Simulation Report

ROADMAP: RandOmised Arthroplasty infection worlDwide Multidomain Adaptive Platform trial - simulation report

Investigator initiated, Randomised Embedded Multifactorial Adaptive Platform (REMAP) trial, conducted across multiple hospitals in several regions of the world.

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Sponsor:	University of Newcastle, NSW, Australia
Registration (ANZCTR):	todo
HREC	todo
Chief Investigator(s):	Professor Joshua Davis Professor Laurens Manning

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Study title:	ROADMAP: RandOmised Arthroplasty infection worlDwide Multidomain Adaptive Platform trial
Intervention:	Surgery type, backbone antibiotic duration, extended prophylaxis, antibiotic type
Study design:	Randomised Embedded Multifactorial Adaptive Platform trial
Sponsor:	University of Newcastle, NSW, Australia
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Version history

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## Local:    main /Users/mark/Documents/project/roadmap/src/roadmap-sap
## Remote:   main @ origin (https://github.com/maj-biostat/roadmap-sap.git)
## Head:     [85f0e55] 2025-06-19: WIP
##
## Branches:          1
## Tags:              0
## Commits:          35
## Contributors:      1
## Stashes:           0
## Ignored files:     2
## Untracked files: 25
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##
## Latest commits:
## [85f0e55] 2025-06-19: WIP
## [4b05961] 2025-06-19: Update to sim report
## [c3dcfe7] 2025-06-18: Add command runner
## [bf83562] 2025-06-18: Update fontsize
## [7368517] 2025-06-18: WIP
```

Preface

This simulation report documents the current set of simulations for the operating characteristics of the ROADMAP study. The simulation report is an operational document that will be updated, as necessary, over the course of the study. It should be read in conjunction with the relevant version of the statistical analysis plan (also contained in this respository).

In this report, reference to the current statistical analysis report, means reference to SAP version 0.2.

1 Introduction

Data generation assumptions, modelling approaches, scenarios and results that were used to explore the ROADMAP design operating characteristics.

2 Data generation

Data is generated based on the empirical distributions obtained from the PIANO study, Browning et al. (2022) and domain experts. The data generated process is a simplification of reality but aims to capture the essential elements of the design. The distributional assumptions of each data component follows.

We simulate silo membership from a multinomial distribution with probabilities 0.3, 0.5 and 0.2 for early, late and chronic. Site of infection is not modelled as decisions are to be made on the overall pattern of response rather than joint specific estimates.

Each of the domain intervention allocations are simulated independently and then design rules are use to enforce the logical structure. We simulate both domain entry and allocation. All participants are assumed to enter into the surgical domain, albeit some receive non-randomised treatment.

For the surgical domain, we simulate clinical preference of revision type from a multinomial distribution with probabilities 0.65, 0.35 (rev(1), rev(2) | early), 0.3, 0.7 (rev(1), rev(2) | late), 0.25, 0.75 (rev(1), rev(2) | chronic). Surgical intervention allocations are simultated based on a binomial distribution with probabilities 0.15 (revision | early), 0.5 (revision | late), 0.8 (revision | chronic). The revision indicator is subsequently decomposed into one and two-stage based on the value of preferences.

For the antibiotic duration domain, we simulate entry from a binomial random variable with a probability of 0.7 across all silos and allocation to randomised treatment is 1:1 across all silos. For the extended prophylaxis domain, we simulate entry from a binomial random variable with a probability of 0.9 across all silos and allocation to randomised treatment is 1:1 across all silos. For the antibiotic choice domain, we simulate entry from a binomial random variable with a probability of 0.6 across all silos and allocation to randomised treatment is 1:1 across all silos.

Based on the unconditional entry and allocations, we overlay the design rules. For the surgical domain, allocation to the control state maps assignment to DAIR and allocation to revision maps to revision type based on preference.

For the antibiotic duration domain, if one-stage has been assigned as the revision type, then conditional on the entry indicator, the participant is assigned to non-randomised treatment or the allocation level.

For the extended prophylaxis domain, if two-stage has been assigned as the revision type, then conditional on the entry indicator, the participant is assigned to non-randomised treatment or the allocation level.

For the antibiotic choice domain, conditional on the entry indicator, the participant is assigned to non-randomised treatment or the allocation level.

The data is generated sequentially at the start of each interim analysis. As the trial progresses, decisions may be made which lead to some allocations being shut off and thus restricting the possible assignments.

The linear predictor is constructed conditional on the surgical domain intervention, see Section 3. Treatment success is simulated as a bernoulli random variable with probability equal to the inverse logit transform of the log-odds from the linear predictor. To speed up the model, we aggregate number of successes and number of trials by covariate group which gives the analogous binomial random variable representation.

3 Modelling

In order to reduce computational burden, we use a simplified version of the primary analysis model presented in the statistical analysis plan, section 2.6. For the simulations, we have a single, multivariable logistic regression model with a linear predictor that incorporates all domains and is specified as follows:

$$
\begin{aligned}
Y &\sim \text{Binomial}(\pi, n) \\
\text{logit}(\pi) &= \alpha + \lambda_s + \delta \\
\delta &= \begin{cases} \beta_{1[d1,s]} + \beta_{4[d4]} + \phi_p & \text{(dair)} \\ \beta_{1[d1,s]} + \beta_{2[d2]} + \beta_{4[d4]} & \text{(one-stage)} \\ \beta_{1[d1,s]} + \beta_{3[d3]} + \beta_{4[d4]} + \phi_p & \text{(two-stage)} \end{cases}
\end{aligned}
$$

where Y is a binomial variable for the number of events out of n trials for a distinct covariate pattern occurring with probability π calculated from the linear predictor as follows:

- α reference level log-odds of a successful outcome
- λ_s silo membership s
- $\beta_{1[d_1,s]}$ surgical intervention d_1 in silo s
- $\beta_{2[d_2]}$ backbone antibiotic duration intervention d_2
- $\beta_{3[d_3]}$ extended prophylaxis duration intervention d_3
- $\beta_{4[d_4]}$ antibiotic choice intervention d_4
- ϕ_p surgeon preference for one/two stage, p, assuming unit randomised to revision

Relative to the primary analysis model, the simulation model is constructed with a binomial likelihood and excludes terms for time, region, site and prognostic variables. The manner in which terms enter the model is convoluted and understanding the dependency implications and consequently care is needed with the data preparation.

