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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Registration (ANZCTR):	todo
HREC	todo
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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
Protocol:	Version 1.1 01AUG2024
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Study date of first consent:	todo
Principal coordinating investigators:	Professor Joshua Davis and Professor Laurens Manning

Version history

Version	Date	Change	Reason
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Repository status

```
## Local:    main /Users/mark/Documents/project/roadmap/src/roadmap-sap
## Remote:   main @ origin (https://github.com/maj-biostat/roadmap-sap.git)
## Head:     [26ec601] 2025-06-24: Update reference to decision quantities in sap
##
## Branches:        1
## Tags:            0
## Commits:        47
## Contributors:    1
## Stashes:         0
## Ignored files:   2
## Untracked files: 24
## Unstaged files:  2
## Staged files:    0
##
## Latest commits:
## [26ec601] 2025-06-24: Update reference to decision quantities in sap
## [0f45713] 2025-06-24: Correct NI decision probability
## [feaa7ce] 2025-06-24: Fix opening introduction
## [e843969] 2025-06-24: Update rendered versions
## [9c5f442] 2025-06-24: Prioritise notes
```

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.

These results are based on simulation ID sim07-05 with 10000 trials run per scenario.

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:

$$Y \sim \text{Binomial}(\pi, n)$$

$$\text{logit}(\pi) = \alpha + \lambda_s + \delta$$

$$\delta = \begin{cases} \beta_{1[d1,s]} + \beta_{4[d4]} + \phi_p & \text{(dair)} \\ \beta_{1[d1,s]} + \beta_{2[d2]} + \beta_{4[d4]} & \text{(one-stage)} \\ \beta_{1[d1,s]} + \beta_{3[d3]} + \beta_{4[d4]} + \phi_p & \text{(two-stage)} \end{cases}$$

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, including thresholds and decision probabilities, follow those that are documented in the current SAP. 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)

| Domain | Decision type | Cumulative probability of decision as applicable to domain | | | | |
		500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1						
Surgical	Superiority (fut)	0.021 (0.538)	0.037 (0.709)	0.051 (0.79)	0.06 (0.839)	0.066 (0.869)
AB Duration	NI (fut)	0.112 (0.088)	0.181 (0.131)	0.231 (0.164)	0.275 (0.185)	0.309 (0.203)
AB Ext-proph	Superiority (fut)	0.04 (0.543)	0.062 (0.685)	0.076 (0.755)	0.085 (0.797)	0.092 (0.824)
AB Choice	Superiority (fut)	0.01 (0.653)	0.016 (0.83)	0.021 (0.905)	0.024 (0.94)	0.027 (0.96)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1						
Surgical	Superiority (fut)	0.318 (0.068)	0.557 (0.091)	0.703 (0.099)	0.795 (0.104)	0.842 (0.105)
AB Duration	NI (fut)	0.115 (0.088)	0.203 (0.145)	0.274 (0.183)	0.336 (0.212)	0.387 (0.231)
AB Ext-proph	Superiority (fut)	0.042 (0.545)	0.067 (0.727)	0.085 (0.818)	0.095 (0.858)	0.1 (0.881)
AB Choice	Superiority (fut)	0.009 (0.661)	0.014 (0.837)	0.02 (0.911)	0.024 (0.946)	0.025 (0.963)
RD = 0.12: surgical revision (one-stage only) +silo specific d1						
Surgical	Superiority (fut)	0.043 (0.393)	0.085 (0.539)	0.117 (0.618)	0.144 (0.671)	0.167 (0.707)
AB Duration	NI (fut)	0.11 (0.092)	0.186 (0.14)	0.243 (0.173)	0.284 (0.194)	0.32 (0.212)
AB Ext-proph	Superiority (fut)	0.037 (0.542)	0.059 (0.69)	0.074 (0.764)	0.086 (0.809)	0.092 (0.837)
AB Choice	Superiority (fut)	0.011 (0.647)	0.019 (0.825)	0.024 (0.901)	0.028 (0.94)	0.03 (0.957)

