

Additional file 1: Comparison of the Informatics Consult with traditional approaches to evidence generation.

Areas	Traditional methods of evidence generation	Informatics Consult
Who initiates the question?	Top down: typically driven by a small number of researchers	Bottom up: democratic, any clinician, any uncertainty and potentially patient driven
Simultaneous delivery of all relevant evidence	Not often possible, one study and one design at a time	Yes
Embedded in health systems (the question or the answer or the means of providing answer)	No	Yes
Clinical trial prioritisation, informing trial design and recruitment	Top down: driven by specific groups of individuals	Bottom up: opportunities for embedding within clinical practice
Involvement of individuals	Researcher centric	Patient and clinician centric
Strength of evidence and levels of evidence	Levels of evidence classified in all major clinical guidelines; however, these are all based on peer reviewed published evidence	Same levels of evidence apply; however, the framework aims to return evidence within clinical timescales to mitigate hurdles in the journal peer-review process. Potential for collating information from past Consults in an open-access repository.
Clinical guideline recommendations based on evidence	Yes, information from randomised trials and peer-reviewed publications are included in clinical guidelines	Raises important questions on what basis might clinicians follow the Consult before it is peer reviewed and published
Regulatory approvals on the labels of drugs and medical devices	Food and Drug Administration (FDA), European Medicines Agency and Medicines and Healthcare products Regulatory Agency established processes for trials and for the Real-world Evidence framework	Largely untested

Additional file 2: Specification and emulation of a target trial of warfarin therapy and mortality or stroke risk using