Bar the surgical domain, for which 'by silo' deviations are implicit in the existing parameterisation, no further interactions are included.

4 Decision procedures

Decision procedures follow those that are documented in the current SAP. In brief, at each interim, we assess the posterior and if a decision threshold is met, we make claims as directed by the results. Within the simulations, we assume the decisions are binding and constrain the subsequent data generation options. Specifically, if a superiority decision is reached in one of the domains for which this decision type is relevant, then we consider that domain complete and all subsequent participants are assigned to receive the superior intervention. Non-inferiority is handled in an analogous manner. If a futility decision is reached (either for superiority of non-inferiority, as applicable for the given domain) then we consider that domain completed and all subsequent participants are assigned to receive the reference intervention.

In all cases, we continue to update the full joint posterior until we get to the point where all questions have been answered across all domains, at which point the trial will stop.

5 Scenarios

Each scenario adopted a maximum sample size of 2500 with interim analyses run after each 500 participants reach the primary endpoint. For simplicity, the treatment effects were specified on the log odds scale with treatment effects calibrated to target the domain level treatment effects in terms of risk differences. All scenarios used the same reference values and decision thresholds. After a long period of iteration, Table 5.1 shows the current set of simulation scenarios considered as the reference set for the design.

Table 5.1: ROADMAP simulation scenarios

ID	Scenario
1	RD = 0 in all domains +silo specific d1
2	RD = 0.12: surgical revision (one and two-stage) +silo specific d1
3	RD = 0.12: surgical revision (one-stage only) +silo specific d1
4	RD = 0.12: surgical revision (two-stage only) +silo specific d1
5	RD = 0.12: abx duration 6wk effect +silo specific d1
6	RD = 0.12: ext-proph 12wk effect +silo specific d1
7	RD = 0.12: abx choice rif effect +silo specific d1
8	RD = 0.12: all domains +silo specific d1
9	RD = -0.05: abx duration 6wk effect +silo specific d1
10	RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1

6 Results

6.1 Probability of triggering decisions

Table 6.1 provides the cumulative probability of decision types by domain. For the Surgical, Extended prophylaxis and Choice domains, the results indicate the cumulative probability of a superiority decision with the probability of futility for the superiority decisions in parentheses. For the Antibiotic duration domain, the results indicate the cumulative probability of a non-inferiority decision with the probability of futility for the non-inferiority decisions in parentheses.

Table 6.1: Cumulative probability of decision at each interim (enrolment by interim)

		Cumulative probability of decision as applicable to domain				
Domain	Decision type	500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1						
Surgical	Superiority (fut)	0.018 (0.515)	0.034 (0.692)	0.049 (0.777)	0.059 (0.826)	0.068 (0.857)
AB Duration	NI (fut)	0.142 (0.09)	0.226 (0.136)	0.284 (0.175)	0.329 (0.195)	0.363 (0.212)
AB Ext-proph	Superiority (fut)	0.039 (0.534)	0.062 (0.67)	0.074 (0.744)	0.086 (0.786)	0.092 (0.818)
AB Choice	Superiority (fut)	0.017 (0.64)	0.026 (0.828)	0.03 (0.898)	0.034 (0.936)	0.036 (0.952)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1						
Surgical	Superiority (fut)	0.316 (0.09)	0.555 (0.11)	0.712 (0.121)	0.793 (0.123)	0.836 (0.125)
AB Duration	NI (fut)	0.146 (0.082)	0.261 (0.145)	0.334 (0.19)	0.398 (0.22)	0.45 (0.236)
AB Ext-proph	Superiority (fut)	0.043 (0.548)	0.065 (0.735)	0.081 (0.82)	0.088 (0.865)	0.092 (0.888)
AB Choice	Superiority (fut)	0.01 (0.654)	0.019 (0.832)	0.024 (0.906)	0.028 (0.937)	0.03 (0.954)
RD = 0.12: surgical revision (one-stage only) +silo specific d1						
Surgical	Superiority (fut)	0.042 (0.406)	0.086 (0.543)	0.122 (0.629)	0.147 (0.684)	0.164 (0.71)
AB Duration	NI (fut)	0.143 (0.092)	0.238 (0.142)	0.299 (0.172)	0.347 (0.192)	0.386 (0.21)
