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THE HONEYPOT RANDOMIZED CONTROLLED TRIAL STATISTICAL ANALYSIS PLAN

Elaine Mary Pascoe,[1] Serigne Lo,[2] Anish Scaria,[1] Sunil V. Badve,[1,3] Elaine Mary Beller,[4] Alan Cass,[2] Carmel Mary Hawley,[1,3,5] and David W. Johnson[1,3,5]

School of Medicine,[1] University of Queensland, Brisbane; The George Institute for Global Health,[2] University of Sydney, Sydney; Department of Nephrology,[3] Princess Alexandra Hospital, Brisbane; Centre for Research in Evidence Based Practice,[4] Bond University, Robina; and Translational Research Institute,[5] Brisbane, Australia.

♦ ***Background:*** **The HONEYPOT study is a multicenter, open-label, blinded-outcome, randomized controlled trial designed to determine whether, compared with standard topical application of mupirocin for nasal staphylococcal carriage, exit-site application of antibacterial honey reduces the rate of catheter-associated infections in peritoneal dialysis patients.**

♦ ***Objective:*** **To make public the pre-specified statistical analysis principles to be adhered to and the procedures to be performed by statisticians who will analyze the data for the HONEYPOT trial.**

♦ ***Methods:*** **Statisticians and clinical investigators who were blinded to treatment allocation and treatment-related study results and who will remain blinded until the central database is locked for final data extraction and analysis determined the statistical methods and procedures to be used for analysis and wrote the statistical analysis plan. The plan describes basic analysis principles, methods for dealing with a range of commonly encountered data analysis issues, and the specific statistical procedures for analyzing the primary, secondary, and safety outcomes.**

♦ ***Results:*** **A statistical analysis plan containing the pre-specified principles, methods, and procedures to be adhered to in the analysis of the data from the HONEYPOT trial was developed in accordance with international guidelines. The structure and content of the plan provide sufficient detail to meet the guidelines on statistical principles for clinical trials produced by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.**

♦ ***Conclusions:*** **Making public the pre-specified statistical analysis plan for the HONEYPOT trial minimizes the potential for bias in the analysis of trial data and the interpretation and reporting of trial results.**

Correspondence to: D.W. Johnson, ARTS Building, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Queensland 4102 Australia.
david_johnson@health.qld.gov.au
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KEY WORDS: Randomized controlled trial; statistical analysis plan; outcome reporting bias; pre-specified statistical analyses; International Conference on Harmonization; intention-to-treat; catheter-associated infections.

The HONEYPOT study is a multicenter randomized controlled trial of exit-site application of antibacterial honey for the prevention of catheter-associated infections in peritoneal dialysis (PD) patients (1). The trial is registered with the Australian New Zealand Clinical Trials Registry (No. 12607000537459). The primary hypothesis is that, in PD patients, daily exit-site application of standardized antibacterial honey in addition to daily cleansing per standard practice will lengthen the time to a catheter-associated infection (exit site, tunnel, peritonitis) relative to daily cleansing and topical mupirocin prophylaxis in nasal staphylococcal carriers. The trial began recruiting patients in August 2008 and reached its recruitment target in June 2011. The final follow-up visit was conducted in June 2012. The central database is expected to be ready for analysis by December 2012.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) recommends that data from clinical trials be analyzed according to a pre-specified statistical analysis plan (SAP) (2). The ICH recommendation aims to promote appropriate analysis and reporting of trial data and avoidance of the bias that can arise from data-driven specification of analyses and selective reporting of statistical results. Some authors have taken the ICH guidelines a step further by suggesting that a pre-specified SAP should be a requirement rather than merely a recommendation and that the SAP

should be placed in the public domain before the people responsible for performing the analyses have access to unblinded data (3).

The SAP for the HONEYPOT trial has been developed and finalized without knowledge of treatment allocation and treatment-related study results. The plan describes the pre-specified statistical analysis principles to be adhered to and the procedures to be performed by statisticians responsible for analyzing the trial data. The present report describes important features of the trial design and the statistical methods and procedures included in the analysis plan.

