POWAR Data analysis report for forthcoming DMEC.

Report from the Centre of Clinical and Health Services Research, University of Hertfordshire.

The files sent from Guys Hospital (GUYS) to us here at the University of Hertfordshire (UH) contained data on 299 patients. When allowing for dummy entrants and duplicate entrants the numbers actively analysed here for the POWAR study and these that completed the study successfully falls to n=285, a drop-out/censoring rate of 4.68%. With 144 (50.5%) presenting in the treatment arm and 141 (49.5%) in the placebo arm of the study. The initial study design which was of a superiority group sequential design type aimed to detect a minimum clinical significant reduction to 5% at a study power of 90%. This applied a Lan-de-Mars spending function over 5 periods of sample recruitment and clearly suggested a maximum sample size needed of 200 patients per arm of study.

When the 285 patients are considered across recruitment site the following distribution is observed:

	SITE					Total
	CAR	CMU	DER	GUY	STG	
Group: Antibiotic	2 (1.4%)	35 (24.3%)	7 (4.9%)	94 (65.3%)	6 (4.2%)	144
Placebo	2 (1.4%)	31 (22.0%)	8 (5.7%)	94 (66.7%)	6 (4.3%)	141
Total	4 (1.41%)	66 (23.2%)	15 (5.3%)	188 (66.0%)	12 (4.2%)	285

When performing a Pearson Chi-square test this gives, P=0.991, a clearly non-significant result showing no real difference across sites. However, it is clear that GUYS is the largest site contributing some 66% of the study patients.

When considering the 283 patients across smoking group (with 2 patients giving no smoking history) the following is observed:

	SMOKE			Total
	1	2	3	
Group: Antibiotic	23 (16.1%)	83 (58.0%)	37 (25.9%)	143
Placebo	20 (14.3%)	83 (59.3%)	37 (26.4%)	140
Total	43 (15.2%)	166 (58.7%)	74 (26.1%)	283

When performing a Pearson Ch-square on this smoking information, P=0.915, a non-significant result showing clearly no statistical difference across smoking type. When considering the smoking history coding we believe that code 1 matches current smoker, code 2 non-smoker and code 3 ex-smoker. However, the data code book sent to us at UH from GUYS failed to have a clear data dictionary attached so it was not possible to verify this.

When considering the 285 patients across gender group the following is observed:

	SEX		Total
	Male	Female	
Group: Antibiotic	80 (55.6%)	64 (44.4%)	144
Placebo	86 (61.0%)	55 (39.0%)	141
Total	166 (58.2%)	119 (41.8%)	285

When performing Fishers' Exact Test on this data a statistically non-significant result was observed, P=0.209 (2-sided test). Indicting no real difference observed for gender in this study.

Baseline descriptive statistics were then performed on the studies main continuous variables across treatment group. Namely: Age, BMI and EQ5D score (at baseline and after 30 days, this being a simple measure of quality of life).

		N	Mean	St Dev
AGE	Placebo	141	44.45	12.5
	Antibiotic	144	46.23	12.5
BMI	Placebo	117	27.26	10.2
	Antibiotic	118	26.08	3.8
Baseline EQ5D	Placebo	137	94.31	7.6
	Antibiotic	141	94.43	7.1
30 Days EQ5D	Placebo	128	79.65	17.8
	Antibiotic	127	82.22	15.1

All 4 of the above variables were tested for normality and were seen to fit the ranges of the normal distribution. The varying sample sizes simply indicating areas of missing patient data.