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

Domain	Decision type	Cumulative probability of decision as applicable to domain				
		500	1000	1500	2000	2500
RD = 0.12: surgical revision (two-stage only) +silo specific d1						
Surgical	Superiority (fut)	0.201 (0.132)	0.379 (0.177)	0.509 (0.202)	0.602 (0.215)	0.664 (0.223)
AB Duration	NI (fut)	0.104 (0.093)	0.185 (0.141)	0.247 (0.177)	0.305 (0.203)	0.353 (0.222)
AB Ext-proph	Superiority (fut)	0.038 (0.545)	0.063 (0.722)	0.079 (0.808)	0.087 (0.854)	0.093 (0.88)
AB Choice	Superiority (fut)	0.01 (0.654)	0.018 (0.832)	0.022 (0.904)	0.026 (0.941)	0.028 (0.959)
RD = 0.12: abx duration 6wk effect +silo specific d1						
Surgical	Superiority (fut)	0.021 (0.518)	0.036 (0.691)	0.049 (0.777)	0.06 (0.827)	0.066 (0.861)
AB Duration	NI (fut)	0.38 (0.012)	0.595 (0.016)	0.717 (0.017)	0.796 (0.018)	0.853 (0.018)
AB Ext-proph	Superiority (fut)	0.038 (0.55)	0.061 (0.692)	0.073 (0.764)	0.082 (0.807)	0.087 (0.835)
AB Choice	Superiority (fut)	0.008 (0.654)	0.016 (0.829)	0.021 (0.906)	0.025 (0.941)	0.027 (0.958)
RD = 0.12: ext-proph 12wk effect +silo specific d1						
Surgical	Superiority (fut)	0.028 (0.486)	0.047 (0.66)	0.061 (0.748)	0.073 (0.801)	0.08 (0.837)
AB Duration	NI (fut)	0.113 (0.087)	0.193 (0.132)	0.241 (0.162)	0.282 (0.184)	0.315 (0.202)
AB Ext-proph	Superiority (fut)	0.385 (0.088)	0.607 (0.106)	0.72 (0.113)	0.785 (0.118)	0.822 (0.119)
AB Choice	Superiority (fut)	0.009 (0.664)	0.017 (0.831)	0.022 (0.905)	0.026 (0.942)	0.029 (0.958)
RD = 0.12: abx choice rif effect +silo specific d1						
Surgical	Superiority (fut)	0.019 (0.538)	0.035 (0.71)	0.045 (0.795)	0.055 (0.842)	0.062 (0.871)
AB Duration	NI (fut)	0.107 (0.09)	0.176 (0.138)	0.227 (0.17)	0.268 (0.193)	0.305 (0.21)
AB Ext-proph	Superiority (fut)	0.042 (0.545)	0.062 (0.688)	0.075 (0.758)	0.083 (0.805)	0.09 (0.831)
AB Choice	Superiority (fut)	0.458 (0.037)	0.802 (0.04)	0.925 (0.041)	0.954 (0.042)	0.96 (0.042)
RD = 0.12: all domains +silo specific d1						
Surgical	Superiority (fut)	0.38 (0.046)	0.618 (0.063)	0.753 (0.07)	0.828 (0.074)	0.872 (0.077)
AB Duration	NI (fut)	0.417 (0.007)	0.728 (0.009)	0.878 (0.009)	0.946 (0.01)	0.97 (0.01)
AB Ext-proph	Superiority (fut)	0.434 (0.074)	0.74 (0.089)	0.861 (0.093)	0.896 (0.094)	0.907 (0.094)
AB Choice	Superiority (fut)	0.473 (0.035)	0.815 (0.04)	0.924 (0.041)	0.953 (0.041)	0.96 (0.041)
RD = -0.05: abx duration 6wk effect +silo specific d1						
Surgical	Superiority (fut)	0.019 (0.533)	0.036 (0.695)	0.048 (0.778)	0.059 (0.826)	0.066 (0.859)
AB Duration	NI (fut)	0.058 (0.166)	0.09 (0.26)	0.109 (0.324)	0.124 (0.374)	0.135 (0.414)
AB Ext-proph	Superiority (fut)	0.035 (0.547)	0.057 (0.684)	0.069 (0.755)	0.078 (0.801)	0.085 (0.832)
AB Choice	Superiority (fut)	0.011 (0.651)	0.016 (0.835)	0.019 (0.91)	0.023 (0.944)	0.025 (0.961)
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1						
Surgical	Superiority (fut)	0.322 (0.07)	0.566 (0.091)	0.709 (0.101)	0.792 (0.107)	0.842 (0.11)

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

| Domain | Decision type | Cumulative probability of decision as applicable to domain |
		500	1000	1500	2000	2500
AB Duration	NI (fut)	0.114 (0.091)	0.206 (0.142)	0.281 (0.179)	0.344 (0.204)	0.4 (0.223)
AB Ext-proph	Superiority (fut)	0.038 (0.56)	0.062 (0.743)	0.077 (0.832)	0.086 (0.873)	0.091 (0.895)
AB Choice	Superiority (fut)	0.482 (0.032)	0.828 (0.035)	0.936 (0.035)	0.963 (0.036)	0.968 (0.036)

6.2 Sample size

6.2.1 Randomised comparisons

Table 6.2 and Figure 6.1 show the expected sample size by interim analysis for the randomised comparisons within 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. Subsequent tables give the expected number of participants by treatment group within each domain when a decision is triggered.