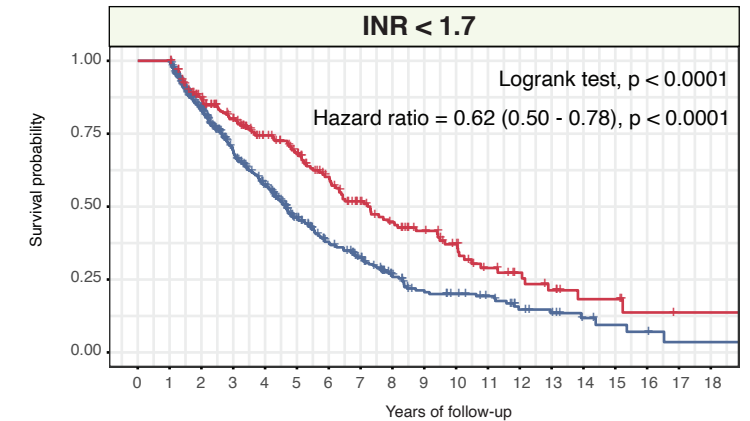
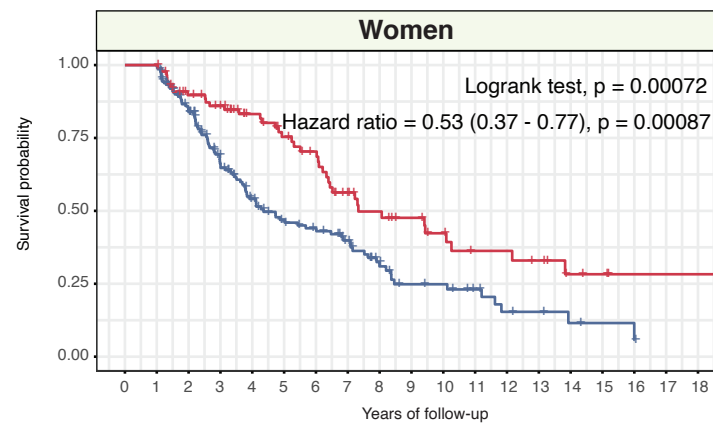
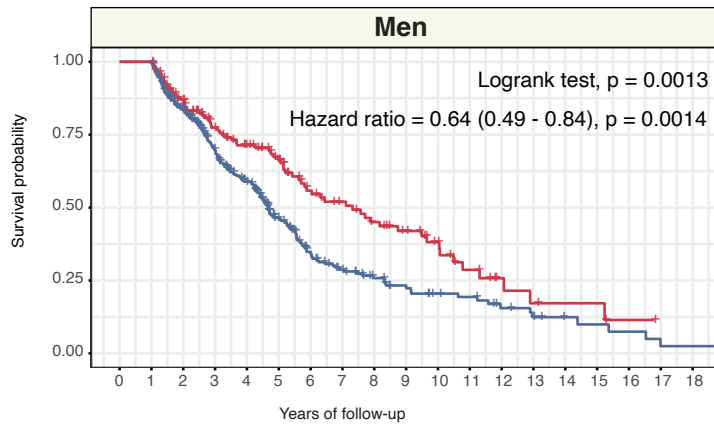
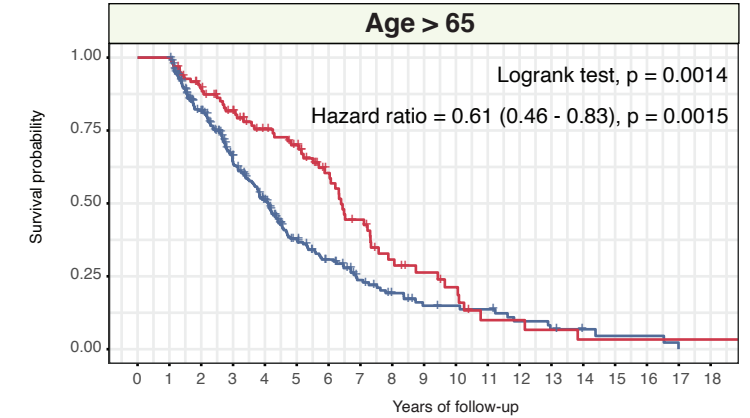
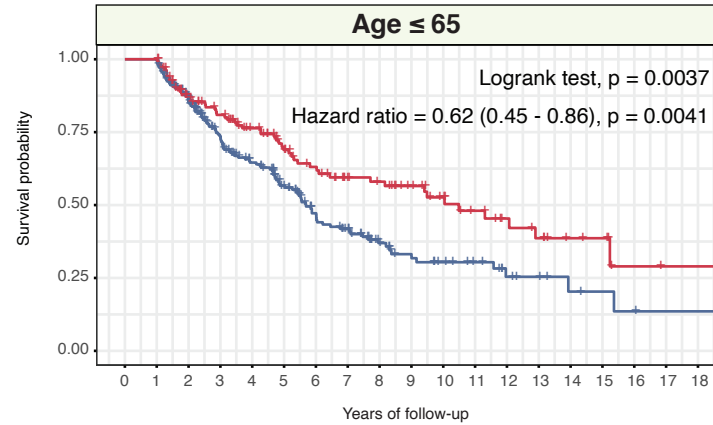
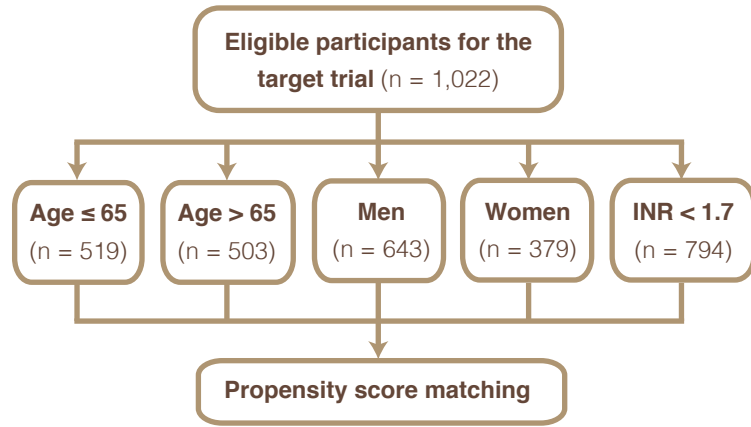
Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	Age \geq 30 between 1 January 1998 and 27 June 2016	Same as for the target trial
	Age \leq 85 at baseline	
	No history of stroke at baseline	
	At least 1 year of up-to-standard data in a CPRD practice	
	At least 1 year of potential follow-up from baseline	
	Baseline is defined as the latest date by which an individual is diagnosed with cirrhosis or atrial fibrillation + 3 months (individuals must have both conditions at baseline), given that all eligibility criteria are met.	
Treatment strategies	Initiation of warfarin therapy versus no initiation of warfarin at baseline	Same as for the target trial. Date of medication initiation is defined as the first date of a prescription.
Treatment assignment	Individuals are randomly assigned to a strategy at baseline	Randomisation is emulated by adjusting for baseline confounders.
Outcomes	All-cause mortality and incident ischaemic stroke.	Same as for the target trial
Follow-up	Starts at baseline and ends at the time of reaching an outcome, death, loss to follow-up (transfer out of the practice) or administrative end of follow-up (end of practice data collection or 27 June 2016), whichever happens first.	Same as for the target trial
Causal contrast	Intention-to-treat effect	Observational analog for the intention-to-treat effect
Statistical analyses	Intention-to-treat analysis	Same as for the target trial, adjusting for baseline covariates via propensity score or regression adjustment.
	Subgroup analyses by age (< 65 or ≥ 65), sex, normal INR (< 1.7).	Same subgroup analyses.