METHODS

TRIAL DESIGN

The trial design was described in detail in a previously published study protocol (1) and is briefly described here. Patients undergoing continuous ambulatory PD or automated PD were randomized 1:1 to one of two treatment arms: honey or control. All patients had nasal swabs taken at baseline to identify nasal staphylococcal carriage for stratification purposes and were instructed to perform routine daily exit-site care according to local practice. Patients allocated to the antibacterial honey group were supplied with Comvita MediHoney Antibacterial Wound Gel (Comvita, Bay of Plenty, New Zealand) and were instructed to apply approximately 10 mg to the exit site every day for the duration of the study. Patients allocated to the control group had nasal swabs taken to identify nasal *Staphylococcus aureus* colonization at trial commencement and every 6 months thereafter until a positive swab was returned. Control group patients identified as nasal carriers were treated with intranasal mupirocin (twice daily for 5 consecutive days each month for the duration of the trial). Patients in both groups received a medical review every 2 months and had their exit sites inspected and classified according to the Twardowski classification system (4).

Outcome Variables: The primary efficacy outcome is a composite variable defined as time from randomization to the first episode of exit-site infection, tunnel infection, or peritonitis (whichever comes first), according to International Society for Peritoneal Dialysis definitions (5).

Secondary efficacy outcomes are time from randomization to each component event of the primary composite outcome, time from randomization to infection-associated catheter removal, the catheter-related infection rate, and the catheter-related infection relapse rate.

Tertiary outcomes are the incidence of mupirocin-resistant isolates of *S. aureus,* the type of growth (bacterial vs fungal), bacterial Gram stain (gram-positive vs gram-negative), and infecting organism (*S. aureus* vs *Pseudomonas aeruginosa*).

Safety outcomes for the trial are treatment-emergent adverse events (that is, events either not present at baseline or present at baseline but of increased severity), any serious adverse event (SAE), death from any cause, any life-threatening event, any initial or prolonged inpatient hospitalization, any persistent or significant disability or incapacity, any important medical event, and any congenital abnormality or birth defect.

Table 1 summarizes the schedule of data collection for the trial. Data were collected in electronic case report forms that allowed information to be entered directly into a central database by staff at participating centers. Data will be queried until screening programs indicate that all data are plausible and that no further missing data are recoverable.

Changes to the Trial Protocol: Interim efficacy analyses were not originally planned (1). Group sequential

TABLE 1
Summary and Schedule of Data to Be Collected in Electronic Case Report Forms

Time point	Data to be collected
Randomization	Date of randomization and treatment group allocation Patient demographics and eligibility criteria Stratification variables Medical history, clinical assessments Peritoneal dialysis (PD) regimen assessment and adequacy assessment Laboratory investigations, nasal swab (control group only)
Patient visits	
Every 2 months	Date of visit Clinical assessment, PD regimen assessment Assessment of primary and secondary outcomes Adverse event assessment
Every 6 months	Nasal swab (control group only)
End of study	Date patient ended study Clinical assessments, PD regimen assessment Adverse event assessment Nasal swab (all patients)

testing with two interim analyses and a final analysis were introduced in a subsequent protocol amendment (6). An independent Data and Safety Monitoring Board comprising experts in clinical trials, biostatistics, and nephrology is in charge of reviewing unblinded data on patient characteristics, treatment compliance, and safety and efficacy outcomes. Two formal interim efficacy analyses were conducted after one third and two thirds of all patients had been recruited and followed for at least 2 months. The Haybittle–Peto boundary was used as a stopping guideline for efficacy (7); however, the trial has proceeded to the final efficacy analysis. Only Data and Safety Monitoring Board members and statisticians compiling closed-session reports for board meetings have had access to unblinded interim data and results.

Two further, but relatively minor, changes to statistical aspects of the original protocol have been made. First, the trial protocol states that "P-values less than 0.05 will be considered significant" [p. 24 (6)]. That approach won't be the case for the primary efficacy analysis based on group sequential testing, which has proceeded to the third of three planned analyses. The final analysis will be performed at the slightly more stringent level of $p < 0.0482$. Second, the trial protocol includes cost as a secondary outcome measure. That measure will be examined at a later date in exploratory analyses that are not detailed in the current SAP.

