Technical description of the decision model

We detail here the computations undertaken in estimating cost effectiveness of IVIG added to standard care compared to standard care alone for the overall sample of severe sepsis and septic shock, and not for the subgroup analyses. The alternative treatments are represented by $i = \{0,1\}$, where 0 represents standard care and 1 represents IVIG added to standard care. Although the ICER was the cost-effectiveness outcome used in presenting cost-effectiveness results, the net monetary benefit (NMB) was used in computations. This measure is defined as $\mathrm{NMB}_i = \mathrm{Q}_i \cdot \lambda - \mathrm{C}_i$, where Q_i represents the total expected benefits from treatment *i* and C_i the expected total costs incurred. The willingness to pay for a unit of benefits is here represented by λ.

The decision model estimates life expectancy by considering two components: a short term (ST) and a long term (LT) component. The overall life expectancy associated with treatment *i*, LE_i, can be expressed as in Equation 2. $LE^{(ST)}$ is a restricted life expectancy for the period in which the patients are hospitalised, $LE^{(LT)}$ a long term life expectancy given that patients survived the short term and $p_i^{(ST)}$ is the probability of patients that received treatment *i,* dying in the short term, i.e. within hospital.

Life expectancy

$$\mathrm{LE}_i = \mathrm{LE}_i^{(ST)} + (1 - p_i^{(ST)}) \cdot \mathrm{LE}^{(LT)} \qquad \text{[Equation 2]}$$

$$\mathrm{LE}_i^{(ST)} = p_i^{(ST)} \cdot time_{dead}^{(ST)} + \left[1 - p_i^{(ST)}\right] \cdot time_{survivor}^{(ST)} \qquad \text{[Equation 3]}$$

$$p_i^{(ST)} = \begin{cases} p_0^{(ST)} = \dfrac{e^{\theta}}{1+e^{\theta}}, & \text{if } i = 0 \\ \dfrac{e^{\theta+d}}{1+e^{\theta+d}}, & \text{if } i = 1 \end{cases} \qquad \text{[Equation 4]}$$

$$\mathrm{LE}^{(LT)} = \sum_{n=1}^{TH} \prod_{t=1}^{n} \left[1 - tp_t\right] \qquad \text{[Equation 5]}$$

$$tp_t = \max\left(p_t^{(LT)}, GP_{age+t}\right) \qquad \text{[Equation 6]}$$

Equations 3 and 4 detail how the model evaluates the short term life expectancy. The calculations consider the short term lifetime as a discrete variable assuming the values $time_{dead}^{(ST)}$ and $time_{survivor}^{(ST)}$ with probability $p_i^{(ST)}$ and (1- $p_i^{(ST)}$), respectively. $time_{dead}^{(ST)}$ represents the within hospital lifetime of a patient that did not survive the initial hospitalisation, whilst $time_{survivor}^{(ST)}$ represents the within hospital lifetime of a patient that did survive the initial hospitalisation

For the standard care group, $p_0^{(ST)}$ was estimated using the overall proportion of patients that died before discharge from acute hospital observed in the ICNARC CMP Database. For the treatment group, the log odds ratio (d) was applied to the standard care estimates as shown in Equation 5.

Long term life expectancy is represented by a Markov model (non-homogeneous), with a cycle length of 1 year and transition probabilities represented by tp_t , i.e. the probability of dying between time *t-1* and *t,* given that the patient survived to time *t-1* (long term). tp_t is calculated as the maximum of the transition probabilities derived from the parametric model fit to the Cuthbertson dataset, $p_t^{(LT)}$, and GP_{age+t} (general population, age and gender specific estimates). The transition probabilities $p_t^{(LT)}$ assume estimates from a Weibull(λ, γ) regression over Cuthbertson's data – model with age at admission only (methods and results reported in Chapter 5 and Appendix 6). To generate predictions from this model we used the mean age observed in the ICNARC CMP Database. Note that the long term transition probabilities, tp_t , are independent of treatment, *i*.

Based on life expectancy calculations, total costs and QALYs were obtained from the decision model as shown below. For simplicity, discounting is not shown, although this was applied. Categories of unit costs used are c.treat_i, representing the costs associated to treatment *i*, uc_{icu} and uc_{ward}, the costs per day of stay in the critical care unit and the ward, respectively, and $c_t^{(LT)}$, the yearly costs associated to costs incurred in year *t* after discharge from hospital. timeicu_d, timeicu_s, timeward_d and timeward_s represent time in the critical care unit and the ward for hospital survivors (index *s*) and non-survivors (index *d*) of the sepsis episode. These parameters were informed by length of stay data from the ICNARC CMP Database.

Total costs

$$C_i = C_i^{(ST)} + (1 - p_i^{(ST)}) \cdot C_i^{(LT)} \quad \text{[Equation 7]}$$

$$C_i^{(ST)} = \text{c.treat}_i + p_i^{(ST)} \cdot \left(\text{timeicu}_\text{d} \cdot uc_\text{icu} + \text{timeward}_\text{d} \cdot uc_\text{ward}\right) + \\ + \left[1 - p_i^{(ST)}\right] \cdot \left(\text{timeicu}_\text{s} \cdot uc_\text{icu} + \text{timeward}_\text{s} \cdot uc_\text{ward}\right) \quad \text{[Equation 8]}$$

$$C^{(LT)} = \sum_{n=1}^{TH} \prod_{t=1}^{n} \left[\left(1 - p_t^{(LT)}\right) \cdot c_t^{(LT)}\right] \quad \text{[Equation 9]}$$

Total QALYs

$$Q_i = Q_i^{(ST)} + (1 - p_i^{(ST)}) \cdot Q^{(LT)} \quad \text{[Equation 10]}$$

$$Q_i^{(ST)} = \text{LE}_i \cdot u^{(ST)} \quad \text{[Equation 11]}$$

$$Q^{(LT)} = \sum_{n=1}^{TH} \prod_{t=1}^{n} \left[\left(1 - p_t^{(LT)}\right) \cdot u_t^{(LT)}\right] \quad \text{[Equation 12]}$$

Utility parameters comprised $u^{(ST)}$ and $u_t^{(LT)}$, where $u^{(ST)}$ is the within hospital utility of patients with severe sepsis and $u_t^{(LT)}$ the utility of survivors of sepsis in the t^{th} year after hospital discharge. The sources of data used to inform the input parameters of the decision model are further summarised in Appendix 9.

Expected value of sample information (EVSI) methods

Detailed methods on calculating EVSI are well described in the literature.[114] The EVSI requires two nested expectations to be evaluated, which is commonly undertaken by implementing two nested Monte Carlo simulation procedures. In the decision model detailed above, relative treatment effects are applied to short term benefits only (structured as a decision tree) and long term outcomes do not depend on the treatment received. Because of this, we were able to express the net benefits of each of the treatments as a linear function of transformed parameters (by re-arranging Equations 7–9 and 10–12). This allowed assuming model linearity between the net benefits and both the relative treatment effect (log odds ratio) and functions of the original set of parameters. By demonstrating linearity, we can calculate expected net benefits from the expected values of its components, and avoid using simulation procedures in evaluating one of the two nested expectations. To compute the expected value of the short term probability of dying (Equation 4) we used a Taylor-series approximation (with two terms) of the expected value function.

In calculating EVSI, there is also the need to combine prior information on the treatment effect with new data. We used the standard Normal-Normal updating for the log odds ratio (in closed form), as described elsewhere.[114] When statistical descriptions of the prior for treatment effects were generated from a random effects model, it was the predictive distribution that was used further (e.g. to sample new data from). The new data was not assumed used to update the random effects parameter (its variance or precision).