Additional file 3: Baseline characteristics of the unmatched and matched cohorts

Characteristics	Unmatched cohort			Matched cohort		
	No warfarin	Warfarin	Standardised difference	No warfarin	Warfarin	Standardised difference
N	579	443		526	235	
Gender, women (%)	199 (34.4)	180 (40.6)	0.13	193 (36.7)	95 (40.4)	0.077
Age at baseline, years (mean (SD))	65.66 (12.50)	61.69 (13.42)	0.306	65.16 (12.56)	61.11 (13.89)	0.306
Type 2 diabetes (%)	136 (23.5)	99 (22.3)	0.027	125 (23.8)	46 (19.6)	0.102
Hypertension (%)	258 (44.6)	183 (41.3)	0.066	220 (41.8)	80 (34.0)	0.161
Ascites (%)	143 (24.7)	125 (28.2)	0.08	130 (24.7)	67 (28.5)	0.086
Hepatic encephalopathy (%)	29 (5.0)	32 (7.2)	0.093	26 (4.9)	14 (6.0)	0.045
Renal disease (%)	78 (13.5)	58 (13.1)	0.011	62 (11.8)	21 (8.9)	0.094
Steatosis (%)	63 (10.9)	48 (10.8)	0.001	56 (10.6)	27 (11.5)	0.027
Lipid regulating drugs (%)	160 (27.6)	130 (29.3)	0.038	144 (27.4)	58 (24.7)	0.061
Hypertension treatment (%)	236 (40.8)	194 (43.8)	0.061	216 (41.1)	94 (40.0)	0.022
Digoxin (%)	107 (18.5)	65 (14.7)	0.103	95 (18.1)	27 (11.5)	0.186
Varices (%)	95 (16.4)	74 (16.7)	0.008	81 (15.4)	33 (14.0)	0.038
Bilirubin ≥ 34.2 µmol/L (%)	130 (22.5)	93 (21.0)	0.035	110 (20.9)	42 (17.9)	0.077
Albumin < 35 g/L (%)	18 (3.1)	21 (4.7)	0.084	17 (3.2)	12 (5.1)	0.094
INR ≥ 1.7 (%)	11 (1.9)	217 (49.0)	1.285	11 (2.1)	12 (5.1)	0.162
Alanine aminotransferase ≥ 35 U/L (%)	246 (42.5)	179 (40.4)	0.042	211 (40.1)	84 (35.7)	0.09
Aspartate transaminase ≥ 40 U/L (%)	119 (20.6)	88 (19.9)	0.017	104 (19.8)	38 (16.2)	0.094
BMI ≥ 30 kg/m2 (%)	227 (39.2)	169 (38.1)	0.022	208 (39.5)	81 (34.5)	0.105
Gamma-glutamyltransferase ≥ 48 U/L (%)	263 (45.4)	183 (41.3)	0.083	223 (42.4)	71 (30.2)	0.255
Alkaline phosphatase ≥ 140 U/L (%)	257 (44.4)	225 (50.8)	0.128	236 (44.9)	104 (44.3)	0.012
Platelet ≤ 150 10⁹/L (%)	67 (11.6)	45 (10.2)	0.045	58 (11.0)	24 (10.2)	0.026
Creatinine > 120 µmol/L (%)	94 (16.2)	66 (14.9)	0.037	76 (14.4)	25 (10.6)	0.115

Blood test measurements are indicated as the presence or absence of a particular measurement above or below the stated threshold.

Additional file 4. Subgroup analyses showing Kaplan-Meier plots of the propensity-matched cohort for all-cause mortality. Flow diagram depicts analysis design. P values from logrank tests were indicated. Hazard ratios from Cox proportional hazards regression analyses were indicated. Numbers in parentheses indicate the 95% confidence intervals.