In addition to the foregoing amendments, the allocation scheme was incorrectly described in a previous manuscript as randomization by permuted blocks within strata formed by three variables (study center, PD epidemiology, nasal staphylococcal carriage) (1). The three "stratification" variables are used in the randomization scheme, but the scheme is based on an adaptive allocation algorithm and not permuted blocks.

OBJECTIVES

The primary objective of the HONEYPOT trial is to determine whether, compared with standard topical mupirocin prophylaxis of nasal staphylococcal carriers, daily exit-site application of standardized antibacterial honey in addition to daily cleansing per standard practice results in a longer time to a catheter-associated infection (exit site, tunnel, peritonitis) in PD patients.

Secondary objectives are to determine whether daily exit-site application of standardized antibacterial honey in PD patients results in

- a longer time to first episode of peritonitis.
- a longer time to first tunnel infection.
- a longer time to first exit-site infection.
- a longer time to infection-associated catheter removal.
- a lower rate of catheter-associated infection.
- a lower incidence of mupirocin-resistant isolates of *S. aureus*.
- a lower incidence of catheter-associated infection relapse.
- a lower incidence of SAEs.

Exploratory objectives include a comparison of various subgroups on time to first occurrence of a composite outcome event, time to first occurrence of each component of the composite outcome, and time to infection-associated catheter removal. Six pre-randomization subgroups were chosen for a known or suspected association with the risk of catheter-associated infection (8–17):

- Dialysis epidemiology (incident vs prevalent)
- *S. aureus* carrier status at screening (no vs yes)
- Type of dialysis (continuous ambulatory vs automated PD)
- Age group (<65 vs ≥65 years)
- Diabetes (no vs yes)
- Obesity (body mass index ≥30 vs <30).

Subgroups formed by *S. aureus* carrier status at screening will also be compared on catheter-associated infection rates and incidence of mupirocin-resistant isolates of *S. aureus*. In addition, for the subset of patients who experience a primary outcome event, randomized treatment groups and pre-randomization subgroups will be compared on the following organism outcomes:

- Type of growth (bacterial vs fungal)
- Bacterial Gram stain (gram-positive vs gram-negative)
- Infecting organism (*S. aureus* vs *P. aeruginosa*)

STATISTICAL METHODS

Analysis Principles: All tests of the effect of treatment on outcomes (except analyses based on subsets) will be conducted on an intention-to-treat (ITT) basis or as close as possible to that ideal by using the "full analysis" set (2). That is, all randomized patients will be analyzed in the group to which they were randomized regardless of whether they received the assigned treatment and regardless of any protocol deviations or violations. Analyses of outcome variables will, however, exclude data from patients who withdrew from study treatment and withdrew consent for use of their data. All primary statistical analyses will be unadjusted and tests of significance will be two-sided. Any departures from ITT will be documented and reported.

Incomplete Follow-up: The planned follow-up period for individual patients is a minimum of 12 months and

a maximum of 24 months. Follow-up will be terminated early for any of the following reasons:

- Withdrawal from the study
- Loss to follow-up
- Tenckhoff catheter removal for any indication (for example, permanent transfer to hemodialysis)
- Transfer to hemodialysis for more than 12 weeks' duration, but Tenckhoff catheter still *in situ*
- Renal transplantation
- Spontaneous recovery of dialysis-independent renal function
- Death
- Administrative end of the study

For analysis of the primary and secondary time-to-event outcomes, patients with incomplete follow-up who did not experience a relevant outcome event will be censored at the time of their last contact (that is, their time data will contribute to analyses).

Missing Outcomes Data: For the analyses of binary outcomes, the amount of missing outcomes data is expected to be small, and patients with missing outcomes will be excluded. However, if more than 5% of data for an outcome variable is missing, the primary analysis will be based on multiple imputation using chained equations (18). This analysis will be followed by sensitivity analyses, including a complete case analysis. Results of the primary analysis will be interpreted in light of results from the sensitivity analyses.