AB Ext-proph	Superiority (fut)	0.031 (0.535)	0.052 (0.69)	0.064 (0.778)	0.075 (0.83)	0.08 (0.854)
AB Choice	Superiority (fut)	0.01 (0.654)	0.016 (0.822)	0.019 (0.897)	0.023 (0.936)	0.026 (0.955)

Table 6.1: Cumulative probability of decision at each interim (enrolment by interim)

		Cumulative probability of decision as applicable to domain				
Domain	Decision type	500	1000	1500	2000	2500
RD = 0.12: surgical revision (two-stage only) +silo specific d1						
Surgical	Superiority (fut)	0.198 (0.134)	0.378 (0.178)	0.511 (0.203)	0.606 (0.216)	0.67 (0.22)
AB Duration	NI (fut)	0.153 (0.094)	0.234 (0.149)	0.325 (0.177)	0.392 (0.204)	0.443 (0.224)
AB Ext-proph	Superiority (fut)	0.044 (0.558)	0.066 (0.727)	0.081 (0.811)	0.089 (0.857)	0.094 (0.879)
AB Choice	Superiority (fut)	0.01 (0.651)	0.016 (0.826)	0.02 (0.908)	0.024 (0.943)	0.026 (0.959)
RD = 0.12: abx duration 6wk effect +silo specific d1						
Surgical	Superiority (fut)	0.018 (0.532)	0.036 (0.695)	0.054 (0.783)	0.064 (0.83)	0.07 (0.864)
AB Duration	NI (fut)	0.444 (0.011)	0.654 (0.014)	0.77 (0.016)	0.842 (0.018)	0.889 (0.018)
AB Ext-proph	Superiority (fut)	0.042 (0.548)	0.065 (0.686)	0.084 (0.751)	0.093 (0.789)	0.1 (0.816)
AB Choice	Superiority (fut)	0.012 (0.648)	0.018 (0.836)	0.023 (0.905)	0.027 (0.939)	0.029 (0.956)
RD = 0.12: ext-proph 12wk effect +silo specific d1						
Surgical	Superiority (fut)	0.022 (0.492)	0.038 (0.67)	0.047 (0.764)	0.058 (0.815)	0.068 (0.85)
AB Duration	NI (fut)	0.138 (0.083)	0.22 (0.131)	0.285 (0.165)	0.325 (0.188)	0.358 (0.205)
AB Ext-proph	Superiority (fut)	0.366 (0.088)	0.586 (0.108)	0.709 (0.115)	0.769 (0.118)	0.819 (0.121)
AB Choice	Superiority (fut)	0.011 (0.648)	0.019 (0.826)	0.025 (0.904)	0.03 (0.94)	0.03 (0.953)
RD = 0.12: abx choice rif effect +silo specific d1						
Surgical	Superiority (fut)	0.02 (0.558)	0.034 (0.727)	0.048 (0.798)	0.06 (0.838)	0.068 (0.866)
AB Duration	NI (fut)	0.144 (0.091)	0.226 (0.131)	0.283 (0.164)	0.339 (0.186)	0.375 (0.21)
AB Ext-proph	Superiority (fut)	0.044 (0.538)	0.065 (0.691)	0.076 (0.76)	0.084 (0.798)	0.09 (0.831)
AB Choice	Superiority (fut)	0.458 (0.03)	0.811 (0.031)	0.932 (0.032)	0.964 (0.032)	0.968 (0.032)
RD = 0.12: all domains +silo specific d1						
Surgical	Superiority (fut)	0.367 (0.05)	0.597 (0.068)	0.742 (0.079)	0.817 (0.086)	0.861 (0.087)
AB Duration	NI (fut)	0.486 (0.012)	0.784 (0.013)	0.91 (0.013)	0.954 (0.013)	0.978 (0.013)
AB Ext-proph	Superiority (fut)	0.424 (0.072)	0.733 (0.088)	0.854 (0.092)	0.896 (0.095)	0.905 (0.095)
AB Choice	Superiority (fut)	0.467 (0.03)	0.817 (0.04)	0.921 (0.04)	0.952 (0.04)	0.959 (0.04)
RD = -0.05: abx duration 6wk effect +silo specific d1						
Surgical	Superiority (fut)	0.02 (0.515)	0.034 (0.68)	0.051 (0.771)	0.062 (0.821)	0.067 (0.858)
AB Duration	NI (fut)	0.078 (0.163)	0.113 (0.248)	0.143 (0.319)	0.156 (0.367)	0.171 (0.413)
AB Ext-proph	Superiority (fut)	0.032 (0.541)	0.056 (0.694)	0.075 (0.766)	0.081 (0.808)	0.087 (0.84)
AB Choice	Superiority (fut)	0.012 (0.66)	0.018 (0.827)	0.024 (0.899)	0.027 (0.943)	0.028 (0.962)
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1						
Surgical	Superiority (fut)	0.304 (0.065)	0.556 (0.09)	0.703 (0.098)	0.794 (0.103)	0.845 (0.106)

Table 6.1: Cumulative probability of decision at each interim (enrolment by interim)

		Cumulative probability of decision as applicable to domain				
Domain	Decision type	500	1000	1500	2000	2500
AB Duration	NI (fut)	0.153 (0.094)	0.269 (0.142)	0.352 (0.178)	0.412 (0.201)	0.463 (0.22)
AB Ext-proph	Superiority (fut)	0.035 (0.56)	0.058 (0.74)	0.071 (0.842)	0.077 (0.881)	0.08 (0.9)
AB Choice	Superiority (fut)	0.472 (0.036)	0.817 (0.04)	0.928 (0.04)	0.96 (0.04)	0.967 (0.04)

6.2 Sample size

6.2.1 Expected sample size for randomised comparisons

Table 6.2 and Figure 6.1 show the expected sample size by interim analysis for the randomised comparisons in each domain. When domain level decisions are triggered, subsequent enrolments are redirected to the remaining arms, which leads to the observed divergence between arms. The figures are to give a sense of how much information is available for estimating quantities that lead to trial decisions.