Table 6.2: Expected number of participants entering into randomised comparisons

| Domain | Treatment arm | Expected sample size for randomised comparisons by enrolment |
		500	1000	1500	2000	2500
*RD = 0 in all domains +silo specific d1*
Surgical	DAIR	125	305	480	640	784
Surgical	rev(1)	37	55	67	76	82
Surgical	rev(2)	88	129	157	177	191
Surgical	Revision	125	185	224	252	273
AB Duration	12 wks	25	43	57	68	78
AB Duration	6 wks	25	44	59	71	82
AB Ext-proph	none	70	141	203	256	301
AB Ext-proph	12 wks	70	95	110	121	130
AB Choice	no-rif	150	384	614	825	1,012
AB Choice	rif	150	203	231	246	257
*RD = 0.12: surgical revision (one and two-stage) +silo specific d1*
Surgical	DAIR	125	217	280	321	350

Table 6.2: Expected number of participants entering into randomised comparisons

Domain	Treatment arm	Expected sample size for randomised comparisons by enrolment				
		500	1000	1500	2000	2500
Surgical	rev(1)	37	82	127	166	198
Surgical	rev(2)	87	192	296	387	462
Surgical	Revision	125	274	423	553	660
AB Duration	12 wks	25	52	77	98	115
AB Duration	6 wks	25	53	80	103	121
AB Ext-proph	none	70	184	302	407	494
AB Ext-proph	12 wks	70	109	136	155	169
AB Choice	no-rif	150	388	615	807	961
AB Choice	rif	150	202	228	242	250

RD = 0.12: surgical revision (one-stage only) +silo specific d1

Domain	Treatment arm	500	1000	1500	2000	2500
Surgical	DAIR	125	286	442	584	711
Surgical	rev(1)	38	62	80	96	108
Surgical	rev(2)	87	144	188	223	252
Surgical	Revision	125	205	268	318	360
AB Duration	12 wks	25	45	62	76	87
AB Duration	6 wks	25	46	63	79	92
AB Ext-proph	none	70	152	227	293	350
AB Ext-proph	12 wks	70	98	115	128	138
AB Choice	no-rif	150	385	620	834	1,025
AB Choice	rif	150	204	232	249	260

RD = 0.12: surgical revision (two-stage only) +silo specific d1

Domain	Treatment arm	500	1000	1500	2000	2500
Surgical	DAIR	125	239	330	403	459
Surgical	rev(1)	38	77	115	150	180
Surgical	rev(2)	88	179	269	350	419
Surgical	Revision	125	255	384	500	599
AB Duration	12 wks	25	50	74	94	112
AB Duration	6 wks	25	51	76	98	117
AB Ext-proph	none	70	176	287	388	477
AB Ext-proph	12 wks	70	105	130	147	160
AB Choice	no-rif	150	390	627	836	1,014
AB Choice	rif	150	203	230	247	257

RD = 0.12: abx duration 6wk effect +silo specific d1

Domain	Treatment arm	500	1000	1500	2000	2500
Surgical	DAIR	125	293	437	548	631
Surgical	rev(1)	37	56	68	75	80
Surgical	rev(2)	88	131	159	176	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	Revision	125	187	226	252	268
AB Duration	12 wks	25	37	43	48	50
AB Duration	6 wks	25	49	68	83	93
AB Ext-proph	none	70	141	196	236	265
AB Ext-proph	12 wks	70	94	109	118	124
AB Choice	no-rif	150	373	567	717	827
AB Choice	rif	150	203	229	243	251

RD = 0.12: ext-proph 12wk effect +silo specific d1

Surgical	DAIR	125	299	469	624	763
Surgical	rev(1)	38	58	71	81	89
Surgical	rev(2)	88	134	166	189	207
Surgical	Revision	125	192	238	271	296
AB Duration	12 wks	25	44	58	70	80
AB Duration	6 wks	25	44	60	74	85
AB Ext-proph	none	70	106	126	139	148
AB Ext-proph	12 wks	70	135	196	250	297
AB Choice	no-rif	150	387	619	830	1,017
AB Choice	rif	150	202	229	244	253

RD = 0.12: abx choice rif effect +silo specific d1

Surgical	DAIR	125	307	484	641	782
Surgical	rev(1)	38	56	67	75	81
Surgical	rev(2)	87	130	157	176	190
Surgical	Revision	125	185	224	251	271
AB Duration	12 wks	25	43	57	69	78
AB Duration	6 wks	25	44	58	71	81
AB Ext-proph	none	70	143	205	256	300
AB Ext-proph	12 wks	70	94	109	120	128
AB Choice	no-rif	150	236	270	283	291
AB Choice	rif	150	355	579	788	972