Additional file 5: Baseline characteristics of the unmatched and matched cohorts in individuals aged ≤ 65

Characteristics	Unmatched cohort			Matched cohort		
	No warfarin	Warfarin	Standardised difference	No warfarin	Warfarin	Standardised difference
N	263	256		239	136	
Gender, women (%)	65 (24.7)	86 (33.6)	0.196	63 (26.4)	44 (32.4)	0.132
Age at baseline, years (mean (SD))	54.64 (8.03)	52.35 (8.71)	0.273	54.25 (8.08)	52.04 (8.83)	0.262
Type 2 diabetes (%)	48 (18.3)	47 (18.4)	0.003	43 (18.0)	24 (17.6)	0.009
Hypertension (%)	87 (33.1)	71 (27.7)	0.116	78 (32.6)	35 (25.7)	0.152
Ascites (%)	76 (28.9)	90 (35.2)	0.134	64 (26.8)	45 (33.1)	0.138
Hepatic encephalopathy (%)	19 (7.2)	26 (10.2)	0.104	17 (7.1)	10 (7.4)	0.009
Renal disease (%)	37 (14.1)	31 (12.1)	0.058	26 (10.9)	10 (7.4)	0.123
Steatosis (%)	36 (13.7)	32 (12.5)	0.035	32 (13.4)	19 (14.0)	0.017
Lipid regulating drugs (%)	59 (22.4)	57 (22.3)	0.004	56 (23.4)	30 (22.1)	0.033
Hypertension treatment (%)	87 (33.1)	85 (33.2)	0.003	80 (33.5)	42 (30.9)	0.055
Digoxin (%)	37 (14.1)	22 (8.6)	0.173	28 (11.7)	10 (7.4)	0.149
Varices (%)	46 (17.5)	46 (18.0)	0.013	36 (15.1)	21 (15.4)	0.011
Bilirubin ≥ 34.2 µmol/L (%)	77 (29.3)	61 (23.8)	0.124	62 (25.9)	29 (21.3)	0.109
Albumin < 35 g/L (%)	10 (3.8)	15 (5.9)	0.096	9 (3.8)	9 (6.6)	0.129
INR ≥ 1.7 (%)	7 (2.7)	123 (48.0)	1.223	7 (2.9)	8 (5.9)	0.144
Alanine aminotransferase ≥ 35 U/L (%)	125 (47.5)	103 (40.2)	0.147	108 (45.2)	51 (37.5)	0.157
Aspartate transaminase ≥ 40 U/L (%)	65 (24.7)	58 (22.7)	0.048	58 (24.3)	25 (18.4)	0.144
BMI ≥ 30 kg/m² (%)	94 (35.7)	83 (32.4)	0.07	81 (33.9)	39 (28.7)	0.113
Gamma-glutamyltransferase ≥ 48 U/L (%)	142 (54.0)	100 (39.1)	0.303	119 (49.8)	40 (29.4)	0.426
Alkaline phosphatase ≥ 140 U/L (%)	116 (44.1)	126 (49.2)	0.103	104 (43.5)	57 (41.9)	0.032
Platelet ≤ 150 10⁹/L (%)	28 (10.6)	28 (10.9)	0.009	24 (10.0)	13 (9.6)	0.016
Creatinine > 120 µmol/L (%)	24 (9.1)	27 (10.5)	0.048	18 (7.5)	10 (7.4)	0.007

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Additional file 6: Baseline characteristics of the unmatched and matched cohorts in individuals aged > 65

