole	115	7.6	138	9.1	111	7.3	96	6.4
Lansoprazole	112	7.4	117	7.8	98	6.5	77	5.1
Allopurinol	93	6.1	98	6.5	75	4.9	46	3.0
Macrogol	86	5.7	74	4.9	108	7.1	71	4.7
Paracetamol	84	5.5	58	3.8	63	4.1	37	2.5
Codeine	76	5.0	88	5.8	67	4.4	63	4.2
Levothyroxine	62	4.1	65	4.3	48	3.2	39	2.6
Naloxon	57	3.8	49	3.2	55	3.6	35	2.3
Gabapentin	53	3.5	46	3.0	53	3.5	38	2.5
Calcium carbonate	50	3.3	56	3.7	41	2.7	43	2.8
Pregabalin	49	3.2	28	1.9	46	3.0	28	1.9
Bendroflumethiazide	48	3.2	40	2.7	33	2.2	33	2.2
Oxycodon	47	3.1	43	2.8	53	3.5	44	2.9
Tamsulosin	44	2.9	45	3.0	36	2.4	32	2.1
Atorvastatin	43	2.8	32	2.1	51	3.4	25	1.7
Triazolam	42	2.8	45	3.0	41	2.7	32	2.1
Phenprocoumon	40	2.6	38	2.5	36	2.4	27	1.8
Isosorbidmononitrat	39	2.6	44	2.9	35	2.3	25	1.7
Cyanocobalamin	38	2.5	34	2.3	44	2.9	26	1.7
Zolpidem	36	2.4	47	3.1	37	2.4	41	2.7

T0=baseline visit. T3=final visit.

Table 6a: Most frequent category D interactions in the control group

T0 control group (n=15199			T3 control group (n=1519)		
Drug-1	**Drug-2**	**Number of inter-actions**	**Drug-1**	**Drug-2**	**Number of inter-actions**
ASA	Phenprocoumon	27	Acetylsalicylic acid	Phenprocoumon	9
ASA	Warfarin	16	Tramadol	Warfarin	4
Diclofenac	Phenprocoumon	8	Acetylsalicylic acid	Warfarin	2
Ibuprofen	Phenprocoumon	6	Levothyroxine	Polystyrolsulfonat	2
Tramadol	Warfarin	6	Diclofenac	Phenprocoumon	2
Acenocoumarol	ASA	3	Codeine	Duloxetine	2
Metoprolol	Verapamil	3	Potassium-chloride	Spironolacton	1
Amlodipine	Carbamazepine	3	Acenocoumarol	Acetylsalicylic acid	1
Acenocoumarol	Diclofenac	2	Apixaban	Phenprocoumon	1
Canrenone	Potassium chloride	2	Apixaban	Rivaroxaban	1
Diltiazem	Domperidon	2	Digoxine	Verapamil	1
Diltiazem	Triazolam	2	Amiodarone	Citalopram	1
Diltiazem	Timolol	2	Amiodarone	Donepezil	1
Levothyroxin-Natrium	Polystyrolsulfonat	2	Canrenone	Potassium-chloride	1
Ibuprofen	Phenprocoumon	2	Amiloride	Potassium-chloride	1
Diclofenac	Phenprocoumon	2	Diltiazem	Triamcinolone	1
Acetylsalicylic acid	Phenprocoumon	2	Metoprolol	Verapamil	1
Carbamazepin	Rivaroxaban	2	Atenolol	Verapamil	1
Carbamazepin	Felodipin	2	Lercanidipin	Primidon	1
Citalopram	Flecainide	2	Diltiazem	Nebivolol	1
Codeine	Paroxetin	2	Diltiazem	Nifedipin	1
Codeine	Duloxetin	2	Diltiazem	Triazolam	1
Kaliumchlorid	Spironolacton	1	Diltiazem	Timolol	1
Kaliumchlorid	Triamteren	1	Diclofenac	Phenprocoumon	1
Kaliumcitrat	Spironolacton	1	Ciproterone	Phenobarbital	1

T0=baseline visit. T3=final visit.