RD = 0.12: all domains +silo specific d1

Surgical	DAIR	125	207	256	285	301
Surgical	rev(1)	38	85	117	133	140
Surgical	rev(2)	88	198	274	311	327
Surgical	Revision	125	282	391	444	467
AB Duration	12 wks	25	43	51	55	56

Table 6.2: Expected number of participants entering into randomised comparisons

Domain	Treatment arm	Expected sample size for randomised comparisons by enrolment				
		500	1000	1500	2000	2500
AB Duration	6 wks	25	64	94	109	116
AB Ext-proph	none	70	122	145	153	156
AB Ext-proph	12 wks	70	176	260	305	326
AB Choice	no-rif	150	234	262	271	274
AB Choice	rif	150	353	514	603	648

RD = -0.05: abx duration 6wk effect +silo specific d1

Domain	Treatment arm					
Surgical	DAIR	125	303	474	628	766
Surgical	rev(1)	37	56	68	76	83
Surgical	rev(2)	87	130	158	178	194
Surgical	Revision	125	185	226	255	276
AB Duration	12 wks	25	45	61	75	86
AB Duration	6 wks	25	41	54	64	73
AB Ext-proph	none	70	142	204	256	300
AB Ext-proph	12 wks	70	94	109	120	129
AB Choice	no-rif	150	382	609	814	996
AB Choice	rif	150	204	230	245	255

RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1

Domain	Treatment arm					
Surgical	DAIR	125	217	278	319	347
Surgical	rev(1)	38	83	128	166	198
Surgical	rev(2)	87	193	298	387	460
Surgical	Revision	125	276	425	553	658
AB Duration	12 wks	25	52	77	98	115
AB Duration	6 wks	25	54	81	103	121
AB Ext-proph	none	70	187	307	411	498
AB Ext-proph	12 wks	70	108	133	150	162
AB Choice	no-rif	150	232	261	272	279
AB Choice	rif	150	361	584	774	928
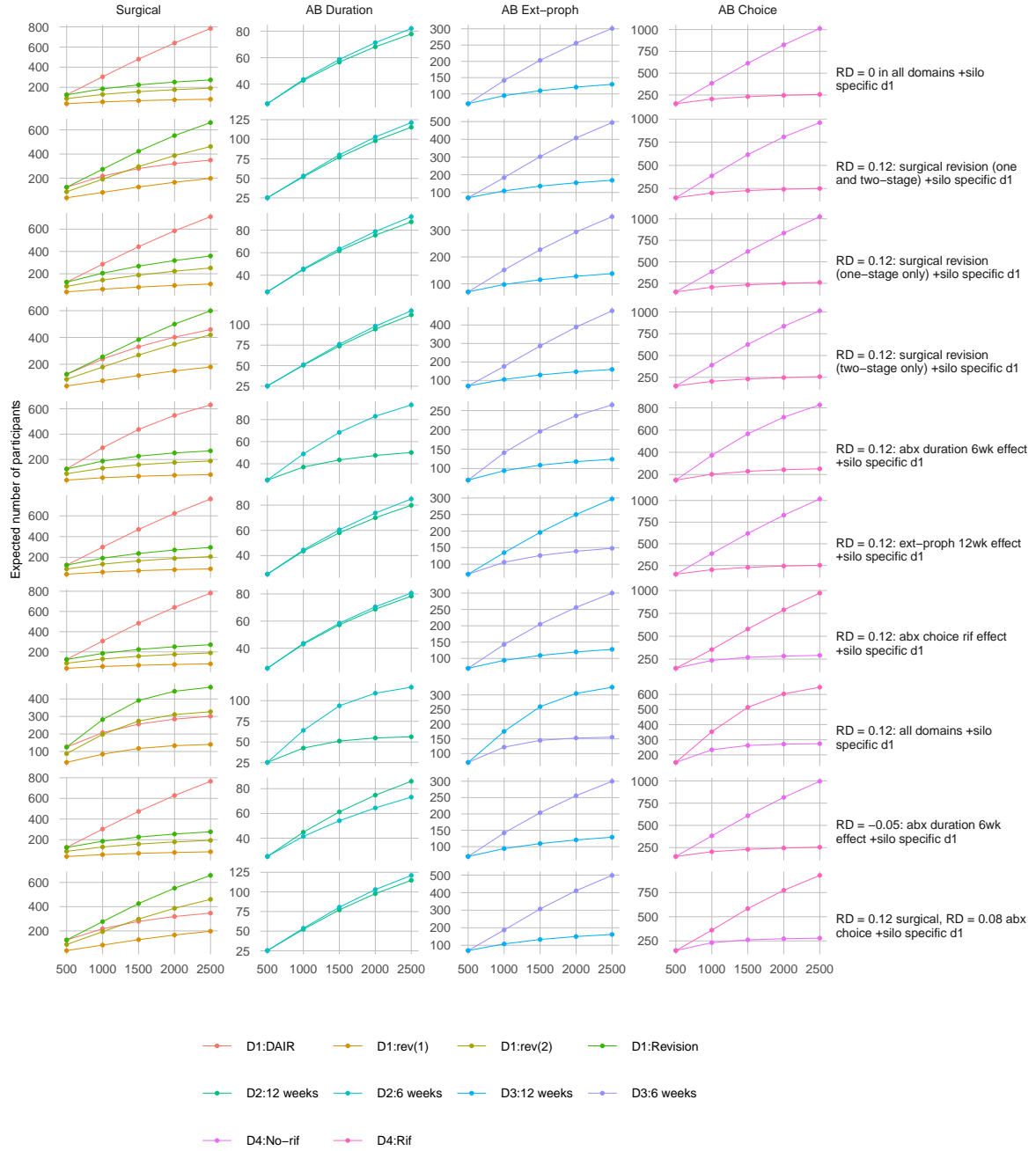
Figure 6.1: Expected number of participants entering into randomised comparisons