Characteristics	Unmatched cohort			Matched cohort		
	No warfarin	Warfarin	Standardised difference	No warfarin	Warfarin	Standardised difference
N	316	187		266	97	
Gender, women (%)	134 (42.4)	94 (50.3)	0.158	117 (44.0)	45 (46.4)	0.048
Age at baseline, years (mean (SD))	74.83 (6.89)	74.47 (6.33)	0.055	74.45 (6.82)	74.26 (6.32)	0.030
Type 2 diabetes (%)	88 (27.8)	52 (27.8)	0.001	67 (25.2)	23 (23.7)	0.034
Hypertension (%)	171 (54.1)	112 (59.9)	0.117	134 (50.4)	43 (44.3)	0.121
Ascites (%)	67 (21.2)	35 (18.7)	0.062	55 (20.7)	21 (21.6)	0.024
Hepatic encephalopathy (%)	10 (3.2)	6 (3.2)	0.003	9 (3.4)	4 (4.1)	0.039
Renal disease (%)	41 (13.0)	27 (14.4)	0.043	29 (10.9)	12 (12.4)	0.046
Steatosis (%)	27 (8.5)	16 (8.6)	<0.001	24 (9.0)	8 (8.2)	0.028
Lipid regulating drugs (%)	101 (32.0)	73 (39.0)	0.148	82 (30.8)	31 (32.0)	0.024
Hypertension treatment (%)	149 (47.2)	109 (58.3)	0.224	127 (47.7)	52 (53.6)	0.117
Digoxin (%)	70 (22.2)	43 (23.0)	0.020	47 (17.7)	16 (16.5)	0.031
Varices (%)	49 (15.5)	28 (15.0)	0.015	40 (15.0)	14 (14.4)	0.017
Bilirubin ≥ 34.2 µmol/L (%)	53 (16.8)	32 (17.1)	0.009	44 (16.5)	12 (12.4)	0.119
Albumin < 35 g/L (%)	8 (2.5)	6 (3.2)	0.041	7 (2.6)	4 (4.1)	0.083
INR ≥ 1.7 (%)	4 (1.3)	94 (50.3)	1.353	4 (1.5)	4 (4.1)	0.159
Alanine aminotransferase ≥ 35 U/L (%)	121 (38.3)	76 (40.6)	0.048	91 (34.2)	31 (32.0)	0.048
Aspartate transaminase ≥ 40 U/L (%)	54 (17.1)	30 (16.0)	0.028	45 (16.9)	13 (13.4)	0.098
BMI ≥ 30 kg/m² (%)	133 (42.1)	86 (46.0)	0.08	116 (43.6)	43 (44.3)	0.015
Gamma-glutamyltransferase ≥ 48 U/L (%)	121 (38.3)	83 (44.4)	0.124	94 (35.3)	31 (32.0)	0.072
Alkaline phosphatase ≥ 140 U/L (%)	141 (44.6)	99 (52.9)	0.167	117 (44.0)	43 (44.3)	0.007
Platelet ≤ 150 10⁹/L (%)	39 (12.3)	17 (9.1)	0.105	31 (11.7)	10 (10.3)	0.043
Creatinine > 120 µmol/L (%)	70 (22.2)	39 (20.9)	0.032	45 (16.9)	14 (14.4)	0.068

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Additional file 7: Baseline characteristics of the unmatched and matched cohorts in men

Characteristics	Unmatched cohort			Matched cohort		
	No warfarin	Warfarin	Standardised difference	No warfarin	Warfarin	Standardised difference
N	380	263		333	142	
Age at baseline, years (mean (SD))	63.63 (12.36)	60.04 (12.44)	0.290	62.82 (12.62)	59.53 (13.14)	0.255
Type 2 diabetes (%)	93 (24.5)	58 (22.1)	0.057	75 (22.5)	26 (18.3)	0.105
Hypertension (%)	155 (40.8)	106 (40.3)	0.010	130 (39.0)	49 (34.5)	0.094
Ascites (%)	102 (26.8)	80 (30.4)	0.079	92 (27.6)	45 (31.7)	0.089
Hepatic encephalopathy (%)	23 (6.1)	22 (8.4)	0.089	19 (5.7)	11 (7.7)	0.082
Renal disease (%)	50 (13.2)	34 (12.9)	0.007	42 (12.6)	15 (10.6)	0.064
Steatosis (%)	36 (9.5)	26 (9.9)	0.014	33 (9.9)	12 (8.5)	0.051
Lipid regulating drugs (%)	95 (25.0)	76 (28.9)	0.088	85 (25.5)	33 (23.2)	0.053
Hypertension treatment (%)	155 (40.8)	121 (46.0)	0.105	140 (42.0)	61 (43.0)	0.019
Digoxin (%)	66 (17.4)	37 (14.1)	0.091	55 (16.5)	19 (13.4)	0.088
Varices (%)	68 (17.9)	44 (16.7)	0.031	45 (13.5)	18 (12.7)	0.025
Bilirubin $\geq 34.2 \mu\text{mol/L}$ (%)	89 (23.4)	55 (20.9)	0.060	71 (21.3)	31 (21.8)	0.012
Albumin $< 35 \text{ g/L}$ (%)	13 (3.4)	15 (5.7)	0.110	11 (3.3)	8 (5.6)	0.113
INR ≥ 1.7 (%)	8 (2.1)	128 (48.7)	1.266	8 (2.4)	9 (6.3)	0.193
Alanine aminotransferase $\geq 35 \text{ U/L}$ (%)	159 (41.8)	102 (38.8)	0.062	135 (40.5)	50 (35.2)	0.110
Aspartate transaminase $\geq 40 \text{ U/L}$ (%)	78 (20.5)	53 (20.2)	0.009	68 (20.4)	24 (16.9)	0.090
BMI $\geq 30 \text{ kg/m}^2$ (%)	142 (37.4)	102 (38.8)	0.03	117 (35.1)	48 (33.8)	0.028
Gamma-glutamyltransferase $\geq 48 \text{ U/L}$ (%)	188 (49.5)	110 (41.8)	0.154	152 (45.6)	47 (33.1)	0.259
Alkaline phosphatase $\geq 140 \text{ U/L}$ (%)	150 (39.5)	123 (46.8)	0.148	135 (40.5)	62 (43.7)	0.063
Platelet $\leq 150 \times 10^9/\text{L}$ (%)	47 (12.4)	25 (9.5)	0.092	35 (10.5)	14 (9.9)	0.022
Creatinine $> 120 \mu\text{mol/L}$ (%)	58 (15.3)	48 (18.3)	0.080	49 (14.7)	20 (14.1)	0.018

