Please note: This is an updated statistical analysis plan with modifications for WP6 (cost effectiveness work).

STATISTICS AND METHODOLOGY

Statistical analysis plan and sample size calculation

Statistical analysis plan for the main RCT

Generalized mixed-effects models with log-link function will be used to analyse the primary outcome. The fixed effects will be the interventions, the country, and the time (to account for the partial confounding of the interventions with time). A cluster-specific random effect will be considered to model the repeated measurements on the same cluster. In the presence of over-dispersion, negative-binomial mixed-effects models with the same parametrization will be used instead. Model-based intervention effects will be reported. Supportive analyses considering more complex random effects structures will also be investigated. (e.g., time within clusters, wards within hospitals). The interaction between time and interventions will also be added as a fixed effect to model a possible time-varying intervention effect.

Sample size calculation for main RCT

Based on findings and modelling from the ECDC point prevalence survey of 2016/2017, mean estimated incidence densities of HAI due to a composite index incorporating CRE, CRPA and CRAB combined for Greece, Italy, Romania, Spain, were 2.99/1000 patient-days, 0.73, 0.62, and 0.51, respectively. Considering the lowest incidence density of 0.5/1000 patient-days, an intra-cluster correlation of 0.9, four randomisation steps, and 25'000 admissions per year in average, the following estimations were calculated for hypothesized effects of the intervention programmes:

- Reduction of 25% of HAI by IPC alone (IPC compared to baseline): 2.3 required hospitals
- Reduction of 35% of HAI by IPC and ABS combined (IPC plus ABS compared to baseline): 1.1 required hospitals
- Reduction of 10% HAI by ABS on top of IPC (ABS compared to IPC): 19.9 required hospitals
- Reduction of 15% HAI by enhanced implementation support on top of 35% reduction by IPC and ABS combined (as compared to basic implementation support): 9.8 required hospitals

Twenty-four acute care hospitals from high AMR prevalence areas provide sufficient power to perform all relevant comparisons for the primary outcome as specified by REVERSE: 1) IPC to baseline; 2) ABS to IPC; 3) IPC and ABS combined to baseline; and 4) enhanced implementation support to basic implementation support.

Additionally, we hypothesise that enhanced implementation will have an added effect on the primary outcome of 15% on top of the IPC- and ABS-modules combined (additional 15% to a 35% reduction). A total of 9.8 hospitals would need to be included in each group considering the same parameters as outlined above. Analysis will be done using a generalized mixed-effects models with log-link function as described. The fixed effects will be the enhanced implementation support, the country, and the time (to account for the partial confounding of the interventions with time).

Statistical analysis plan for within-trial cost-effectiveness analysis

Provided sufficient data become available with time to undertake the analysis, in line with the statistical analysis plan, generalised linear models will be used to assess the impact of the

interventions on outcomes relevant to the within-trial cost-effectiveness analysis, including mortality, infection incidence, and healthcare cost due re-admissions and changed length of stay.

For each intervention, the effectiveness in terms of these outcomes will be estimated using a counterfactual approach: that is, fitting a model to the data to predict what would happen if all hospitals had implemented the intervention simultaneously (on the day the first hospital implemented the intervention), compared to what would have happened if none of the hospitals had implemented the intervention. Where possible, the statistical modelling will account for heterogeneity across the trial, by including an interaction with pre-intervention setting-specific characteristics such as the local prevalence of carbapenem-resistant organisms. Posterior samples will be drawn, using the modified model matrix, the coefficients and the variance-covariance matrix, from the different regression models to be able to incorporate uncertainty in estimated effects in probabilistic sensitivity analyses.

After estimating the intervention implementation costs and potential changes in resource use and costs, as well as potential effects on QALYs through changes in mortality and infections (latter obtained from the quality of life study), we will estimate the incremental net monetary benefit (iNMB) of implementing the intervention in the different countries. This analysis directly incorporates estimates from the regression models above, and hence implicitly assumes – without re-design of the intervention – no effect beyond the end of the trial follow-up. When estimating the iNMB, cost and QALYs will adhere to country-specific cost-effectiveness guidance.

Handling of missing data and drop-outs

Missing data

Quarterly checks on data completeness with feedback to the centres will be organised. Delays or errors of data collection will be discussed in the quarterly videoconferences with the hospitals.

Drop-outs

Hospitals dropping out of the study will be replaced until month 9, which allows a minimum baseline of 6 months. Thereafter, hospitals dropping out will not be replaced. The power calculation is conservative, and the primary outcome can still be analysed.