Table 6.3 shows the expected number of participants on each treatment arm until a decision is triggered, for each domain and each decision type. For example, for the surgical domain, some of the simulated trials will result in a superiority decision, some will result in a futility (of superiority) decision and some of the simulated trials will run until their maximum sample

size without any decision being made. Earlier results show approximately what proportion of decision types are made under each scenario.

Table 6.3: Expected number of participants entering into randomised comparisons

| | Expected sample size for by stopping rule and domain | | | | | | | | |
| | Surgical | | | AB Duration | | AB Ext-proph | | AB choice | |
Decision	DAIR	rev(1)	rev(2)	12 wk	6 wk	none	12 wk	no-rif	rif
RD = 0 in all domains +silo specific d1									
superiority	305	91	214	-	-	120	120	342	340
futility (sup)	210	63	147	-	-	100	99	230	230
ni	-	-	-	51	51	-	-	-	-
futility (ni)	-	-	-	46	47	-	-	-	-
no decision	624	187	438	88	89	221	220	748	751
RD = 0.12: surgical revision (one and two-stage) +silo specific d1									
superiority	272	81	190	-	-	158	159	336	337
futility (sup)	193	58	136	-	-	124	124	227	227
ni	-	-	-	76	76	-	-	-	-
futility (ni)	-	-	-	64	64	-	-	-	-
no decision	623	188	437	149	149	364	362	749	750
RD = 0.12: surgical revision (one-stage only) +silo specific d1									
superiority	328	99	230	-	-	131	131	342	342
futility (sup)	231	69	162	-	-	105	105	230	230
ni	-	-	-	56	56	-	-	-	-
futility (ni)	-	-	-	49	49	-	-	-	-
no decision	625	187	437	98	99	239	239	750	751
RD = 0.12: surgical revision (two-stage only) +silo specific d1									
superiority	305	91	214	-	-	156	154	329	330
futility (sup)	217	65	152	-	-	121	121	228	228
ni	-	-	-	73	73	-	-	-	-
futility (ni)	-	-	-	60	61	-	-	-	-
no decision	625	188	437	134	134	306	305	750	749
RD = 0.12: abx duration 6wk effect +silo specific d1									
superiority	312	93	217	-	-	121	121	362	359
futility (sup)	216	65	152	-	-	100	100	228	228
ni	-	-	-	45	45	-	-	-	-
futility (ni)	-	-	-	33	33	-	-	-	-

Table 6.3: Expected number of participants entering into randomised comparisons

| | Surgical | | | AB Duration | | AB Ext-proph | | AB choice | |
Decision	DAIR	rev(1)	rev(2)	12 wk	6 wk	none	12 wk	no-rif	rif
no decision	624	187	439	81	81	219	219	752	750

RD = 0.12: ext-proph 12wk effect +silo specific d1

superiority	295	89	206	-	-	117	117	361	358
futility (sup)	221	66	155	-	-	87	87	226	226
ni	-	-	-	51	51	-	-	-	-
futility (ni)	-	-	-	48	48	-	-	-	-
no decision	625	188	436	91	92	208	208	749	748

RD = 0.12: abx choice rif effect +silo specific d1

superiority	311	94	218	-	-	117	117	259	259
futility (sup)	210	63	147	-	-	100	100	172	170
ni	-	-	-	52	52	-	-	-	-
futility (ni)	-	-	-	47	47	-	-	-	-
no decision	625	187	437	88	88	217	217	753	753