Missing Baseline Covariate Data: Excluding randomized patients with observed outcomes data is incompatible with the ITT principle and reduces statistical efficiency in the estimation of treatment effects (19). Hence, where values are missing for baseline variables used as covariates in secondary covariate-adjusted analyses of treatment effect, missing values will be replaced using mean imputation. Although mean imputation can bias statistical estimates, such bias is not the case in a randomized trial in which no outcomes are missing, because randomization ensures that baseline variables are independent of treatment group (20–22). Using pooled data from both treatment groups, mean values will be calculated from the non-missing values for the baseline variable. For binary (coded 0 or 1) variables, the imputed mean will be rounded up to 1 or down to 0, whichever is nearest. For computed variables such as body mass index, mean imputation will be performed at the level of the component variables of height and weight. The number and percentage of missing values will be reported for baseline covariates with missing data. Further, covariate-adjusted statistical models will include a missing value indicator (0 = observed, 1 = missing) for each covariate with missing data (20,22).

Outliers: Outliers will be identified by examining residual plots. Cases that "stand out" visually will be assessed for possible influence on the results and conclusions by comparing results from analyses with and without the outlier or outliers. Where results from the two analyses are discrepant, that fact will be reported and discussed.

Multicenter Study: This is a multicentric study to which 26 centers have contributed data for at least 2 patients. Although study center is included as a variable in the randomization scheme, analyses of primary and secondary efficacy outcomes will not adjust for study center because it is anticipated that some centers may be too small and may not contribute any events to the pooled data. However, if a positive treatment effect on the primary composite outcome or the component events emerges, study centers will be combined within Australian states and within New Zealand (6 strata in total) to assess the homogeneity of the treatment effect across centers. Potential heterogeneity will be tested by including a treatment-by-center interaction term in a multivariate model with treatment and center as the main effects.

Multiple Comparisons and Multiplicity: The Heybittle–Peto boundary with a maximum of 3 analyses (2 interims and 1 final) is being used to control the overall type 1 error rate for analysis of the effect of treatment on the composite primary outcome variable. The critical value for the final analysis will be $c = 1.975$ ($\alpha = 0.0482$). There will be no other adjustments for multiplicity (all other tests will be assessed against an α of 0.05) because outcomes and objectives are categorized by degree of importance, and results will be interpreted accordingly.

Covariate Adjustment: All primary statistical analyses will be unadjusted. For the primary efficacy outcome and key secondary efficacy outcomes (that is, those involving time-to-event variables), the robustness of estimates of treatment effect will be assessed by analyses adjusted for baseline characteristics known or suspected *a priori* to be associated with the primary outcome (23). The baseline characteristics are dialysis epidemiology (incident, prevalent), nasal *S. aureus* carrier status at screening (no, yes), type of dialysis (continuous ambulatory PD, automated PD), age (<65, ≥65), diabetes (no, yes), and

obesity (not obese, obese) (8–17). Covariate-adjusted models will include main effects for the treatment group and the 6 covariates, but will not include interaction terms. An adjusted analysis will be viewed as supportive, providing additional context for interpreting the primary unadjusted analysis.

Subgroups: The main analysis for each subgroup variable will be an unadjusted test of the treatment-by-subgroup variable interaction in a statistical model appropriate for the particular outcome (23). Those analyses will be performed regardless of the results of the primary tests of the main effect of treatment.

Subsets: Some secondary and exploratory analyses will be performed on the subset of patients who experience a primary composite outcome. The binary outcomes for those analyses are type of growth (bacterial vs fungal), bacterial Gram stain (positive vs negative), infecting organism (*S. aureus* vs *P. aeruginosa*), and infection relapse. Patients will be analyzed in the group to which they were randomized, but those analyses will not conform to the ITT principle because they will not include all randomized patients.

STATISTICAL ANALYSES

Trial Profile: A CONSORT-style flow diagram will illustrate patient progression through the trial from initial screening for eligibility to completion of the final primary outcome assessment (see Figure 1).