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Additional file 8: Baseline characteristics of the unmatched and matched cohorts in women

Characteristics	Unmatched cohort			Matched cohort		
	No warfarin	Warfarin	Standardised difference	No warfarin	Warfarin	Standardised difference
N	199	180		164	90	
Age at baseline, years (mean (SD))	69.54 (11.86)	64.10 (14.44)	0.412	68.85 (11.80)	63.40 (14.65)	0.409
Type 2 diabetes (%)	43 (21.6)	41 (22.8)	0.028	34 (20.7)	18 (20.0)	0.018
Hypertension (%)	103 (51.8)	77 (42.8)	0.181	75 (45.7)	28 (31.1)	0.304
Ascites (%)	41 (20.6)	45 (25.0)	0.105	34 (20.7)	21 (23.3)	0.063
Hepatic encephalopathy (%)	6 (3.0)	10 (5.6)	0.126	6 (3.7)	5 (5.6)	0.091
Renal disease (%)	28 (14.1)	24 (13.3)	0.021	18 (11.0)	7 (7.8)	0.110
Steatosis (%)	27 (13.6)	22 (12.2)	0.040	24 (14.6)	13 (14.4)	0.005
Lipid regulating drugs (%)	65 (32.7)	54 (30.0)	0.057	54 (32.9)	27 (30.0)	0.063
Hypertension treatment (%)	81 (40.7)	73 (40.6)	0.003	64 (39.0)	31 (34.4)	0.095
Digoxin (%)	41 (20.6)	28 (15.6)	0.131	28 (17.1)	9 (10.0)	0.208
Varices (%)	27 (13.6)	30 (16.7)	0.087	24 (14.6)	14 (15.6)	0.026
Bilirubin \geq 34.2 μmol/L (%)	41 (20.6)	38 (21.1)	0.013	30 (18.3)	12 (13.3)	0.136
Albumin < 35 g/L (%)	5 (2.5)	6 (3.3)	0.049	4 (2.4)	4 (4.4)	0.110
INR \geq 1.7 (%)	3 (1.5)	89 (49.4)	1.317	3 (1.8)	3 (3.3)	0.095
Alanine aminotransferase \geq 35 U/L (%)	87 (43.7)	77 (42.8)	0.019	68 (41.5)	34 (37.8)	0.075
Aspartate transaminase \geq 40 U/L (%)	41 (20.6)	35 (19.4)	0.029	29 (17.7)	14 (15.6)	0.057
BMI \geq 30 kg/m² (%)	85 (42.7)	67 (37.2)	0.11	69 (42.1)	31 (34.4)	0.157
Gamma-glutamyltransferase \geq 48 U/L (%)	75 (37.7)	73 (40.6)	0.059	57 (34.8)	24 (26.7)	0.176
Alkaline phosphatase \geq 140 U/L (%)	107 (53.8)	102 (56.7)	0.058	80 (48.8)	38 (42.2)	0.132
Platelet \leq 150 10^9/L (%)	20 (10.1)	20 (11.1)	0.034	18 (11.0)	10 (11.1)	0.004
Creatinine > 120 μmol/L (%)	36 (18.1)	18 (10.0)	0.234	13 (7.9)	4 (4.4)	0.145