Student's independent sample t-tests were then performed on these continuous variables across treatment groups to check for any clearly observed differences across arm of study.

		t-test for Equality of means			
		t value	2-tailed sig	Mean difference	95% CI of the difference
AGE	Equal variances	-1.201	0.231	-1.775	-4.686, 1.135
	Not equal variances	-1.201	0.231	-1.775	-4.686, 1.135
BMI	Equal variances	1.171	0.243	1.175	-0.802, 3.151
	Not equal variances	1.167	0.245	1.175	-0.814, 3.164
Baseline EQ5D	Equal variances	-0.134	0.893	-0.119	-1.863, 1.625
	Not equal variances	-0.134	0.894	-0.119	-1.865, 1.627
30 Day EQ5D	Equal variances	-1.246	0.214	-2.572	-6.638, 1.494
	Not equal variances	-1.246	0.214	-2.572	-6.636, 1.492

As can be seen from the above table no statistically significant differences were observed for these 4 variables across treatment group. However, EQ5D is showing a suggestion of an improvement in

mean difference from baseline to 30 days follow up, with a drop in mean difference of approximately 2.5. Indicting a possible improvement in quality of life when simply measured by mean score difference.

The study's primary endpoint will now be considered. This primary outcome measure is a composite endpoint of any infection and considers surgical site infections as well as urinary tract, respiratory and any other infections within 30 days of surgery.

Primary Endpoint:

	Primary Endpoint		Total
	No	Yes	
Group: Antibiotic Placebo	105 83	39 (27.1%) 58 (41.1%)	144 141
Total	188	97 (34.0%)	285

When using Fisher's Exact test, a highly statistically significant result is observed (P =0.009). Showing clearly that there is statistical difference between the two infection rates of 27% for the treatment group and 41% for the placebo group.

For SSSI alone:

	SSSI		Total
	No	Yes	
Group: Antibiotic Placebo	127 111	17 (11.8%) 30 (21.3%)	144 141
Total	238	47 (16.5%)	285

With Fisher's Exact test, a statistically significant result is observed (P=0.023. Again, indicting a difference in the arms of the arm with 12% observed in the treatment group compared to 21% in the placebo group.

For DSSI alone:

	DSSI		Total
	No	Yes	
Group: Antibiotic Placebo	142 138	2 (1.4%) 3 (2.1%)	144 141
Total	280	5 (1.8%)	285

With Fisher's Exact test, a statistically non-significant result is observed (P=0.490). Implying no observable statistical difference in the arms of the arm for DSSI.

For OSI alone:

	OSI		Total
	No	Yes	
Group: Antibiotic	138	6 (4.2%)	144
Placebo	136	5 (3.5%)	141
Total	274	11 (3.9%)	285

With Fisher's Exact test, a further statistically non-significant result is observed (P=0.515). Implying no observable statistical difference in the arms of the arm for OSI.

For UTI alone:

	UTI		Total
	No	Yes	
Group: Antibiotic	134	10 (6.9%)	144
Placebo	131	10 (7.0%)	141
Total	265	20 (7.0%)	285

With Fisher's Exact test, a further statistically non-significant result is observed (P=0.590). Implying no observable statistical difference in the arms of the arm for UTI.

For LRTI alone:

	LRTI		Total
	No	Yes	
Group: Antibiotic	139	5 (3.5%)	144
Placebo	129	12 (8.5%)	141
Total	268	17 (6.0%)	285

With Fisher's Exact test, a borderline statistically significant result is observed (P=0.06). Implying a potentially observable statistical difference in the arms of the arm for LRTI.

For other infections:

	Other Infections		Total
	No	Yes	
Group: Antibiotic	140	4 (2.8%)	144
Placebo	132	9 (6.4%)	141
Total	272	13 (4.6%)	285

With Fisher's Exact test, a further statistically non-significant result is observed (P=0.103). Implying no observable statistical difference in the arms of the arm for other infections.

Adverse events:

When considering adverse events alone (not serious events), the following is a breakdown of these over the arms of the study:

	Any adverse event		Total
	No	Yes	
Group: Antibiotic Placebo	72 59	72 (50.0%) 82 (58.2%)	144 141
Total	131	154 (54.0%)	285

With Fisher's Exact test, a non-significant result is observed (P=0.113). Implying no statistical difference in the rates observed across the arms of the study.

When considering serious adverse events, the following is a breakdown of these over the arms of the study:

	Any serious adverse event		Total
	No	Yes	
Group: Antibiotic Placebo	123 119	21 (14.6%) 22 (15.6%)	144 141
Total	242	43 (15.1%)	285

With Fisher's Exact test, a non-significant result is observed (P=0.470). Implying no statistical difference in the rates observed across the arms of the study. The rate is high but appears even across the arms of the study.