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1						
Surgical	DAIR	125	302	471	624	758
Surgical	rev(1)	37	56	68	77	83
Surgical	rev(2)	88	131	160	180	195
Surgical	Revision	125	188	228	256	278
AB Duration	12 weeks	25	42	56	67	76
AB Duration	6 weeks	25	44	60	72	83
AB Ext-proph	6 weeks	70	143	204	256	299
AB Ext-proph	12 weeks	70	94	110	121	130
AB Choice	No-rif	150	381	605	806	982
AB Choice	Rif	150	206	234	251	262
RD = 0.12: surgical revision (one and two-stage) +silo specific d1						
Surgical	DAIR	125	220	283	323	351
Surgical	rev(1)	37	81	124	159	188

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
Surgical	rev(2)	87	189	287	371	437
Surgical	Revision	125	271	411	530	625
AB Duration	12 weeks	25	51	74	93	108
AB Duration	6 weeks	25	54	80	101	118
AB Ext-proph	6 weeks	70	182	294	390	467
AB Ext-proph	12 weeks	70	109	135	153	165
AB Choice	No-rif	150	385	603	779	915
AB Choice	Rif	150	203	230	245	255
RD = 0.12: surgical revision (one-stage only) +silo specific d1						
Surgical	DAIR	125	288	440	576	695
Surgical	rev(1)	37	61	80	94	106
Surgical	rev(2)	87	142	186	221	247
Surgical	Revision	125	204	266	315	353
AB Duration	12 weeks	25	44	60	72	83
AB Duration	6 weeks	25	46	65	80	93
AB Ext-proph	6 weeks	70	151	225	289	342
AB Ext-proph	12 weeks	70	97	115	127	136
AB Choice	No-rif	150	386	616	821	999
AB Choice	Rif	150	203	231	248	258
RD = 0.12: surgical revision (two-stage only) +silo specific d1						
Surgical	DAIR	125	239	330	401	454
Surgical	rev(1)	37	76	113	145	171
Surgical	rev(2)	87	177	263	338	399
Surgical	Revision	125	253	377	483	570
AB Duration	12 weeks	25	49	71	90	104
AB Duration	6 weeks	25	52	77	98	115
AB Ext-proph	6 weeks	70	175	282	375	452
AB Ext-proph	12 weeks	70	104	128	145	157
AB Choice	No-rif	150	387	617	815	974
AB Choice	Rif	150	204	232	247	255
RD = 0.12: abx duration 6wk effect +silo specific d1						
Surgical	DAIR	125	292	427	529	604
Surgical	rev(1)	37	56	67	74	78
Surgical	rev(2)	87	129	156	172	183
Surgical	Revision	125	185	223	246	262

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
AB Duration	12 weeks	25	36	41	44	47
AB Duration	6 weeks	25	49	69	82	92
AB Ext-proph	6 weeks	70	140	191	227	252
AB Ext-proph	12 weeks	70	94	108	118	125
AB Choice	No-rif	150	368	550	687	787
AB Choice	Rif	150	204	229	243	251
RD = 0.12: ext-proph 12wk effect +silo specific d1						
Surgical	DAIR	125	301	474	629	763
Surgical	rev(1)	38	57	71	80	87