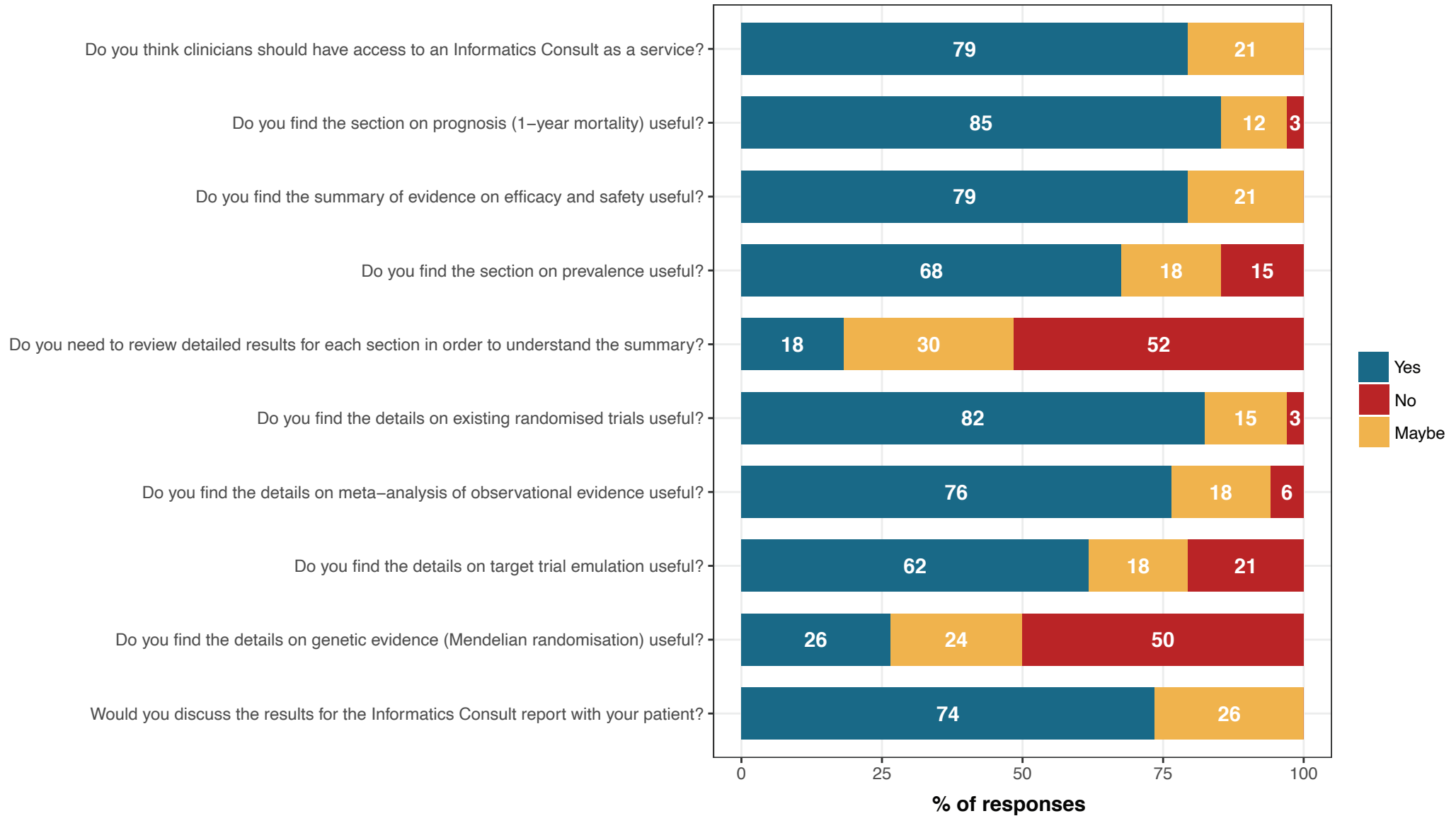
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Additional file 9: Baseline characteristics of the unmatched and matched cohorts in individuals with INR < 1.7