Table 7a: Most frequent category D interactions in the decision support tool group

Decision support tool group at T0 (n=1509)			Decision support tool group at T3 (n=1509)		
Drug-1	**Drug-2**	**Number of inter-actions**	**Drug-1**	**Drug-2**	**Number of inter-actions**
ASA	Phenprocoumon	23	Acetylsalicylic acid	Phenprocoumon	7
ASA	Warfarin	15	Acetylsalicylic acid	Warfarin	4
Diclofenac	Phenprocoumon	8	Diclofenac	Phenprocoumon	3
Ibuprofen	Warfarin	5	Acetylsalicylic acid	Phenprocoumon	3
Tramadol	Warfarin	5	Aliskiren	Ramipril	2
Digoxin	Verapamil	4	Naproxen	Phenprocoumon	2
Diltiazem	Timolol	4	Celecoxib	Phenprocoumon	2
Ibuprofen	Phenprocoumon	4	Ibuprofen	Phenprocoumon	2
Acetylsalicylic acid	Phenprocoumon	4	Domperidon	Donepezil	1
Amiodarone	Citalopram	3	Phenprocoumon	Piroxicam	1
Ibuprofen	Phenprocoumon	3	Phenprocoumon	Tiaprofenic acid	1
Carbamazepin	Tamsulosin	3	Clopidogrel	Repaglinide	1
Duloxetin	Tramadol	3	Apixaban	Dabigatran	1
Codeine	Paroxetine	3	Digoxine	Verapamil	1
Clopidogrel	Repaglinide	2	Amiodarone	Citalopram	1
Amiodarone	Domperidon	2	Glyceroltrinitrate	Vardenafil	1
Amiodarone	Diltiazem	2	Ibuprofen	Phenprocoumon	1
Ibuprofen	Phenprocoumon	2	Metoprolol	Verapamil	1
Amilorid	Potassium-chloride	2	Atenolol	Diltiazem	1
Metoprolol	Verapamil	2	Amlodipin	Primidon	1
Bisoprolol	Diltiazem	2	Amlodipin	Carbamazepin	1
Nebivolol	Paroxetin	2	Diltiazem	Timolol	1
Amlodipin	Primidone	2	Aliskiren	Telmisartan	1
Amlodipin	Carbamazepin	2	Gemfibrozil	Lovastatin	1
Diltiazem	Triazolam	2	Colestyramine	Warfarin	1

T0=baseline visit. T3=final visit.

Table 8a: Top 25 drugs eliciting reminders regarding renal dosing adjustment

	Control group at T0		Decision support tool group at T0		Control group at T3		Decision support tool group at T3	
Drug	**Number of drugs causing renal dosing problems**	**% of all patients (n=1519)**	**Number of drugs causing renal dosing problems**	**% of all patients (n=1509)**	**Number of drugs causing renal dosing problems**	**% of all patients (n=1519)**	**Number of drugs causing renal dosing problems**	**% of all patients (n=1509)**
Total reminders	877		896		488		473	
Patients with at least 1 renal dosing reminder	290	19.1	297	19.7	167	10.5	159	10.5
Allopurinol	94	6.2	105	7.0	48	3.2	49	3.2
Metamizole	66	4.3	41	2.7	51	3.4	30	2.0
Acetylsalicylic acid	52	3.4	46	3.0	26	1.7	6	0.4
Spironolactone	37	2.4	40	2.7	21	1.4	19	1.3
Metformin	36	2.4	40	2.7	21	1.4	16	1.1
Candesartan	34	2.2	46	3.0	18	1.2	23	1.5
Simvastatin	32	2.1	34	2.3	18	1.2	20	1.3
Furosemide	29	1.9	25	1.7	15	1.0	19	1.3
Ramipril	29	1.9	23	1.5	5	0.3	9	0.6
Calcium carbonate	19	1.3	26	1.7	17	1.1	13	0.9
Mirtazapine	16	1.1	14	0.9	9	0.6	7	0.5
Bisoprolol	14	0.9	22	1.5	9	0.6	14	0.9
Hydrochlorothiazide	13	0.9	13	0.9	7	0.5	4	0.3
Ibuprofen	13	0.9	9	0.6	5	0.3	3	0.2
Moxonidin	13	0.9	14	0.9	16	1.1	7	0.5
Sitagliptin	13	0.9	11	0.7	5	0.3	2	0.1
Tiotropium bromide	13	0.9	13	0.9	7	0.5	8	0.5
Amitriptylin	12	0.8	9	0.6	6	0.4	4	0.3
Codein	12	0.8	17	1.1	5	0.3	5	0.3
Insulin glargin	12	0.8	11	0.7	6	0.4	5	0.3