Patient Characteristics and Baseline Comparisons: Demographic and other baseline characteristics will be summarized by assigned treatment group. Table 2 sets out characteristics and their categories (categorical variables) or measurement units (numeric or continuous variables). Categorical variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator, which will be less than the number of patients assigned to the treatment group, will

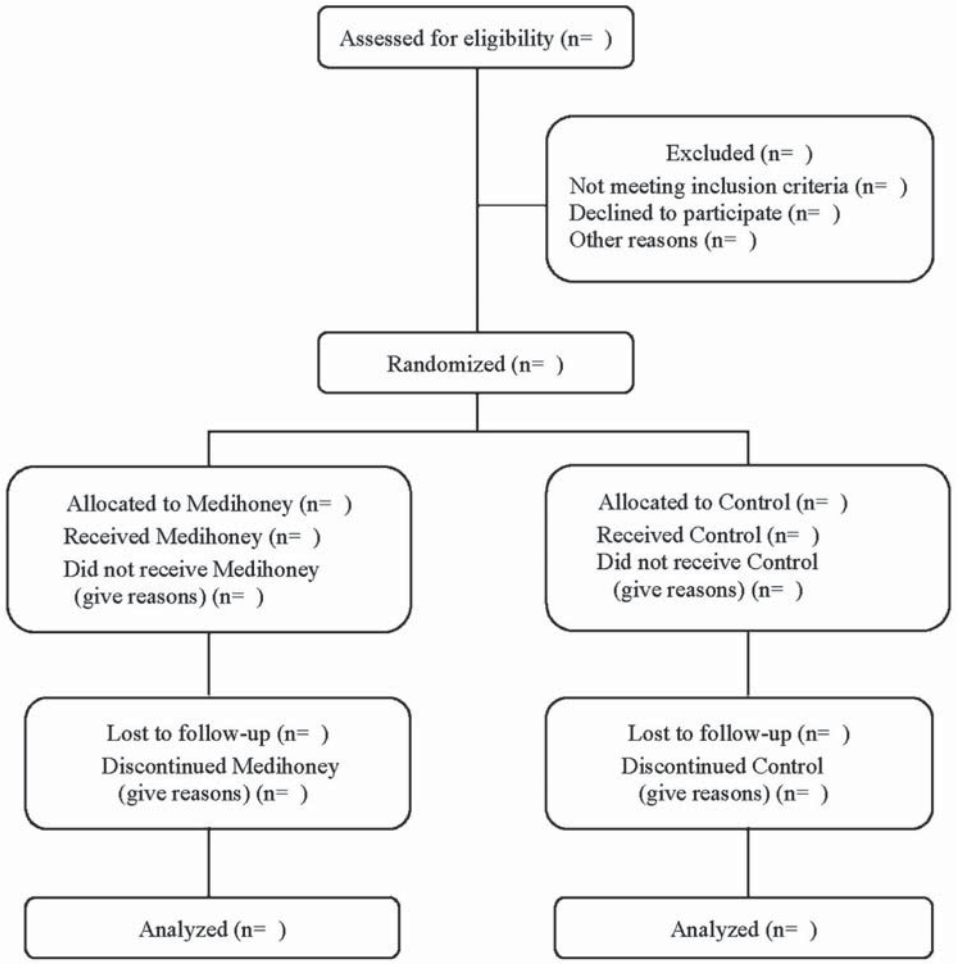

Figure 1 — Flowchart of patient progression through the trial.