Characteristics	Unmatched cohort			Matched cohort		
	No warfarin	Warfarin	Standardised difference	No warfarin	Warfarin	Standardised difference
N	568	226		471	217	
Gender, women (%)	196 (34.5)	91 (40.3)	0.119	173 (36.7)	85 (39.2)	0.050
Age at baseline, years (mean (SD))	65.74 (12.47)	61.20 (13.62)	0.348	64.64 (12.43)	61.90 (13.33)	0.213
Type 2 diabetes (%)	133 (23.4)	45 (19.9)	0.085	111 (23.6)	43 (19.8)	0.091
Hypertension (%)	251 (44.2)	76 (33.6)	0.218	198 (42.0)	76 (35.0)	0.145
Ascites (%)	137 (24.1)	63 (27.9)	0.086	117 (24.8)	60 (27.6)	0.064
Hepatic encephalopathy (%)	26 (4.6)	15 (6.6)	0.090	24 (5.1)	12 (5.5)	0.019
Renal disease (%)	74 (13.0)	20 (8.8)	0.134	54 (11.5)	19 (8.8)	0.090
Steatosis (%)	62 (10.9)	25 (11.1)	0.005	57 (12.1)	24 (11.1)	0.033
Lipid regulating drugs (%)	156 (27.5)	58 (25.7)	0.041	128 (27.2)	57 (26.3)	0.021
Hypertension treatment (%)	232 (40.8)	88 (38.9)	0.039	196 (41.6)	84 (38.7)	0.059
Digoxin (%)	104 (18.3)	26 (11.5)	0.192	76 (16.1)	25 (11.5)	0.134
Varices (%)	89 (15.7)	32 (14.2)	0.042	66 (14.0)	32 (14.7)	0.021
Bilirubin ≥ 34.2 µmol/L (%)	124 (21.8)	41 (18.1)	0.092	93 (19.7)	39 (18.0)	0.045
Albumin < 35 g/L (%)	17 (3.0)	11 (4.9)	0.097	17 (3.6)	10 (4.6)	0.050
Alanine aminotransferase ≥ 35 U/L (%)	240 (42.3)	78 (34.5)	0.160	187 (39.7)	76 (35.0)	0.097
Aspartate transaminase ≥ 40 U/L (%)	115 (20.2)	39 (17.3)	0.077	90 (19.1)	37 (17.1)	0.053
BMI ≥ 30 kg/m² (%)	223 (39.3)	78 (34.5)	0.10	180 (38.2)	76 (35.0)	0.066
Gamma-glutamyltransferase ≥ 48 U/L (%)	258 (45.4)	67 (29.6)	0.330	186 (39.5)	67 (30.9)	0.181
Alkaline phosphatase ≥ 140 U/L (%)	251 (44.2)	98 (43.4)	0.017	204 (43.3)	93 (42.9)	0.009
Platelet ≤ 150 10⁹/L (%)	64 (11.3)	24 (10.6)	0.021	54 (11.5)	22 (10.1)	0.043
Creatinine > 120 µmol/L (%)	90 (15.8)	22 (9.7)	0.184	72 (15.3)	22 (10.1)	0.155

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Additional file 10. Summary of survey responses.



Additional file 11. Survey questionnaire.

1. Do you think clinicians should have access to an Informatics Consult as a service?
Yes | No | Maybe

2. Do you find the section on prognosis (1-year mortality) useful?
Yes | No | Maybe

3. Do you find the summary of evidence on efficacy and safety useful?
Yes | No | Maybe

4. Do you find the section on prevalence useful?
Yes | No | Maybe

5. Do you need to review detailed results for each section in order to understand the summary?
Yes | No | Maybe

6. Do you find the details on existing randomised trials useful?
Yes | No | Maybe

7. Do you find the details on meta-analysis of observational evidence useful?
Yes | No | Maybe

8. Do you find the details on target trial emulation useful?
Yes | No | Maybe

9. Do you find the details on genetic evidence (Mendelian randomisation) useful?
Yes | No | Maybe

10. Would you discuss the results for the Informatics Consult report with your patient?
Yes | No | Maybe