Quality of Life:

When considering quality of life as defined by the EQ5D, this has been split into sections of Mobility, Self-Care, Usual Activities, Pain and Discomfort, and Anxiety and Depression. This was measured at the 2-time points, baseline and 30 days after operation. The higher the level of the Likert scale implying that more issues/problems for each EQ5D dimension are present. The varying total samples sizes indicating not complete returns on these variables.

Mobility:

Group	Mobility baseline					Total
	1	2	3	4	5	
Antibiotic	133 (94.3%)	3	-	-	-	141
Placebo	135 (97.8%)	2	-	-	-	137
Total	273 (98.2%)	5	-	-	-	278

With a Chi-square test, based on level 1 versus the rest, a non-significant result is observed (P=0.514). Implying no statistical difference in mobility issues across the arms of the study at baseline. With less than 2% of the patients overall reporting any issues.

Group	Mobility 30 days					Total
	1	2	3	4	5	
Antibiotic	93 (72.7%)	29	5	1	-	128
Placebo	84 (64.6%)	37	9	-	-	130
Total	177 (68.6%)	66	14	1	-	258

With a Chi-squared test, again based on level 1 versus the rest, a non-significant result is observed (P=0.314). Implying no statistical difference in mobility issues across the arms of the study at 30 days. However, as can be seen the numbers reporting issues in mobility has grown to over 30% of the patients. When this difference is considered over follow-up time by treatment group a non-significant result was observed, P=0.206, implying no difference in the increased mobility concerns over treatment group.

Self-Care:

Group	Self-Care baseline					Total
	1	2	3	4	5	
Antibiotic	140 (99.3%)	-	1	-	-	141
Placebo	136 (99.3%)	-	1	-	-	137
Total	276 (99.3%)	-	2	-	-	278

With a Chi-square test, based on level 1 versus the rest, a non-significant result is observed (P=0.744). Implying no statistical difference in self-care issues across the arms of the study at baseline, with only 0.7% of the patients overall reporting any issues.

Group	Self-Care 30 Days					Total
	1	2	3	4	5	
Antibiotic	111 (86.7%)	3	14	-	-	128
Placebo	110 (84.6%)	2	17	1	-	130
Total	221 (85.7%)	5	31	1	-	258

With a Chi-squared test, based on level 1 versus the rest, a non-significant result is observed (P=0.687). Implying no statistical difference in self-care issues across the arms of the study at 30 days. With about 14% overall reporting issues, implying an increase overall of approximately 13% since baseline. This difference was non-significant when considered over follow time by arm of study (P=0.310).

Usual Activities:

Group	Usual Activities baseline					Total
	1	2	3	4	5	
Antibiotic	139 (98.6%)	1	-	1	-	141
Placebo	135 (98.5%)	2	-	-	-	137
Total	274 (98.6%)	3	-	1	-	278

With a Chi-square test, a non-significant result is observed (P=0.513). Implying no statistical difference in usual activities issues across the arms of the study at baseline. Only 1.4% overall reporting any issues.

Group	Usual Activities 30 days					Total
	1	2	3	4	5	
Antibiotic	71 (55.7%)	37	16	1	3	128
Placebo	63 (48.5%)	41	19	3	4	130
Total	134 (51.9%)	78	35	4	7	258

With a Chi-squared test, a non-significant result is observed (P=0.760). Implying no statistical difference in usual activities issues across the arms of the study at 30 days. However, just over 48% are reporting issues/concerns in their usual activities when compared to baseline, an increase of approximately 47% overall. When this difference is compared across arm of study a non-significant result is observed (P=0.187), implying no statistical difference in the increased levels of concern over treatment group.