T0=baseline visit. T3=final visit.

Table 9a: Top 25 drugs newly prescribed

Control group				Decision support tool group			
Drug	**Number of prescriptions at T0**	**Number of prescriptions at T3**	**Increase in number of prescriptions from T0 to T3**	**Drug**	**Number of prescriptions at T0**	**Number of prescriptions at T3**	**Increase in number of prescriptions from T0 to T3**
Total	2992*	3762*	770	Total	2274*	2793*	519
Apixaban	22	77	55	Apixaban	8	60	52
Cholecalciferol	399	444	45	Macrogol	90	104	14
Atorvastatin	230	267	37	Rivaroxaban	50	64	14
Macrogol	104	131	27	Atorvastatin	230	244	14
Metamizol	218	239	21	Edoxaban	0	13	13
Rivaroxaban	59	73	14	Xipamid	25	37	12
Tapentadol	18	32	14	Febuxostat	17	29	12
Linagliptin	1	14	13	Metamizol	171	182	11
Spironolacton	102	113	11	Linagliptin	7	16	9
Hydromorphon	22	33	11	Tapentadol	8	16	8
Glycopyrronium	12	23	11	Natriumhydrogencarbonat	8	16	8
Edoxaban	0	10	10	Insulin detemir	23	31	8
Sertraline	24	34	10	Prednisolone	13	21	8
Xipamid	22	31	9	Beclometasone	47	54	7
Indacaterol	7	16	9	Hypromellose	8	14	6
Ipratropium	23	31	8	Fentanyl	19	25	6
Cyanocobalamin	42	49	7	Formoterol	103	109	6
Insulin glargin	92	98	6	Vilanterol	0	6	6
Folic acid	46	52	6	Dorzolamid	16	22	6
Ezetimib	45	51	6	Hydroxocobalamin	7	12	5
Quetiapin	8	14	6	Bumetanide	9	14	5
Trazodon	25	31	6	Ibuprofen (topical)	36	41	5
Melperon	9	14	5	Mirtazapin	57	62	5
Donepezil	3	8	5	Brimonidine	8	13	5
Latanoprost	32	37	5	Salbutamol	132	136	4

T0=baseline visit. T3=final visit.

* Only drugs with an increase in prescriptions from T0 to T3

Table 10a: Total number of symptoms or possibly adverse drug reactions per patient at baseline and at final visit

	Decision support tool group			Control group			
Symptoms	n	mean	SD	n	mean	SD	p-value*
at T0 (baseline)	1681	4.0	2.9	1705	4.2	3.1	-
Symptoms at T3 (final visit)	1553	2.8	2.6	1632	3.1	2.6	0.338
* p-value from Poisson regression analysis, controlled for pre-specified covariates, number of symptoms at baseline, and clustering of patients in practices.							