Surgical	rev(2)	87	134	164	185	201
Surgical	Revision	125	191	234	265	288
AB Duration	12 weeks	25	43	57	68	78
AB Duration	6 weeks	25	45	61	74	85
AB Ext-proph	6 weeks	70	107	128	142	152
AB Ext-proph	12 weeks	70	133	192	243	286
AB Choice	No-rif	150	386	618	824	1,003
AB Choice	Rif	150	204	232	248	259
RD = 0.12: abx choice rif effect +silo specific d1						
Surgical	DAIR	125	308	478	625	752
Surgical	rev(1)	38	55	66	73	79
Surgical	rev(2)	88	128	154	172	186
Surgical	Revision	125	183	219	245	265
AB Duration	12 weeks	25	42	55	65	73
AB Duration	6 weeks	25	44	59	71	81
AB Ext-proph	6 weeks	70	140	199	248	288
AB Ext-proph	12 weeks	70	95	109	119	127
AB Choice	No-rif	150	234	265	277	282
AB Choice	Rif	150	354	571	767	938
RD = 0.12: all domains +silo specific d1						
Surgical	DAIR	125	208	259	286	302
Surgical	rev(1)	37	83	114	129	135
Surgical	rev(2)	88	195	267	301	315
Surgical	Revision	125	278	381	430	450
AB Duration	12 weeks	25	40	47	50	51
AB Duration	6 weeks	25	65	95	110	117

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
AB Ext-proph	6 weeks	70	122	145	154	156
AB Ext-proph	12 weeks	70	172	251	291	311
AB Choice	No-rif	150	234	261	270	273
AB Choice	Rif	150	350	507	589	630
RD = -0.05: abx duration 6wk effect +silo specific d1						
Surgical	DAIR	125	301	471	620	749
Surgical	rev(1)	37	56	69	78	85
Surgical	rev(2)	88	131	161	182	198
Surgical	Revision	125	187	229	260	282
AB Duration	12 weeks	25	45	61	74	85
AB Duration	6 weeks	25	42	55	66	75
AB Ext-proph	6 weeks	70	143	207	260	303
AB Ext-proph	12 weeks	70	94	110	120	127
AB Choice	No-rif	150	384	610	808	981
AB Choice	Rif	150	203	231	247	257
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1						
Surgical	DAIR	125	219	279	319	346
Surgical	rev(1)	37	82	125	160	187
Surgical	rev(2)	88	192	292	373	438
Surgical	Revision	125	274	417	533	625
AB Duration	12 weeks	25	51	75	93	108
AB Duration	6 weeks	25	54	81	102	118
AB Ext-proph	6 weeks	70	186	301	398	475
AB Ext-proph	12 weeks	70	107	132	147	157
AB Choice	No-rif	150	234	265	278	284
AB Choice	Rif	150	358	570	745	881

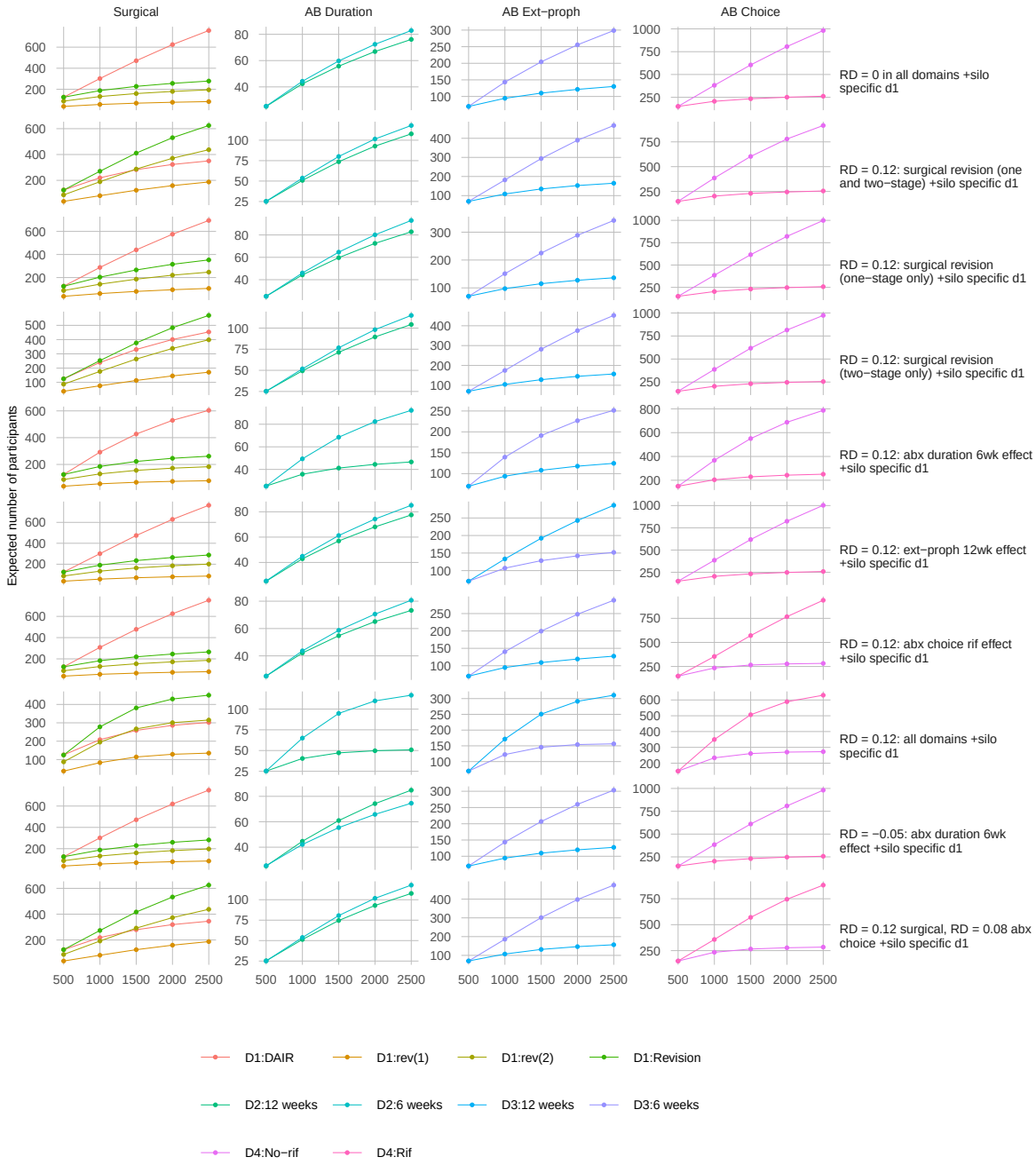

Figure 6.1: Expected number of participants entering into randomised comparisons

6.2.2 Expected sample size

Table 6.3 shows the expected sample size at which each decision is made by domain and scenario and, in parentheses, the proportion of trials on which the decision type was made.