TABLE 2
Baseline Characteristics to Be Reported by Treatment Group

Characteristic	Measure	Characteristic	Measure	Characteristic	Measure
Age	Years	Primary cause of ESRF	Diabetes	Duration of dry periods	Hours
Sex	Male		Hypertension		
	Female		Glomerulonephritis	Tidal exchanges	No
Ethnic origin	Caucasian		Analgesic nephropathy		Yes
	Aboriginal/ Torres Strait Islander		Polycystic kidney disease	Weekly peritoneal Kt/V	Units
	Maori/Pacific Islander		Interstitial nephritis	Weekly residual Kt/V	Units
	Asian		Obstructive nephropathy	Weekly peritoneal CCr	Liters/1.73 m^2
	Other		Reflux nephropathy	Weekly residual CCr	Liters/1.73 m^2
	Unknown		Renovascular disease	Peritoneal ultrafiltration	Milliliters/day
Height	Centimeters		Other	D/P Cr at 4 hours	Ratio
Weight	Kilograms		Unknown	Peritoneal transport category	Low
BMI	Units	Failing renal graft	No		Low-average
Obesity	BMI<30		Yes		High-average
	BMI≥30	PD first form of RRT?	Yes		High
Heart rate	Beats per minute		No	Type of PD fluid	Dextrose
BP (mmHg)	Systolic	PD modality	Automated		Low-GDP
	Diastolic		Continuous ambulatory		Icodextrin
Smoking status	Never	Diabetes mellitus	No		Amino acid
	Former		Yes	Exit-site condition	Perfect
	Current	Ischemic heart disease	No		Good
PD epidemiology	Incident		Yes		Equivocal
	Prevalent	Cerebrovascular disease	No		Acute infection
Nasal *S. aureus* carrier	No		Yes		Chronic infection
	Yes	Peripheral vascular disease	No	Hemoglobin	Grams/liter
PD catheter	Coiled		Yes	Sodium	Millimoles/liter
	Straight	Congestive cardiac failure	No	Potassium	Millimoles/liter
Catheter cuffs	One		Yes	Bicarbonate	Millimoles/liter
	Two	Immunosuppressed for preceding 4 weeks	No	Urea	Millimoles/liter
Catheter neck type	Swan		Yes	Creatinine	Micromoles/liter
	No swan	Total daily PD exchanges	Number	Albumin	Grams/liter
		Total daily PD volume	Liters	Total calcium	Millimoles/liter
				Phosphate	Millimoles/liter
				Serum ferritin	Micrograms/liter

BMI = body mass index; BP = blood pressure; PD = peritoneal dialysis; *S. aureus* = *Staphylococcus aureus*; ESRF = end stage renal failure; RRT = renal replacement therapy; CCr = creatinine clearance; Cr = creatinine; GDP = glucose degradation products.

be reported either in the body or a footnote of the summary table. Continuous variables will be summarized by mean and standard deviation as well as by quartiles.

The representativeness of the sample of patients in the full analysis set will be assessed by comparing the demographic characteristics of patients in the trial with

those of patients who were on the Australia and New Zealand Dialysis and Transplant Registry (24) during the recruitment period for the trial (25 August 2008 to 16 June 2011) and who met the eligibility criteria for the trial. Chi-square tests will be used to compare the two samples on categorical variables, and depending on the distributional characteristics of continuous data, independent-sample t-tests or Wilcoxon rank-sum tests will be used to compare the samples.

Analysis of the Primary Efficacy Outcome: Time from randomization to the first occurrence of the composite primary efficacy outcome (first episode of exit-site infection, tunnel infection, or peritonitis) will be displayed using Kaplan-Meier survival curves by treatment group. Survival curves for treatment groups will be summarized using median survival times and survival probabilities and their 95% confidence intervals for relevant follow-up times (6, 12, and 18 months). Survival curves will be statistically compared using the log-rank test. The proportional hazards assumption on which the log-rank test is based will be tested using graphical methods and likelihood ratio tests based on Schoenfeld residuals. If the proportional hazards assumption is not met, survival curves will be compared using Cox regression with two covariates, treatment group and a treatment group–by–time interaction, to allow for a time-varying effect of treatment on survival.

Patients who are withdrawn from the study without experiencing a primary outcome event will be censored in the described survival analyses. For approximately half those patients, the event leading to their withdrawal will be informative of the primary outcome. That is, the events of death, catheter removal, transfer to hemodialysis, renal transplant, and spontaneous recovery either prevent or alter the probability of occurrence of the 3 infections forming the composite outcome. Informative events are called "competing risks" (25). Kaplan–Meier estimation in the presence of competing risks may produce biased results. Hence, a competing-risks survival analysis will be performed as a sensitivity analysis. Because the proportions of patients experiencing the individual categories of competing events are likely to be small, the competing risks analysis will use a composite competing event. The analysis will use the Gray test to compare cumulative incidence functions for the composite primary efficacy outcome by treatment group (26). Patients who do not experience a primary outcome event or a competing risk event will be censored in the competing-risks analysis. Results from the primary analyses will be interpreted in the context of the competing-risks results.