Table 11a: Symptoms or possibly adverse drug reactions within one month before or at baseline

	Control group (n=1705)*		Decision support tool group (n=1681)*	
Symptom	n	%	n	%
constipation	367	21.5	332	19.8
nausea	164	9.6	140	8.3
diarrhea	171	10.0	166	9.9
dyspepsia	347	20.4	357	21.2
cough	361	21.2	372	22.1
dyspnea	512	30.0	554	33.0
dizziness	633	37.1	618	36.8
fatigue	774	45.4	761	45.3
sleeping	547	32.1	520	30.9
cognitive	225	13.2	192	11.4
pain	992	58.2	951	56.6
swollen legs	469	27.5	429	25.5
nycturia	477	28.0	464	27.6
skin rash	227	13.3	184	10.9
xerostomia	335	19.6	267	15.9
bleeding	48	2.8	48	2.9
weight loss	82	4.8	65	3.9
sweating	177	10.4	191	11.4
other	176	10.3	154	9.2

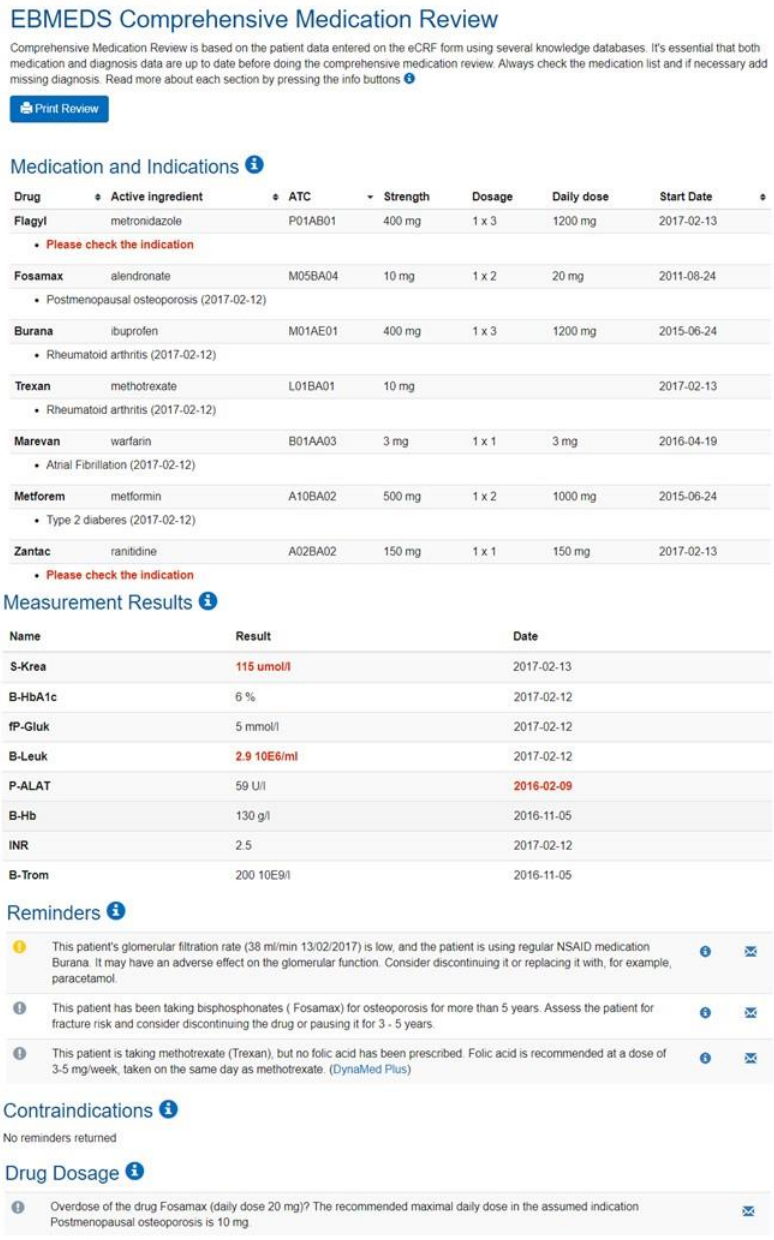
* n's differ from PPA of primary endpoint due to missing data

Table 12a: Symptoms or possibly adverse drug reactions within one month before or at final visit

