The random effects appropriately account for the correlation between observations related to the same patient or same site. GLMM has some advantages over GEE. For one, GLMM provides an estimate of the unexplained variation between patients with respect to transmission risk (as represented by the variance of the random patient effect). Secondly, GLMM allows us to account for a more complex correlation structure than GEE, accounting for the clustering both by patient and by location. Thirdly, GLMM utilizes all available data and can produce unbiased estimates when missing is at random. In addition, we will combine the data from both settings and examine whether the effect of each risk factor differs by setting by examining interactions between each risk factor of interest and setting using GLMM. Data analysis will be performed using Stata/SE (version 16).

D10. Potential Problems and Strategies to Ensure a Robust and Unbiased Approach for Aims 1 and 2

We have experience with all steps of aims 1 and 2. In our non-VA studies, we enrolled over 400 MRSA patients and collected the same number of glove and gown cultures in a two-year period at a smaller number of hospitals (enrollment for this study is a three-year period). Thus, we are confident that we can meet enrollment goals. If we have difficulty meeting target enrollment goals or want to enroll in additional states, we already have two additional sites interested in being part of the study.

Aim 3: Develop a dynamic transmission model to compare the cost-effectiveness of different contact precaution strategies.

D11. Overview of cost-effectiveness analysis

When determining which settings and patients should be prioritized for use of contact precautions, the efficiency and effectiveness of this approach must be considered. Economic evaluations, such as those proposed here, can help determine the optimal strategy when taking into account the resources used and the outcomes to be achieved among a list of various targeted contact precautions strategies.

We will develop a dynamic transmission model to compare the cost-effectiveness of different contact precaution strategies. For pragmatic considerations, the analysis will compare the costs and effectiveness of four different contact precaution strategies across diverse hospital settings: 1) having no MRSA patients on contact precautions; 2) having all MRSA patients on contact precautions; 3) having all MRSA patients in the ICU only on contact precautions; 3) having certain healthcare professionals (respiratory therapists, physical therapists, occupational therapists, nurses, physicians) use contact precautions and other professions not; in both ICU and non-ICU settings and 4) having admitted MRSA patients with certain risk factors on contact precautions.[46]

For each strategy, costs will include both direct medical and indirect (i.e., productivity losses) costs. Effectiveness measures will include MRSA colonizations and infections averted, infection-related deaths averted, and life-years. An additional effectiveness measure will be PPE saved that could then be used for other purposes, which is an especially relevant metric in the current COVID-19 pandemic when PPE is scarce and has so many other important uses. After eliminating dominated strategies, we will identify the optimal strategy by constructing incremental cost-effectiveness ratios by dividing the incremental cost by the incremental effectiveness between two strategies. We will analyze this model from the VA perspective using VA-specific cost inputs whenever possible including those from our previous studies which estimated the attributable mortality and both pre-[49] and post-discharge[50] attributable costs from MRSA HAIs in VA facilities.

