Primary / Secondary Analysis

Analysis Plan

The primary analysis was a hospital-level analysis. All hospitals had observations on the baseline period and on the intervention period. There are two types of outcome variables:

- those for which a patient can experience once, such as *Hospital Mortality* (binary)
- those for which a patient can experience more than once, such as *Clinical Deterioration Events* (count).

For each outcome a 'numerator' and a 'denominator' was identified. For a binary outcome, the numerator was the number of events in a hospital during a particular period (baseline or intervention), and the denominator was the number of discharges. For a count outcome the numerator was the number of events in a hospital during a particular period, and the denominator was the number of patient-days. See following table for variable and macro names.

Generalized estimating equations (GEE) methods were used to account for clustering by hospital, with an exchangeable correlation structure.

Binary outcomes:
For a binary outcome, a GEE binomial model was used. There were two separate analyses, both using the number of events (x) and the number of discharges (n):

- a logit link was used, so that the log-odds of the outcome was modelled as a function of the predictors
- an identify link was used, so that the probability of the outcome was modelled as a function of the predictors

The predictor variables were:

(1) the treatment dummy indicator and
(2) the corresponding summary statistic (log odds or probability) for that hospital during the baseline period.

R code for GEE model of binary outcomes at the group level

```
# load geepack library
# n is the number of discharges at a hospital
# x is the number of events at that hospital in the post-
#   randomization period
# Hospital is the categorical variable indicating which hospital
#   the above numbers come from
# logitBaseline logit of baseline probability for this hospital,
```

```
#   calculated with addition of 0.5 to numerator and 1 to
#   denominator if x = 0
# probBaseline baseline probability for this hospital,



#model for log-odds of outcome at the group level

GEEfit.OR <- geeglm(cbind(x, n-x)~Intervention + logitBaseline,
                          id = Hospital,
                          family = binomial,
                          data=EPOCH,
                          corstr = "exchangeable")


# model for probability of outcome at the group level

GEEfit.RD <- geeglm(cbind(x, n-x)~Intervention + probBaseline,
                    id = Hospital,
                    family =binomial(link=make.link("identity")),
                    data=EPOCH,
                    corstr = "exchangeable")


# model for probability of outcome at the indovidual level

# y = 1 for outcome, 0 for no outcome

GEEfit.RD <- geeglm(y~Intervention + probBaseline,
                     id = Hospital,
                    family =binomial(link=make.link("identity")),
                    data=EPOCH,
                    corstr = "exchangeable")
```

Count outcomes:

For a count outcome, a GEE Poisson model was used. There were two separate analyses, both using the number of events (x) and the number of patient-days (time):

- a log link was used, so that the log-rate was modelled as a function of the predictors
- an identify link was used, so that the rate was modelled as a function of the predictors

Both models included the number of patient days. With the log link, include log(patient days) as the offset. With the identity link, the code below shows how patient days were included

The predictor variables were

(1) the treatment dummy indicator and

(2) the corresponding summary statistic (log rate or rate) for that hospital during the baseline period.

See following example R code for details.

```
# Modelling the log-rate
# N is the number of patient days in the post-randomization
#     period
# x is the number of events in the post-randomization period
# Hospital is the categorical variable indicating which hospital
#   the above numbers come from
# logBaseline is log of baseline rate for this hospital,
#   calculated with addition of 0.5 to numerator if x = 0
# Baseline is baseline rate for this hospital


geefit.RR <- geeglm(x ~offset(log(N)+Intervention + logBaseline,
                    id = Hospital,
                    family = poisson,
                    data=EPOCH,
                    corstr = "exchangeable"))

# The linear model needs this rearrangement of the data to
# incorporate the time at risk
# Nlin – its coefficient is the usual care intercept
# NlinG – its coefficient is the rate difference
# NlinB – its coefficient is the increase in the rate per unit
#    increase of the baseline rate

 EPOCH$Nlin    <- EPOCH$N/1000
 EPOCH$GNlin   <- EPOCH$N*(d$Group=="BedsidePEWS")
 EPOCH$$BNlin  <- EPOCH$N*(EPOCH$Baseline)

# modelling the rate

 geefit.RD <- geeglm(x~Nlin+GNlin+BNlin-1,
                    id = Hospital,
                    family = poisson("identity"),
                    data=EPOCH,
                    corstr = "exchangeable"))
```

Continuous outcomes at the individual level:

The patient level continuous outcomes in Tables 2 and S4 were also modelled with a GEE, using a Gaussian model. Although the data are not normal at the individual level, the large sample size and the robustness of GEE implies that comparisons of means are largely unaffected by this non-normality.