	Control group (n=1632)*		Decision support tool (n=1553)*	
symptom	n	%	n	%
constipation	210	12.9	177	11.4
nausea	129	7.9	75	4.8
diarrhea	100	6.1	67	4.3
dyspepsia	176	10.8	147	9.5
cough	228	14.0	187	12.0
dyspnea	330	20.2	294	18.9
dizziness	446	27.3	399	25.7
fatigue	615	37.7	509	32.8
sleeping	312	19.1	261	16.8
cognitive	378	23.2	330	21.2
pain	616	37.7	573	36.9
swollen legs	299	18.3	245	15.8
nycturia	235	14.4	236	15.2
skin rash	95	5.8	83	5.3
xerostomia	328	20.1	271	17.5
bleeding	60	3.7	47	3.0
weight loss	136	8.3	98	6.3
sweating	194	11.9	200	12.9
other	105	6.4	82	5.3

* n's differ from PPA of primary endpoint due to missing data

Fig. 1a: Electronic decision support comprehensive medication review Part 1



EBMEDS Comprehensive Medication Review

Comprehensive Medication Review is based on the patient data entered on the eCRF form using several knowledge databases. It's essential that both medication and diagnosis data are up to date before doing the comprehensive medication review. Always check the medication list and if necessary add missing diagnosis. Read more about each section by pressing the info buttons

Print Review

Medication and Indications

Drug	Active ingredient	ATC	Strength	Dosage	Daily dose	Start Date
Flagyl	metronidazole	P01AB01	400 mg	1 x 3	1200 mg	2017-02-13
• Please check the indication						
Fosamax	alendronate	M05BA04	10 mg	1 x 2	20 mg	2011-08-24
• Postmenopausal osteoporosis (2017-02-12)						
Burana	ibuprofen	M01AE01	400 mg	1 x 3	1200 mg	2015-06-24
• Rheumatoid arthritis (2017-02-12)						
Trexan	methotrexate	L01BA01	10 mg			2017-02-13
• Rheumatoid arthritis (2017-02-12)						
Marevan	warfarin	B01AA03	3 mg	1 x 1	3 mg	2016-04-19
• Atrial Fibrillation (2017-02-12)						
Metforem	metformin	A10BA02	500 mg	1 x 2	1000 mg	2015-06-24
• Type 2 diaberes (2017-02-12)						
Zantac	ranitidine	A02BA02	150 mg	1 x 1	150 mg	2017-02-13
• Please check the indication						

Measurement Results

Name	Result	Date
S-Krea	**115 umol/l**	2017-02-13
B-HbA1c	6 %	2017-02-12
fP-Gluk	5 mmol/l	2017-02-12
B-Leuk	**2.9 10E6/ml**	2017-02-12
P-ALAT	59 U/l	**2016-02-09**
B-Hb	130 g/l	2016-11-05
INR	2.5	2017-02-12
B-Trom	200 10E9/l	2016-11-05

Reminders

- This patient's glomerular filtration rate (38 ml/min 13/02/2017) is low, and the patient is using regular NSAID medication Burana. It may have an adverse effect on the glomerular function. Consider discontinuing it or replacing it with, for example, paracetamol.
- This patient has been taking bisphosphonates (Fosamax) for osteoporosis for more than 5 years. Assess the patient for fracture risk and consider discontinuing the drug or pausing it for 3 - 5 years.
- This patient is taking methotrexate (Trexan), but no folic acid has been prescribed. Folic acid is recommended at a dose of 3-5 mg/week, taken on the same day as methotrexate. (DynaMed Plus)