Analysis of Secondary Efficacy Outcomes: The time-to-event secondary efficacy outcomes (first peritonitis, tunnel infection, exit-site infection, and infection-associated catheter removal) will be analyzed using the survival methods described for analysis of the composite primary efficacy outcome.

Catheter-associated infection rates will be analyzed by treatment group using a Poisson regression model. If overdispersion is present, a negative binomial model will be used instead. The incident rate ratios and 95% confidence intervals from the appropriate model will be reported. In addition, within each treatment group, catheter-associated infection rates will be calculated as the number of infections divided by the total time at risk and expressed as episodes per patient–year at risk, with associated 95% confidence intervals.

The secondary outcome of catheter-related infection relapse is a binary outcome variable relevant to the subset of patients who experience at least 1 catheter-related infection. Relapse rates by treatment group will be analyzed using a binary logistic regression model. If patients experience more than 1 relapse, then the data will be analyzed using logistic regression based on generalized estimating equations to account for the correlated data.

Analysis of Safety Outcomes: Safety outcomes will be defined as present (coded 1) or absent (coded 0) for each patient. Each binary safety outcome will be analyzed by treatment group using a chi-square test or the Fisher exact test, as appropriate. Treatment group differences in percentages and exact (binomial) 95% confidence intervals will be calculated. The relationship of each SAE to the study medication will be rated as none, unlikely, possible, or probable. For each SAE, ratings by treatment group will be summarized by frequencies and percentages of total ratings within each rating category.

The SAEs will be classified according to body system, with reference to the Medical Dictionary for Regulatory Activities central coding dictionary, version 15. Body system by treatment group will be summarized using frequencies and percentages of total events within each body system.

Exploratory Analyses—Treatment Groups: Randomized treatment groups will be compared on the organism outcomes (type of growth, bacterial Gram stain, infecting organism) using logistic regression models. These analyses will be performed on data from the subset of patients who experience at least 1 infection. Logistic regression models based on generalized estimating equations will

be used instead of ordinary logistic regression if some patients experience more than 1 infection. Associations with treatment group will be summarized as frequencies and percentages and as odds ratios and 95% confidence intervals. In addition, all patients will be included in a preliminary analysis that uses a logistic regression model to compare treatment groups on the presence or absence of any infection.

Exploratory Analyses—Subgroups: The main analysis for each subgroup will be an unadjusted test of interaction in a statistical model appropriate for the given outcome. The time-to-event primary efficacy outcome variable and the 4 time-to-event secondary efficacy outcome variables will be analyzed by the 6 pre-randomization subgroups (dialysis epidemiology, *S. aureus* carrier status at screening, type of dialysis, age group, diabetes at screening, obesity) in multivariate Cox regression models with treatment group, subgroup, and a treatment-by-subgroup interaction as factors in the models. Hazard ratios and 95% confidence intervals for the treatment effect within each subgroup will be displayed in a forest plot.

Catheter-associated infection rates will be analyzed by *S. aureus* carrier status at screening (no vs yes) using a Poisson regression model with treatment group, carrier status, and a treatment-by-carrier status interaction variable as factors in the model. If overdispersion is present, a negative binomial model will be used instead. Rate ratios and 95% confidence intervals within each subgroup will be reported. Binary outcomes (mupirocin-resistant isolate, type of growth, bacterial Gram stain, infecting organism) by *S. aureus* carrier status at screening will be analyzed using analogous terms in multivariate logistic regression models.

TABLES AND FIGURES

The SAP describes the conventions to be used for presenting results in text and in tables and figures. Those conventions are based on the ICH guideline for reporting clinical trial results (27). The 12 planned tables are these:

- Randomization by study center, stratified by country
- Stratification variables by treatment group
- Baseline demographic and clinical characteristics by treatment group
- Baseline blood investigations by treatment group
- Clinical assessments by treatment group across study visits
- Withdrawals, protocol deviations, and violations by treatment group
- Primary and secondary efficacy outcomes by treatment group
- Infectious organisms by treatment group
- SAEs by treatment group
- Relationship of SAEs to study medication by treatment group
- SAE body systems by treatment group
- Effect of treatment on infectious organisms, by subgroup