Table 6.3: Expected number of enrolments by decision type (including reaching maximum sample size)

	Expected number of total enrolments to hit stopping rule by domain			
Decision	Surgical	AB Duration	AB Ext-proph	AB choice
RD = 0 in all domains +silo specific d1				
superiority	1,307 (7%)		1,066 (9%)	1,006 (3%)
futility (sup)	857 (85%)		826 (82%)	764 (95%)
ni		1,151 (36%)		
futility (ni)		1,095 (21%)		
-	2,500 (8%)	2,500 (42%)	2,500 (9%)	2,500 (1%)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1				
superiority	1,069 (83%)		971 (9%)	1,151 (3%)
futility (sup)	707 (12%)		825 (89%)	755 (95%)
ni		1,234 (45%)		
futility (ni)		1,152 (24%)		
-	2,500 (5%)	2,500 (31%)	2,500 (2%)	2,500 (2%)
RD = 0.12: surgical revision (one-stage only) +silo specific d1				
superiority	1,276 (16%)		1,088 (8%)	1,164 (3%)
futility (sup)	900 (71%)		841 (85%)	767 (95%)
ni		1,170 (39%)		
futility (ni)		1,073 (21%)		
-	2,500 (13%)	2,500 (40%)	2,500 (7%)	2,500 (2%)
RD = 0.12: surgical revision (two-stage only) +silo specific d1				
superiority	1,232 (67%)		996 (9%)	1,138 (3%)
futility (sup)	836 (22%)		814 (87%)	764 (96%)
ni		1,254 (44%)		
futility (ni)		1,107 (22%)		
-	2,500 (11%)	2,500 (33%)	2,500 (4%)	2,500 (2%)
RD = 0.12: abx duration 6wk effect +silo specific d1				
superiority	1,256 (7%)		1,059 (10%)	1,106 (3%)
futility (sup)	854 (86%)		799 (82%)	759 (96%)

Table 6.3: Expected number of enrolments by decision type (including reaching maximum sample size)

	Expected number of total enrolments to hit stopping rule by domain			
Decision	Surgical	AB Duration	AB Ext-proph	AB choice
ni		976 (89%)		
futility (ni)		818 (2%)		
-	2,500 (7%)	2,500 (9%)	2,500 (9%)	2,500 (2%)
RD = 0.12: ext-proph 12wk effect +silo specific d1				
superiority	1,274 (7%)		1,011 (81%)	1,093 (3%)
futility (sup)	884 (85%)		716 (12%)	757 (95%)
ni		1,147 (36%)		
futility (ni)		1,120 (21%)		
-	2,500 (9%)	2,500 (44%)	2,500 (7%)	2,500 (2%)
RD = 0.12: abx choice rif effect +silo specific d1				
superiority	1,296 (7%)		1,011 (9%)	863 (97%)
futility (sup)	809 (86%)		819 (83%)	556 (3%)
ni		1,177 (37%)		
futility (ni)		1,135 (21%)		
-	2,500 (7%)	2,500 (42%)	2,500 (8%)	2,500 (0%)
RD = 0.12: all domains +silo specific d1				
superiority	1,034 (86%)		890 (90%)	854 (96%)
futility (sup)	869 (9%)		671 (9%)	630 (4%)
ni		897 (98%)		
futility (ni)		547 (1%)		
-	2,500 (5%)	2,500 (1%)	2,500 (0%)	2,500 (0%)
RD = -0.05: abx duration 6wk effect +silo specific d1				
superiority	1,242 (7%)		1,091 (9%)	1,086 (3%)
futility (sup)	873 (86%)		824 (84%)	767 (96%)
ni		1,062 (17%)		
futility (ni)		1,173 (41%)		
-	2,500 (8%)	2,500 (42%)	2,500 (8%)	2,500 (1%)
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1				
superiority	1,100 (84%)		977 (8%)	852 (96%)
futility (sup)	816 (11%)		818 (90%)	559 (4%)
ni		1,218 (46%)		
futility (ni)		1,103 (22%)		

Table 6.3: Expected number of enrolments by decision type (including reaching maximum sample size)

	Expected number of total enrolments to hit stopping rule by domain			
Decision	Surgical	AB Duration	AB Ext-proph	AB choice
-	2,500 (5%)	2,500 (32%)	2,500 (2%)	2,500 (0%)

6.3 Parameter estimation

Table 6.4 and Figure 6.2 show the expected value of the posterior means for the treatment effects by domain and interim analyse under each scenario along with the 95% interval of the posterior means.

Table 6.4: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

	Risk difference (expectation of posterior means and 95 pct interval)				
Domain	500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1					
Surgical	0 (-0.13, 0.13)	0 (-0.12, 0.11)	0 (-0.11, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
AB Duration	0 (-0.22, 0.23)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.19, 0.2)