RD = 0.12: all domains +silo specific d1

superiority	255	77	179	-	-	135	135	255	255
futility (sup)	212	64	149	-	-	92	92	181	181
ni	-	-	-	54	54	-	-	-	-
futility (ni)	-	-	-	35	36	-	-	-	-
no decision	625	187	438	124	125	275	276	755	746

RD = -0.05: abx duration 6wk effect +silo specific d1

superiority	314	94	220	-	-	125	125	340	340
futility (sup)	212	64	148	-	-	101	101	228	228
ni	-	-	-	46	46	-	-	-	-
futility (ni)	-	-	-	49	49	-	-	-	-
no decision	625	187	437	89	89	222	220	748	751

RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1

superiority	269	81	188	-	-	160	160	251	252
futility (sup)	204	61	142	-	-	123	123	172	171
ni	-	-	-	77	78	-	-	-	-
futility (ni)	-	-	-	64	64	-	-	-	-
no decision	624	188	436	150	149	336	338	743	747

6.2.2 Total enrolments

Table 6.4 shows the average total number of enrolments until each decision type by domain and scenario and, in parentheses, the proportion of trials on which the decision type was made.

Table 6.4: 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	1,220 (7%)		1,061 (9%)	1,137 (3%)
futility (sup)	839 (86%)		811 (82%)	766 (96%)
ni		1,208 (31%)		
futility (ni)		1,101 (20%)		
no decision	2,500 (7%)	2,500 (49%)	2,500 (9%)	2,500 (1%)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1				
superiority	1,085 (84%)		1,035 (10%)	1,127 (2%)
futility (sup)	775 (10%)		823 (88%)	757 (96%)
ni		1,300 (39%)		
futility (ni)		1,135 (23%)		
no decision	2,500 (6%)	2,500 (38%)	2,500 (3%)	2,500 (1%)
RD = 0.12: surgical revision (one-stage only) +silo specific d1				
superiority	1,315 (16%)		1,092 (9%)	1,141 (3%)
futility (sup)	924 (70%)		821 (83%)	767 (95%)
ni		1,212 (32%)		
futility (ni)		1,090 (21%)		
no decision	2,500 (13%)	2,500 (47%)	2,500 (8%)	2,500 (2%)
RD = 0.12: surgical revision (two-stage only) +silo specific d1				
superiority	1,221 (66%)		1,055 (9%)	1,100 (3%)
futility (sup)	866 (22%)		832 (88%)	761 (96%)
ni		1,308 (35%)		
futility (ni)		1,117 (22%)		
no decision	2,500 (12%)	2,500 (42%)	2,500 (3%)	2,500 (2%)
RD = 0.12: abx duration 6wk effect +silo specific d1				
superiority	1,245 (7%)		1,047 (9%)	1,203 (3%)

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Table 6.4: Expected number of enrolments by decision type (including reaching maximum sample size)

| Decision | Expected number of total enrolments to hit stopping rule by domain | | | |
	Surgical	AB Duration	AB Ext-proph	AB choice
futility (sup)	865 (86%)		813 (83%)	761 (96%)
ni		1,041 (85%)		
futility (ni)		771 (2%)		
no decision	2,500 (7%)	2,500 (13%)	2,500 (8%)	2,500 (2%)

RD = 0.12: ext-proph 12wk effect +silo specific d1

Decision	Surgical	AB Duration	AB Ext-proph	AB choice
superiority	1,177 (8%)		976 (82%)	1,200 (3%)
futility (sup)	884 (83%)		718 (12%)	754 (96%)
ni		1,186 (32%)		
futility (ni)		1,099 (20%)		
no decision	2,500 (9%)	2,500 (48%)	2,500 (6%)	2,500 (1%)

RD = 0.12: abx choice rif effect +silo specific d1

Decision	Surgical	AB Duration	AB Ext-proph	AB choice
superiority	1,244 (6%)		1,032 (9%)	862 (96%)
futility (sup)	840 (87%)		817 (83%)	571 (4%)
ni		1,225 (31%)		
futility (ni)		1,094 (21%)		
no decision	2,500 (7%)	2,500 (48%)	2,500 (8%)	2,500 (0%)

RD = 0.12: all domains +silo specific d1

Decision	Surgical	AB Duration	AB Ext-proph	AB choice
superiority	1,019 (87%)		881 (90%)	849 (96%)
futility (sup)	850 (8%)		640 (9%)	603 (4%)
ni		970 (97%)		
futility (ni)		670 (1%)		
no decision	2,500 (5%)	2,500 (2%)	2,500 (0%)	2,500 (0%)

RD = -0.05: abx duration 6wk effect +silo specific d1

Decision	Surgical	AB Duration	AB Ext-proph	AB choice
superiority	1,254 (6%)		1,091 (8%)	1,136 (2%)
futility (sup)	848 (86%)		824 (83%)	762 (96%)
ni		1,094 (14%)		
futility (ni)		1,143 (41%)		
no decision	2,500 (8%)	2,500 (45%)	2,500 (8%)	2,500 (1%)

RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1

Decision	Surgical	AB Duration	AB Ext-proph	AB choice
superiority	1,074 (83%)		1,032 (9%)	838 (96%)
futility (sup)	815 (11%)		812 (89%)	571 (4%)
ni		1,318 (40%)		

Table 6.4: Expected number of enrolments by decision type (including reaching maximum sample size)

Decision	Expected number of total enrolments to hit stopping rule by domain			
	Surgical	AB Duration	AB Ext-proph	AB choice
futility (ni)		1,120 (22%)		
no decision	2,500 (6%)	2,500 (38%)	2,500 (2%)	2,500 (0%)

6.3 Parameter estimation

Table 6.5 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 6.5: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

Domain	Risk difference (expectation of posterior means and 95 pct interval)				
	500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1					
Surgical	0 (-0.14, 0.14)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
AB Duration	0 (-0.22, 0.22)	0 (-0.21, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.2)
AB Ext-proph	0 (-0.16, 0.16)	0 (-0.13, 0.13)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)
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 (one and two-stage) +silo specific d1					
Surgical	0.11 (-0.03, 0.24)	0.11 (-0.01, 0.23)	0.12 (0, 0.22)	0.12 (0, 0.22)	0.12 (0, 0.22)
AB Duration	0 (-0.21, 0.21)	0 (-0.19, 0.19)	0 (-0.18, 0.19)	0 (-0.18, 0.18)	0 (-0.18, 0.18)
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.13, 0.12)	0 (-0.12, 0.11)	-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 (-0.08, 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, 0.14)	0.02 (-0.09, 0.13)	0.02 (-0.09, 0.13)	0.02 (-0.09, 0.13)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0 (-0.16, 0.15)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)	-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 (two-stage only) +silo specific d1					
Surgical	0.08 (-0.06, 0.22)	0.09 (-0.03, 0.2)	0.09 (-0.03, 0.2)	0.09 (-0.02, 0.2)	0.09 (-0.02, 0.2)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 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, 0.12)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.1)
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: abx duration 6wk effect +silo specific d1					
Surgical	0 (-0.14, 0.14)	0 (-0.13, 0.12)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)
AB Duration	0.1 (-0.12, 0.31)	0.11 (-0.08, 0.3)	0.12 (-0.06, 0.3)	0.12 (-0.04, 0.3)	0.13 (-0.03, 0.3)
AB Ext-proph	0 (-0.15, 0.16)	0 (-0.14, 0.13)	0 (-0.13, 0.13)	-0.01 (-0.13, 0.13)	-0.01 (-0.13, 0.13)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.09, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)