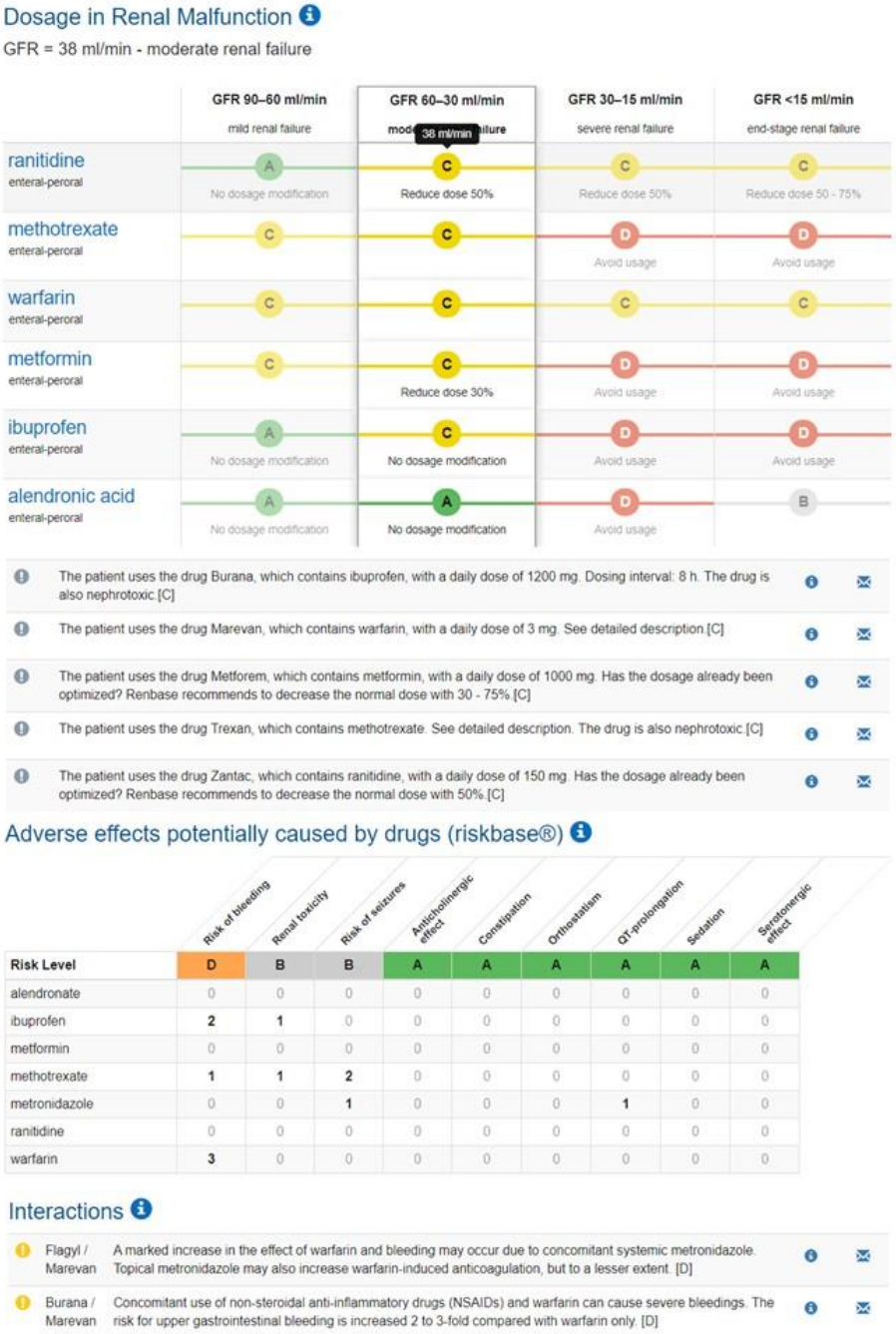
Contraindications

No reminders returned

Drug Dosage

- Overdose of the drug Fosamax (daily dose 20 mg)? The recommended maximal daily dose in the assumed indication Postmenopausal osteoporosis is 10 mg.