D12. Transmission model

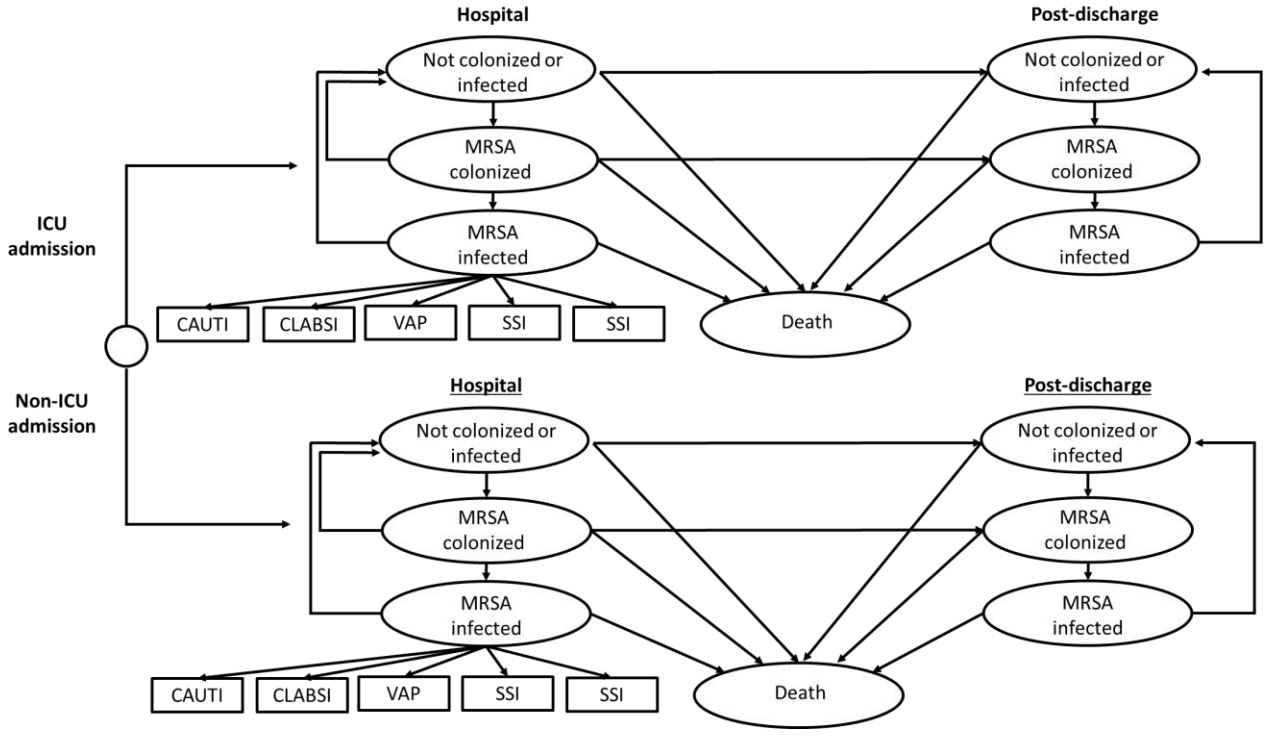
Figure 4 represents a graphical presentation of our dynamic transmission model. At baseline, patients enter the simulation model based on their ICU- vs. non-ICU admission location status. According to the initial prevalence of MRSA colonization and MRSA infection in ICU or non-ICU settings, we will model the natural history of MRSA for patients during the hospital stay and post discharge. We will assume that non-colonized patients have a risk of acquiring MRSA colonization based on where they were originally admitted to and the colonization prevalence of MRSA colonization in the corresponding setting (the higher the prevalence of MRSA colonization, the higher the risk of acquiring MRSA colonization amongst non-colonized patients). An MRSA colonized patient may face four possibilities: 1) progressing to MRSA infection; 2) remaining asymptomatically

colonized; 3) transitioning to not colonized or infected state; and 4) dying. In addition, an MRSA infected patient will stay in the same health state until the treatment is complete or he/she dies.

We will model five types of MRSA infection; “catheter-associated urinary tract infection (CAUTI)”, “central line-associated bloodstream infection (CLABSI)”, “ventilator-associated pneumonia (VAP)”,” skin and soft tissue infection (SSTI)”, and “surgical site infection (SSI)”. Also, patients discharged from hospital who are still MRSA colonized have a chance of developing an infection which can be treated in an outpatient setting or can lead to another subsequent hospitalization. We will use a similar model structure with different sets of probabilities and rates for non-ICU admitted patients.

Model parameters: We will inform our core model parameters including transition probabilities and rates, direct medical costs, indirect costs, baseline MRSA colonization and infection prevalence rates for ICU and non-ICU settings, and incidence of MRSA colonization and infection rates for ICU and non-ICU settings from the published literature.[81–84] Data from previously published studies coupled with data from aims 1 and 2 of this proposal will inform effectiveness of precaution policies in ICU and non-ICU settings. In the event that we find multiple studies reporting on a model parameter, we will conduct an appropriate meta-analysis method to inform the pooled estimates.[85] To inform the second- and first-order uncertainty, we will assign probabilistic distributions to the model parameters of our model in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-Society for Medical Decision Making (SMDM) Modeling Good Research Practices Task Force.[86]