Table 6.5: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

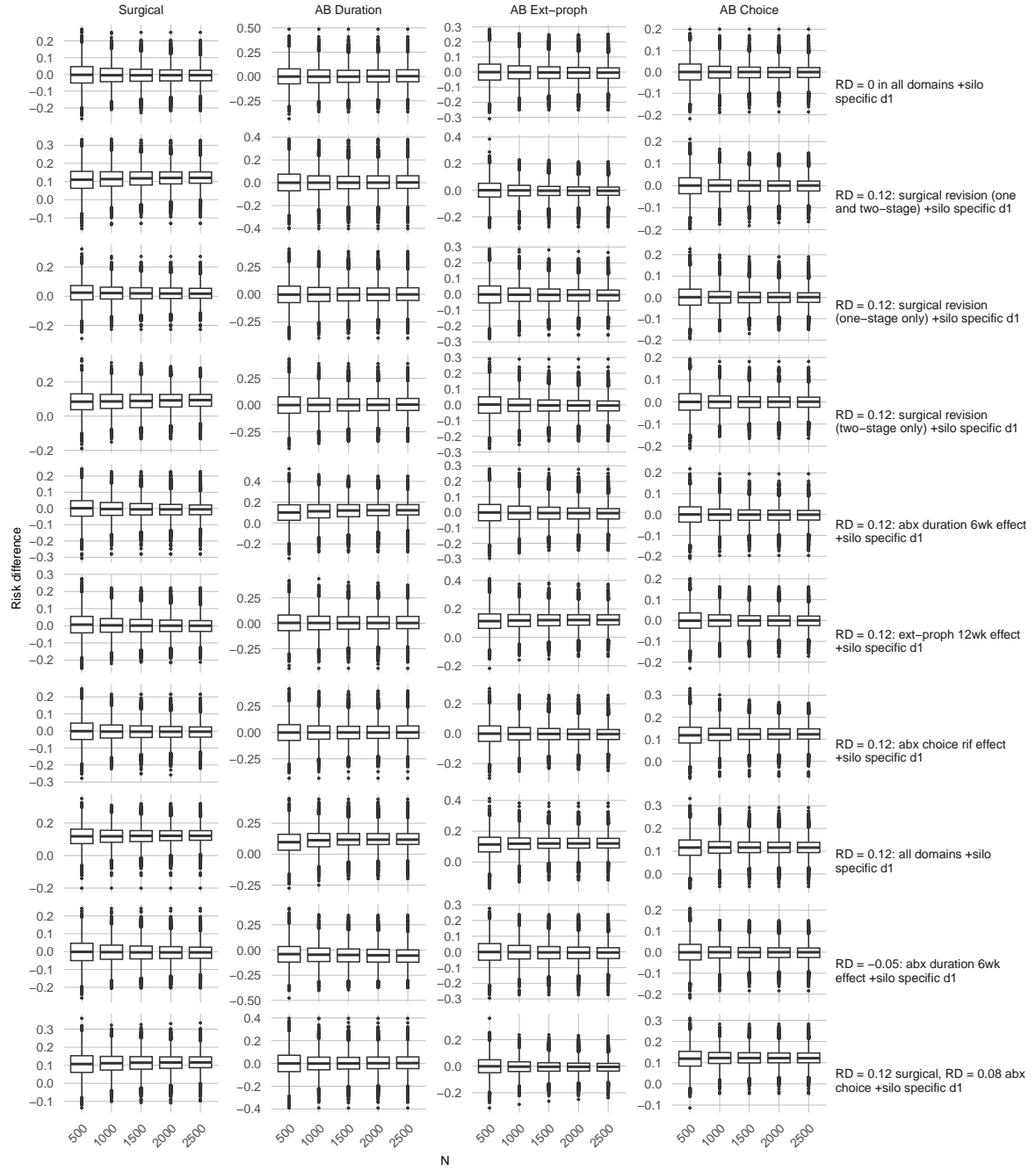|	Risk difference (expectation of posterior means and 95 pct interval)				
Domain	500	1000	1500	2000	2500
RD = 0.12: ext-proph 12wk effect +silo specific d1					
Surgical	0.01 (-0.13, 0.15)	0 (-0.11, 0.12)	0 (-0.11, 0.11)	0 (-0.11, 0.11)	0 (-0.11, 0.1)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.19, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0.11 (-0.04, 0.26)	0.12 (-0.02, 0.24)	0.12 (-0.01, 0.24)	0.12 (-0.01, 0.24)	0.12 (-0.01, 0.24)
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: abx choice rif effect +silo specific d1					
Surgical	0 (-0.14, 0.13)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.09)	-0.01 (-0.11, 0.09)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0 (-0.16, 0.15)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	0 (-0.12, 0.12)	-0.01 (-0.12, 0.12)
AB Choice	0.12 (0.01, 0.22)	0.12 (0.04, 0.2)	0.12 (0.05, 0.2)	0.12 (0.05, 0.2)	0.12 (0.06, 0.2)
RD = 0.12: all domains +silo specific d1					
Surgical	0.12 (-0.01, 0.24)	0.12 (0, 0.23)	0.12 (0.01, 0.22)	0.12 (0.01, 0.22)	0.12 (0.01, 0.22)
AB Duration	0.1 (-0.09, 0.29)	0.11 (-0.04, 0.28)	0.12 (-0.01, 0.28)	0.12 (0, 0.28)	0.13 (0.01, 0.28)
AB Ext-proph	0.11 (-0.02, 0.25)	0.12 (0, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.23)
AB Choice	0.12 (0.02, 0.22)	0.12 (0.04, 0.2)	0.12 (0.05, 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, 0.14)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
AB Duration	-0.04 (-0.26, 0.18)	-0.05 (-0.25, 0.16)	-0.05 (-0.24, 0.16)	-0.05 (-0.24, 0.16)	-0.05 (-0.24, 0.16)
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 (-0.11, 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, RD = 0.08 abx choice +silo specific d1					
Surgical	0.11 (-0.03, 0.24)	0.11 (0, 0.22)	0.11 (0, 0.22)	0.11 (0, 0.22)	0.12 (0.01, 0.21)
AB Duration	0 (-0.2, 0.2)	0 (-0.18, 0.18)	0 (-0.17, 0.17)	0 (-0.17, 0.17)	0 (-0.17, 0.17)
AB Ext-proph	0 (-0.15, 0.14)	0 (-0.12, 0.11)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
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)

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 6.6 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 6.6: 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	-	0.68	0.68
AB Ext-proph	-	0.59	0.59
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 6.6: 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	-	0.63	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	0.58	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	-	0.66	0.78
AB Choice	-	0.64	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