Fig 2a: Electronic decision support comprehensive medication review Part 2



Dosage in Renal Malfunction

GFR = 38 ml/min - moderate renal failure

	GFR 90–60 ml/min mild renal failure	GFR 60–30 ml/min mod… failure (38 ml/min)	GFR 30–15 ml/min severe renal failure	GFR <15 ml/min end-stage renal failure
ranitidine enteral-peroral	A No dosage modification	C Reduce dose 50%	C Reduce dose 50%	C Reduce dose 50 - 75%
methotrexate enteral-peroral	C	C	D Avoid usage	D Avoid usage
warfarin enteral-peroral	C	C	C	C
metformin enteral-peroral	C	C Reduce dose 30%	D Avoid usage	D Avoid usage
ibuprofen enteral-peroral	A No dosage modification	C No dosage modification	D Avoid usage	D Avoid usage
alendronic acid enteral-peroral	A No dosage modification	A No dosage modification	D Avoid usage	B

- The patient uses the drug Burana, which contains ibuprofen, with a daily dose of 1200 mg. Dosing interval: 8 h. The drug is also nephrotoxic.[C]
- The patient uses the drug Marevan, which contains warfarin, with a daily dose of 3 mg. See detailed description.[C]
- The patient uses the drug Metforem, which contains metformin, with a daily dose of 1000 mg. Has the dosage already been optimized? Renbase recommends to decrease the normal dose with 30 - 75% [C]
- The patient uses the drug Trexan, which contains methotrexate. See detailed description. The drug is also nephrotoxic.[C]
- The patient uses the drug Zantac, which contains ranitidine, with a daily dose of 150 mg. Has the dosage already been optimized? Renbase recommends to decrease the normal dose with 50% [C]

Adverse effects potentially caused by drugs (riskbase®)

	Risk of bleeding	Renal toxicity	Risk of seizures	Anticholinergic effect	Constipation	Orthostatism	QT-prolongation	Sedation	Serotonergic effect
Risk Level	D	B	B	A	A	A	A	A	A
alendronate	0	0	0	0	0	0	0	0	0
ibuprofen	2	1	0	0	0	0	0	0	0
metformin	0	0	0	0	0	0	0	0	0
methotrexate	1	1	2	0	0	0	0	0	0
metronidazole	0	0	1	0	0	0	1	0	0
ranitidine	0	0	0	0	0	0	0	0	0
warfarin	3	0	0	0	0	0	0	0	0

Interactions

Flagyl / Marevan	A marked increase in the effect of warfarin and bleeding may occur due to concomitant systemic metronidazole. Topical metronidazole may also increase warfarin-induced anticoagulation, but to a lesser extent. [D]
Burana / Marevan	Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and warfarin can cause severe bleedings. The risk for upper gastrointestinal bleeding is increased 2 to 3-fold compared with warfarin only. [D]

Fig 3a: Electronic case report form (eCRF)

Needed patient data/further explanation and information

PATIENT IDENTITY

- Internal Study ID
- Year of birth
- Gender (male/female)
- Patient has signed informed consent ➔ tick box for "yes" (this is necessary for entering the following data/ to perform medication review)

after this section the "new patient" will be created and baseline data can be entered

CURRENT MEDICATION

Please provide current continuous and temporary medication including over-the-counter medication, herbal treatment and treatment prescribed by other medical specialists.
You can search directly by the drug's ATC code or by the generic name. Drug brand names are not included.
For combination drugs all active components must be entered separately as if they were separate drugs.
Exact start dates are not needed at baseline. It is sufficient to use the default value 1.1.2013.

- Name + ATC code (out of drop-down menu)
- Frequency (daily - weekly -as needed- other)
- Administration route (oral - rectal -parenteral – topical)
- Start date of medication
- End date and reason for discontinuation (ending a temporary treatment - adverse drug event - after reconsideration - patient´s choice or whish – false entry– other)
- total daily dose + unit

DIAGNOSES

the following list shows the most frequent chronic diseases, please select:

- Primary hypertension
- Type2 diabetes
- Hypercholesterolemia
- History of myocardial infarction
- Chronic heart failure
- Chronic ischemic heart disease
- Atrial fibrillation
- Stroke or TIA
- Asthma
- COPD
- Depression
- Insomnia
- Gastroesophageal reflux
- Benign prostatic hyperplasia
- Osteoporosis without fracture
- Arthrosis
- Back pain
- Gout
- Hypothyroidism

- Rheumatoid arthritis

Renal insufficiency is automatically calculated from the GFR.