AB Ext-proph	0 (-0.15, 0.16)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	0 (-0.12, 0.12)	0 (-0.12, 0.12)
AB Choice	0 (-0.11, 0.11)	0 (-0.08, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.07)	0 (-0.08, 0.07)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1					
Surgical	0.11 (-0.03, 0.24)	0.11 (-0.01, 0.22)	0.12 (-0.01, 0.22)	0.12 (0, 0.22)	0.12 (0, 0.22)
AB Duration	0 (-0.21, 0.22)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0.01 (-0.19, 0.19)
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.13, 0.12)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)
AB Choice	0 (-0.11, 0.11)	0 (-0.08, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: surgical revision (one-stage only) +silo specific d1					
Surgical	0.02 (-0.12, 0.16)	0.02 (-0.1, 0.15)	0.02 (-0.09, 0.14)	0.02 (-0.08, 0.13)	0.02 (-0.08, 0.13)
AB Duration	0 (-0.22, 0.22)	0 (-0.19, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.18, 0.19)
AB Ext-proph	0 (-0.16, 0.15)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)	-0.01 (-0.13, 0.11)	-0.01 (-0.13, 0.11)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: surgical revision (two-stage only) +silo specific d1					
Surgical	0.08 (-0.06, 0.21)	0.09 (-0.03, 0.2)	0.09 (-0.03, 0.2)	0.09 (-0.02, 0.2)	0.09 (-0.02, 0.2)

Table 6.4: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

	Risk difference (expectation of posterior means and 95 pct interval)				
Domain	500	1000	1500	2000	2500
AB Duration	0 (-0.23, 0.24)	0 (-0.19, 0.21)	0.01 (-0.19, 0.2)	0.01 (-0.18, 0.2)	0.01 (-0.18, 0.2)
AB Ext-proph	0 (-0.15, 0.16)	0 (-0.12, 0.12)	-0.01 (-0.12, 0.12)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)
AB Choice	0 (-0.1, 0.1)	0 (-0.08, 0.08)	0 (-0.07, 0.07)	0 (-0.08, 0.06)	0 (-0.07, 0.06)
RD = 0.12: abx duration 6wk effect +silo specific d1					
Surgical	0 (-0.15, 0.13)	-0.01 (-0.13, 0.12)	-0.01 (-0.13, 0.11)	-0.01 (-0.13, 0.11)	-0.01 (-0.13, 0.11)
AB Duration	0.1 (-0.11, 0.31)	0.12 (-0.07, 0.31)	0.12 (-0.05, 0.31)	0.13 (-0.04, 0.31)	0.13 (-0.02, 0.31)
AB Ext-proph	0 (-0.15, 0.16)	0 (-0.13, 0.13)	0 (-0.13, 0.13)	0 (-0.13, 0.13)	-0.01 (-0.13, 0.13)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.07)	0 (-0.08, 0.06)
RD = 0.12: ext-proph 12wk effect +silo specific d1					
Surgical	0.01 (-0.14, 0.14)	0 (-0.11, 0.11)	0 (-0.11, 0.11)	0 (-0.11, 0.1)	0 (-0.11, 0.1)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.19, 0.2)	0 (-0.2, 0.2)
AB Ext-proph	0.11 (-0.04, 0.26)	0.12 (-0.01, 0.25)	0.12 (-0.01, 0.24)	0.12 (-0.01, 0.24)	0.12 (-0.01, 0.24)
AB Choice	0 (-0.1, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: abx choice rif effect +silo specific d1					
Surgical	0 (-0.14, 0.13)	-0.01 (-0.12, 0.11)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
AB Duration	0 (-0.21, 0.21)	0 (-0.19, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.13, 0.13)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)
AB Choice	0.12 (0.02, 0.22)	0.12 (0.04, 0.2)	0.12 (0.05, 0.2)	0.12 (0.06, 0.2)	0.12 (0.06, 0.2)
RD = 0.12: all domains +silo specific d1					
Surgical	0.12 (-0.02, 0.24)	0.12 (-0.01, 0.22)	0.12 (0, 0.22)	0.12 (0, 0.22)	0.12 (0, 0.22)
AB Duration	0.09 (-0.1, 0.28)	0.11 (-0.04, 0.28)	0.12 (-0.01, 0.28)	0.12 (0, 0.28)	0.12 (0.01, 0.28)
AB Ext-proph	0.11 (-0.02, 0.25)	0.12 (0.01, 0.24)	0.12 (0.01, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.23)
AB Choice	0.12 (0.02, 0.21)	0.12 (0.03, 0.2)	0.12 (0.04, 0.19)	0.12 (0.05, 0.19)	0.12 (0.05, 0.19)
RD = -0.05: abx duration 6wk effect +silo specific d1					
Surgical	0 (-0.14, 0.13)	0 (-0.12, 0.11)	0 (-0.12, 0.11)	0 (-0.12, 0.1)	-0.01 (-0.12, 0.1)
AB Duration	-0.04 (-0.26, 0.19)	-0.04 (-0.24, 0.16)	-0.05 (-0.23, 0.15)	-0.05 (-0.23, 0.15)	-0.05 (-0.23, 0.15)