For an individual-level outcome, these models all had the same structure

```
# y is a continuous outcome for a patient
# Hospital is the hospital the patient is in
# x0 is the mean value at baseline for the hospital a
#  patient is in

geefit.RR <- geeglm(x ~Intervention + x0,
                    id = Hospital,
                    data=EPOCH,
                    corstr = "exchangeable")
```

Sensitivity to model choice

As the results of the analysis of cluster RCTs can vary somewhat with the method of analysis, models for odds ratios, probabilities, and rate ratios were also run using several other approaches

Logit and log-rate models

- GEE on only post-intervention values
- Generalized linear mixed effects regression model (GLMER) on only post-intervention values
- GEE with both pre and post values as outcomes, estimating interaction between time and intervention
- GLMER with both pre and post values as outcomes, estimating interaction between time and intervention
- GEE on post-intervention values with baseline value as a covariate
- Generalized linear mixed effects regression model (GLMER) on post-intervention values with baseline value as a covariate
- Weighted linear model (weight = 1/(variance of logit) or weight = 1/variance (log-rate))) for logits (or log-rates), with baseline logit (or log-rate)as covariate.
- Quasibinomial logistic or Poisson regression (which allows for more variance than the binomial or Poisson) on post-data, with baseline logit (or log rate) as covariate

Models for probability or rate

- GEE on only post-intervention values (binomial or Poisson variance, identity link)
- GEE with both pre and post values as outcomes, estimating interaction between time and intervention (binomial or Poisson variance, identity link)

- GEE on post-intervention values with baseline value as a covariate (binomial or Poisson variance, identity link)
- Weighted linear model for post-probabilities (weight=1/(variance probability) or 1/(variance weight)), with baseline probability or rate as covariate
- Quasibinomial regression (which allows for more variance than the binomial or Poisson) on post-data, with baseline probability as covariate (binomial or Poisson variance, identity link)

Shell Tables

Continuous outcomes

Resuscitation Team Calls	*B_rt/B_PatientDays*	*P_rt/P_PatientDays*	Poisson
Stat Calls	*B_sc/B_PatientDays*	*P_sc/P_PatientDays*	Poisson
Urgent ICU Consultations	*B_rr/B_PatientDays*	*P_rr/P_PatientDays*	Poisson
Urgent ICU Admissions	*B_uicu/B_PatientDays*	*P_uicu/P_PatientDays*	Poisson
Unplanned ICU Readmissions	*B_icur/ B_PatientDischargesICU*	*P_icur/ P_PatientDischargesICU*	Poisson
Unplanned Hospital Readmission	*B__hr/ B_PatientDischarges*	*P__hr/ P_PatientDischarges*	Poisson

Subgroup Analysis Plan

Two subgroup analyses are planned using the same methodology described in the previous section. In the first, ECMO, the hospitals will be divided into two groups: those that have ECMO service and those who do not. In the second, MET, the hospitals will be divided into two groups: those that have MET service and those who do not.

For each subgroup analysis, the treatment effect (BedsidePEWS vs. usual care) will be estimated in each group of hospitals and the presence of a subgroup effect will be assessed in a single GEE model with a one-term treatment by subgroup interaction term.

ICU Analysis

Analysis Plan

This was a patient-level analysis that followed the same general procedures as outlined above. However, the data has a record for each admission to the ICU, and a patient may have more than one admission; the table below shows how these were handled. Furthermore, a few patients had admissions to the same ICU in both study periods; these patients were eliminated from this analysis. The analysis was done with one record per patient as described in the table below.

Outcome	**Description of the per patient outcome variable**
Total length of stay	The sum over admissions of the lengths of stay
Average length of stay	The average over admissions of the lengths of stay
PIM at admission	The average over admissions of the PIM at admission
PIM II Prediction Mortality (/1000 urgent ICU discharges) (inverse-logit of *PIM*)	The average probability over admissions of the PIM II predicted mortality
Ventilation Free Days	The days free of ventilation for the first admission
Days of technology use	Sum of all days over all admissions of mechanical ventilation days, nitric oxide days, ECMO days and dialysis days
Use of a technology (HFOV, ECMO, NO. Dialysis, MV)	Binary indicator of whether the technology was used on any of the days in the ICU.
24-hour PELOD	The average over admissions of the PELOD score for the first 24 hours
PELOD ICU Stay	The average over admissions of the PELOD score for the entire admission