OTHER DIAGNOSES RELEVANT TO THE MEDICATION

Please provide all permanent diagnoses, current temporary diagnoses and previous diagnoses possibly significant for the treatment.
You can search directly by the ICD-10 code or by the name of the disease in the eCRF.
Exact diagnosis start dates are not needed at baseline. It is sufficient to use the default value 1.1.2013.

- Name + ICD 10 Code as drop down menu
- Start date
- End date (remove diagnosis from the list)
- If an end date is set: Reason for removal (False entry – cured/not active)

SYMPTOMS WITHIN ONE MONTH

Please provide all symptoms compromising the patient's quality of life within the time frame of the previous month by ticking the appropriate box.

- Constipation
- Nausea/ vomiting
- Diarrhea
- Dyspepsia/abdominal discomfort
- Dizziness/vertigo
- Fatigue
- Sleeping problems
- Confusion/delirium
- Pain
- Dyspnea
- Cough
- Rash or itching
- Nycturia
- Leg swelling
- Other (please list)

FALLS

Please enter the number of falls and the severity of injury of falls of this patient during the last 3 months - select out of the following:

- None
- Number of falls with moderate/severe injury

Information on falls

- Serious injury: Medically recorded fracture, head or internal injury requiring accident and emergency or inpatient treatment.
- Moderate injury: Wounds, bruises, sprains, cuts requiring a medical/health professional examination such as physical examination, x-ray, suture.
- Minor injury: Minor bruises or abrasions not requiring health professional assistance; reduction in physical function (e.g. due to pain, fear of falling) for at least three days.
- No injury: No physical injury detected.

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 in your records. Otherwise please leave blank as we want to avoid additional laboratory analyses.

- Height
- Weight + date
- BP (Blood Pressure) + date (enter a typical/average BP based on several recent measurements. Use latest measurement if several recent measurements are not available)
- Smoking status (non-smoker - smoker - ex-smoker - not known)
- Creatinine + date
- Total Cholesterol
- HDL Cholesterol
- Triglycerides
- LDL Cholesterol
- Fasting Glucose
- HbA1c + date
- INR + date
- B-Hb + date
- Platelet count + date
- ALT + date
- Potassium + date
- Sodium +date
- Proteinuria (Yes/No)

PROCEDURES (Yes/No)

- Drug Eluting Stent + date
- Transcatheter Aortic Valve Replacement + date
- Heart Valve Replacement mechanical + date

FRAILTY

Frailty scale - Read more about frailty scale on the link on the eCRF or on
http://www.ebmeds.org/cmr/Annex_II_Frailty_scale.pdf

Please select:

- Managing Well: Medical problems well controlled, patient not regularly active beyond routine walking.
- Vulnerable: Not dependent on others for daily help. Being "slowed up", and/or being tired during the day.
- Mildly Frail: More evident "slowed up", and/or being tired during the day, need help in some daily activities (i.e. finances, heavy housework).
- Moderately Frail: Need help with all outside activities/keeping house. Have problems with stairs, need help for bathing and minimal assistance with dressing.
- Severely Frail: Completely dependent for personal care, from whatever cause (physical or cognitive). Not at high risk of dying (within ~ 6 months).
- Very Severely Frail/Terminally Ill: Completely dependent, approaching the end of life (life expectancy < 6 months).

HOSPITALIZATIONS

Please provide information about all non-elective hospitalisations of this patient during the course of the study. If you wish to add a diagnosis and cannot find it on the list, please give your feedback on the link in the eCRF.	
None	
Reason: disease name or ICD10 code	
Admission date	
Length (nights)	
DEATH	
Please provide information about date and cause of death	
Date of death	
Cause of death: disease name or ICD10 code	