The 7 planned figures are these:

- Flowchart of patient progression through the study
- Kaplan–Meier survival curves for primary efficacy outcome by treatment group
- Kaplan–Meier curves for time to first episode of peritonitis by treatment group
- Kaplan–Meier curves for time to first tunnel infection by treatment group
- Kaplan–Meier curves for time to first exit-site infection by treatment group
- Kaplan–Meier curves for time to infection-associated catheter removal by treatment group
- Forest plot of effect of treatment on primary and secondary efficacy outcomes for all patients and for pre-specified subgroups

RESULTS AND DISCUSSION

The SAP for the HONEYPOT randomized controlled trial describes analysis principles, methods for dealing with a range of commonly encountered data analysis issues, and specific statistical procedures for analyzing the primary, secondary, and safety outcomes. The statisticians and clinical investigators who developed the plan were blinded to the treatment allocation and treatment-related study results and will remain blinded until the central database is locked for final data extraction and analysis.

The HONEYPOT SAP is being published in accordance with the ICH guideline on statistical principles for clinical trials (2), which recommends making a pre-determined SAP publicly available before unblinding to minimize the risk of outcome reporting bias. Such bias, defined as the selection for publication of a subset of the original recorded outcome variables on the basis of the known results (28), can arise from multiple *post hoc* analyses or selectively reported results that are more sensational (typically positive) or aligned with the preconceived bias of investigators. Indeed, one systematic review of randomized controlled trials (29) found that between 40% and 62% of trials had at least one primary outcome that was changed, introduced, or omitted. Moreover, it

found that, compared with nonsignificant outcomes, statistically significant outcomes were far more likely to be fully reported (range of odds ratios: 2.2 – 4.7). In another cohort study of 102 randomized controlled trials approved by ethics committees in Denmark between 1994 and 1995, 86% of survey responders (42 of 49) denied the existence of unreported outcomes despite clear evidence to the contrary (30). A more recent cohort analysis of systematic reviews of randomized controlled trials found that outcome reporting bias was suspected in at least one trial in more than a third of reviews, that one fifth of significant results became nonsignificant after adjustment for outcome reporting bias, and that a quarter of reviews would have overestimated treatment effect by 20% or more because of outcome reporting bias (31). Although major medical journals have tried to minimize the risk of non-publication of studies with negative results by publishing only trials that have been publicly registered before commencement of recruitment, calls are increasing for this restriction to be extended to publishing only trials that have published a predefined SAP before investigators and statisticians access unblinded outcome data (3). That concept has been embraced in recent times by critical care journals (32–34).

CONCLUSIONS

A SAP containing pre-specified principles, methods, and procedures to be adhered to in the analysis of data for the HONEYPOT trial has been developed in accordance with international guidelines. Making public this pre-specified analysis plan will minimize the potential for bias in the analysis of trial data and in the interpretation and reporting of trial results.

DISCLOSURES

The HONEYPOT trial is funded by grants from Baxter Healthcare (Extramural Grant Program), the Queensland Government (Smart Health Research Grant), and Gambro Pty Ltd. DWJ is a consultant for Baxter Healthcare Pty Ltd. and has previously received research funds from that company. He has also received speakers' honoraria and research grants from Fresenius Medical Care. He has previously been a consultant to Gambro Pty Ltd. and was the recipient of a Gambro Research Grant that partly funded the HONEYPOT trial. DWJ received a Baxter Healthcare Renal Discoveries Extramural Program Grant that partly funded the HONEYPOT trial. He is an International Society of Peritoneal Dialysis Councillor and a current recipient of a Queensland Government Health Research Fellowship. CMH has received speakers' honoraria and research grants from Fresenius Medical Care and has been a consultant to Fresenius Medical Care. She has received research funds from Gambro Pty Ltd. and was the recipient of a Queensland Health Smart Health Research Grant. AC is a consultant for and has received research funds from Baxter Healthcare Pty Ltd. He has also received speakers' honoraria from Fresenius Medical Care. He is a recipient of a National Health and Medical Research Council Principal Research Fellowship. All other authors have no financial conflicts of interest to declare.

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