Pain and Discomfort:

Group	Pain and Discomfort baseline					Total
	1	2	3	4	5	
Antibiotic	134 (95.0%)	6	1	-	-	141
Placebo	128 (93.4%)	8	1	-	-	137
Total	262 (94.2%)	14	2	-	-	278

With a Chi-square test, a non-significant result is observed (P=0.833). Implying no statistical difference in pain and discomfort issues across the arms of the study at baseline. With just over 5% overall reporting any concerns at baseline.

Group	Pain and Discomfort 30 days					Total
	1	2	3	4	5	
Antibiotic	60 (46.5%)	51	18	-	-	129
Placebo	53 (41.1%)	59	14	2	1	129
Total	113 (43.8%)	110	32	2	1	258

With a Chi-squared test, a non-significant result is observed (P=0.341). Implying no statistical difference in pain and discomfort issues across the arms of the study at 30 days. However, when compare to baseline this EQ5D dimension has increased form just over 5% to 56% reporting concerns in pain and discomfort. When considered by arm of study this is a non-significant difference (P=0.313).

Anxiety and Depression:

Group	Anxiety and Depression baseline					Total
	1	2	3	4	5	
Antibiotic	117 (83.0%)	22	2	-	-	141

Placebo	115 (84.0%)	18	4	-	-	137
Total	232 (83.4%)	40	6	-	-	278

With a Chi-square test, a non-significant result is observed (P=0.599). Implying no statistical difference in anxiety and depression issues across the arms of the study at baseline. However, overall approximately 17% are reporting concerns.

Group	Anxiety and Depression 30 days					Total
	1	2	3	4	5	
Antibiotic	109 (85.2%)	15	3	-	1	128
Placebo	106 (81.5%	19	5	-	-	130
Total	215 (83.3%)	34	8	-	1	258

With a Chi-squared test, a non-significant result is observed (P=0.573). Implying no statistical difference in pain and discomfort issues across the arms of the study at 30 days. Patents level of anxiety and depression remain unchanged statistically when comparing baseline to 30 days follow up. A non-significant finding is seen also over treatment group (P=0.926).

A further measure of quality of life is the sum of the Likert scores, and its possible difference across arm of study. A t-test comparison of this was shown earlier and no statistically significant difference of EQ5D average score was shown for either baseline or at 30 days across treatment group. A simple re-evaluation can be undertaken simply taking the difference of EQ5D score (baseline – 30 day score) and comparing this to treatment group. The negative mean values in the following table showing an "improved" overall EQ5D score from baseline to 30 day follow up.

Difference in EQ5D Score	N	Mean	St Dev
Placebo	127	-14.50	17.1
Antibiotic	127	-12.23	14.9

Performing an independent sample t-test on the above means across treatment groups gives the following:

Difference in EQ5D Score	**t-test for Equality of means**			
	t value	2-tailed sig	Mean difference	95% CI of the difference
Equal variances	-1.124	0.262	-2.268	-6.240, 1.740
Not equal variances	-1.124	0.262	-2.268	-6.240, 1.740

As can be seen no statistically significant difference was observed for this overall quality of life measure across treatment arms of this study.

Statistical conclusion:

The study has reached a sample size of n=285. Findings around the primary efficacy parameters are clearly indicating that statistical differences are appearing in the arms of the study. These are observed in the study's primary endpoint and in SSSI and again in LRTI. However, I would express that caution is needed when interpreting these results. They clearly appear to be moving in the right direction, however, we have not reached the required sample size of 200 patients per arm of study quoted in the initial research protocol for 90% power, and since differences are appearing in the study parameters the smaller protocol quoted study size of 142 per arm cannot be considered, since this was for the case of no differences occurring. Also considered in the research protocol was the use of non-parametric techniques in case of non-normally of data, these were not needed. It was also felt that the use of generalized linear techniques to give a more robust statistical modelling approach to the analysis was not needed. To assist with the DMEC considerations it should be noted that the trial has reach a study power of between 70%-75% using the same binomial two-sided test with 5% type I error quoted in the initial research protocol, this is however not using an applied Lan-de-Mars spending function over 5 periods of sample, since this is only the second POWAR dataset extraction sent to UH.