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)	-0.01 (-0.13, 0.12)
AB Choice	0 (-0.1, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1					
Surgical	0.11 (-0.03, 0.23)	0.11 (0, 0.22)	0.11 (0, 0.21)	0.11 (0, 0.21)	0.12 (0.01, 0.21)
AB Duration	0 (-0.2, 0.21)	0 (-0.18, 0.19)	0 (-0.17, 0.18)	0.01 (-0.17, 0.18)	0.01 (-0.17, 0.18)

Table 6.4: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

	Risk difference (expectation of posterior means and 95 pct interval)				
Domain	500	1000	1500	2000	2500
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.11, 0.11)	0 (-0.11, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.09)
AB Choice	0.12 (0.01, 0.22)	0.12 (0.04, 0.2)	0.12 (0.05, 0.2)	0.12 (0.06, 0.2)	0.12 (0.06, 0.2)

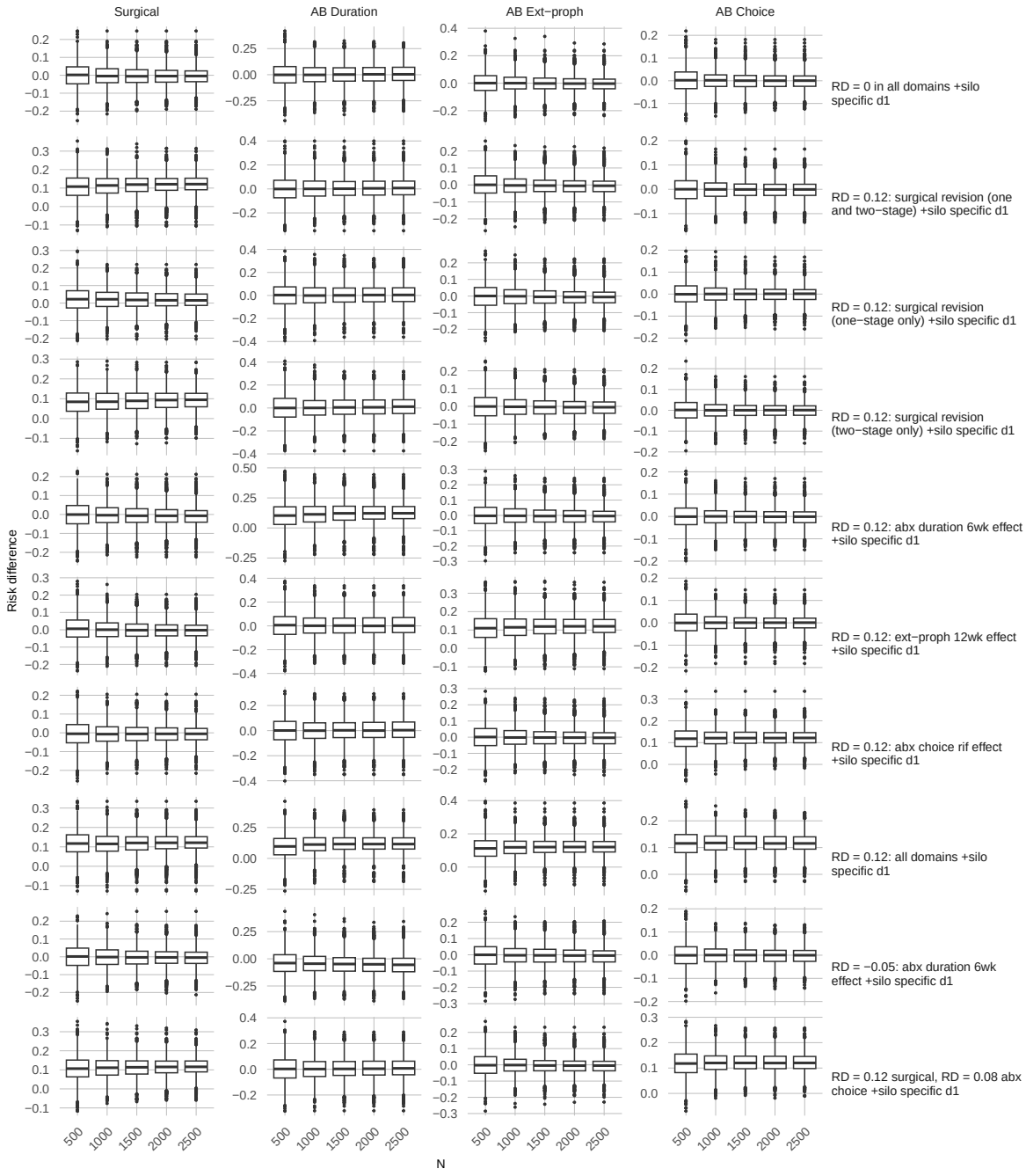

Figure 6.2: Expectation of posterior means for risk difference treatment effects by domain and simulation scenario

6.4 Observed proportion with treatment success

Table 6.5 shows the observed proportion with treatment success by domain and treatment arm. For simplicity, the treatment arms have been represented generically by the numbers 1 to 3 and have a domain specific interpretation.

For the surgical domain, 1 corresponds to DAIR, 2 corresponds to one-stage revision and 3 corresponds to two-stage revision. For the antibiotic duration domain, 2 corresponds to 12 weeks and 3 corresponds to 6 weeks. For the extended prophylaxis domain, 2 corresponds to 6 weeks and 3 corresponds to 12 weeks. For the antibiotic choice domain, 2 corresponds to no rifampacin and 3 corresponds to rifampacin.

Table 6.5: Observed proportion with treatment success

Empirical risk by domain and treatment arm			
Domain	1	2	3
RD = 0 in all domains +silo specific d1			
Surgical	0.59	0.62	0.57
AB Duration	-	0.65	0.65
AB Ext-proph	-	0.6	0.6
AB Choice	-	0.62	0.62
RD = 0.12: surgical revision (one and two-stage) +silo specific d1			
Surgical	0.56	0.71	0.67
AB Duration	-	0.7	0.7
AB Ext-proph	-	0.65	0.65
AB Choice	-	0.64	0.64
RD = 0.12: surgical revision (one-stage only) +silo specific d1			
Surgical	0.56	0.68	0.55
AB Duration	-	0.67	0.68
AB Ext-proph	-	0.59	0.58
AB Choice	-	0.61	0.61
RD = 0.12: surgical revision (two-stage only) +silo specific d1			
Surgical	0.56	0.6	0.68
AB Duration	-	0.63	0.63
AB Ext-proph	-	0.66	0.66
AB Choice	-	0.63	0.63

Table 6.5: Observed proportion with treatment success

Empirical risk by domain and treatment arm			
Domain	1	2	3
RD = 0.12: abx duration 6wk effect +silo specific d1			
Surgical	0.59	0.66	0.57
AB Duration	-	0.62	0.75
AB Ext-proph	-	0.6	0.6
AB Choice	-	0.62	0.62
RD = 0.12: ext-proph 12wk effect +silo specific d1			
Surgical	0.59	0.62	0.62
AB Duration	-	0.65	0.65
AB Ext-proph	-	0.58	0.7
AB Choice	-	0.63	0.63
RD = 0.12: abx choice rif effect +silo specific d1			
Surgical	0.62	0.65	0.61
AB Duration	-	0.69	0.69
AB Ext-proph	-	0.63	0.63
AB Choice	-	0.6	0.72
RD = 0.12: all domains +silo specific d1			
Surgical	0.6	0.79	0.76
AB Duration	-	0.71	0.83
AB Ext-proph	-	0.67	0.78
AB Choice	-	0.65	0.76
RD = -0.05: abx duration 6wk effect +silo specific d1			
Surgical	0.59	0.62	0.57
AB Duration	-	0.67	0.62
AB Ext-proph	-	0.6	0.6
AB Choice	-	0.62	0.62
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1			
Surgical	0.6	0.75	0.71
AB Duration	-	0.74	0.74
AB Ext-proph	-	0.69	0.69
AB Choice	-	0.62	0.74

6.5 References

Browning, S., Manning, L., Metcalf, S., Paterson, D., Robinson, J., Clark, B., Davis, J., 2022. Characteristics and outcomes of culture-negative prosthetic joint infections from the prosthetic joint infection in australia and new zealand observational (PIANO) cohort study. Journal of Bone and Joint Infection 7, 203–211. https://doi.org/10.5194/jbji-7-203-2022