Figure 4. *Graphical representation of the dynamic transmission model.*



ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*; CAUTI: catheter-associated urinary tract infection; CLABSI: central line-associated bloodstream infection; VAP: ventilator-associated pneumonia; SSI: surgical site infections; SSTI: skin and soft tissue infection

Analysis: Our model will consist of two elements; an underlying transmission model which will be used to simulate the underlying patient health states, and then an economic model which will incorporate the cost components associated with the underlying patient events and histories. We will simulate patient flow, and MRSA transmission and infection in a 100-bed hospital having 15 ICU beds for one year, following patient movement after discharge during that period, allowing for hospital readmissions. Model parameters incorporated in the transmission component of the model will be treated as fixed, estimated as the mean of the

underlying parameter distribution. For each run of the transmission model, key events and patient outcomes will be tracked recorded to and output for the cost analysis evaluation, as we have done previously.[48] The economic analysis will then be implemented as a Monte Carlo based simulation that accounts for second-order variation in the uncertainty of the economic parameter inputs. This analysis will be repeated across a range of transmission model parameters based on our estimated distributions, representing a sensitivity analysis for our model outputs and evaluating the robustness of our results. Given the choice of one-year time horizon in the base case analysis, we will not discount future health and economic values. Nevertheless, we will run separate scenario analysis to run the model for 2 and 5 years, in which case, we will discount the future health and economic values by using a 3% discount rate as recommended by the guidelines.[87] We will build our dynamic transmission model in R version 3.5.1.

One-way sensitivity analysis: Our model will be capable of performing multiple one-way sensitivity analyses to measure the robustness of our model outcomes against changes in core parameters including all costs, effect measures, and probabilities and rates. We will report the results of one-way sensitivity analyses graphically for ease of interpretation.

Graphical representation of probabilistic outcomes: We will quantify probabilistic outcomes using cost-effectiveness plane and cost-effectiveness acceptability curves (CEAC). A cost-effectiveness plane is a two-dimensional representation of incremental costs vs. incremental effectiveness (either in number of MRSA colonization averted or number of MRSA infection averted) that enables estimation of the probability distribution of cost-effectiveness outcomes. We will plot the results of the Monte Carlo simulation as scatterplots on the cost-effectiveness plane to compare different MRSA precaution policies of our model against each other. The CEAC represents the probability that a particular interventions strategy will be cost-effective at different willingness-to-pay values, indicating the extent to which society is willing to pay to gain one unit of health.[87] We will calculate the probability of cost-effectiveness associated with each of the policies being considered in our model for different willingness-to-pay values and represent them in a CEAC.

D13. Veteran Engagement

Veteran engagement has already occurred through a Veteran engagement board and will occur through Veteran patient focus groups. The Veteran engagement board was convened on Monday May 4. We presented the proposed research to a group of five Veterans by video teleconferencing. They provided commentary and feedback that was incorporated into this proposal and into the below plans relative to the focus group work.

We will also have focus groups with VA patients and healthcare workers. We will conduct focus groups to explore perceived barriers and facilitators to implementation of a risk-based approach to contact precautions among Veteran patients and healthcare workers. We will include one healthcare worker focus group and one Veteran patient focus group at each of three sites: Baltimore, Portland and Houston. Each group will consist of at least six participants. Healthcare personnel will include medical doctors, nurses, and allied healthcare providers such as physical therapists and respiratory therapists. Participants will be recruited via posters and email and direct recruitment of patients while in hospital. Inclusion of geographically diverse hospitals will allow for inclusion of various perspectives and experiences. Discussions will be audio recorded. Information generated will be used to inform and compliment the parameters used in the cost effectiveness model.

Focus group discussions will be summarized immediately following the session. The moderator or note taker and/or technician will debrief immediately afterwards. Thematic analysis will be utilized to analyze the qualitative findings that emerge from the discussions. This is an appropriate method to extract unique information from unstructured interviews such as those described in this study.[88,89] Thematic analysis approach offers fewer preconceptions than other qualitative methods and is therefore subject to less bias.[90] Two reviewers will independently code data collected from the discussions. Emergent themes and patterns in the data will be identified by initial inductive analysis. Through reviewer consensus, themes will be condensed into overarching categories that represented and accurately explained the dataset. Nvivo 9 Software will be used to help facilitate management and analysis of the data.