Appendix 1

Value of information analysis

We started the analysis by estimating the EVPI. For a cost-effectiveness analysis informing a decision on a number of interventions (i) with unknown parameters (θ), Monte Carlo simulation takes K samples from the joint distribution of θ, and generates a corresponding set of K net benefits (NB (i, θ^1),…, NB (i, θ^K)), for each intervention. Averaging these values, the optimal decision with current information is to adopt the intervention with the maximum expected NB, $max_i \; E_\theta \; NB \; (i, \theta)$. If we have perfect information on θ, the maximized NB becomes $max_i \; NB \; (i, \theta)$; however, because the true value of θ is unknown, averaging the maximized values gives the expected maximum NB under perfect information, $E_\theta \; max_i \; NB \; (i, \theta)$. The EVPI is the difference between the expected NB of a decision with perfect information and the decision based on current information:

$$EVPI = E\theta \; maxi \; NB \; (i, \theta) - maxi \; E\theta \; NB \; (i, \theta) \qquad \text{Equation 1}$$

EVPI calculated using Equation 1 is an estimate for an individual patient episode (i.e., per-patient EVPI); however, because decisions are taken at the population level, population VOI measures should be determined, which is the per-patient estimate multiplied by the total number of patients who will benefit from additional information over the expected lifetime of the intervention. Given the acute nature of the interventions, the population VOI measure can be expressed as follows:

$$Population \; VOI \; measure = \; VOI \; mesure \; . \left(\sum_{t=1}^{T} \frac{I_t}{(1+r)^t}\right) \qquad \text{Equation 2}$$

Where T is the lifetime of the intervention, I_t is the incidence in each future time period t, and r is the annual discount rate which we set at 5%. Time horizons in this study ranged from five to ten years. Sensitivity analyses were performed to test the impact of varying the time horizon and the WTP threshold on VOI estimates.

When the population EVPI appears to be too small compared with the expected research costs, additional research would not be required, and accordingly, the decision would be to adopt or reject the intervention based on the current evidence. On the other hand, when the population EVPI is likely to exceed the costs of additional research, then further research is potentially worthwhile. In this case the EVPPI would be calculated to know the focus and type of the additional research.

For a subset of one or more parameters where (θ_I) is the parameters of interest and (θ_C) is the complementary set of parameters, the optimal decision would be that with the maximum expected NB after averaging over the distribution of θ_C, conditional on θ_I, $max_i \, E_{(\theta_C|\theta_I)} NB(i, \theta_I, \theta_C)$. Again, because we do not have perfect information on θ_I we must take the expectation with respect to θ_I which is $E_{\theta_I} max_i \, E_{(\theta_C|\theta_I)} NB(i, \theta_I, \theta_C)$. The EVPPI is the difference between the expected NB with perfect information and the expected NB with current information:

$$EVPPI_{\theta_I} = E_{\theta_I} max_i \, E_{(\theta_C|\theta_I)} NB(i, \theta_I, \theta_C) - max_i \, E_\theta NB(i, \theta) \quad \textit{Equation 3}$$

The Monte Carlo solution to the conditional term in Equation 3 is to run a two-level simulation. The outer-loop samples from θ_I, and then the inner loop samples from θ_C conditional on the outer sampled value of θ_I. Convergence of the EVPPI estimates informed the number of inner and outer simulations. Nevertheless, When the model is linear (e.g., decision tree) with no correlation between input parameters, a one-level simulation approach can be used in which we sample from θ_I, but keep the complementary parameters θ_C fixed at their prior means:

$$EVPPI_{\theta_I} = E_{\theta_I} max_i \, NB(i, \theta_I, E(\theta_C)) - max_i \, E_\theta NB(i, \theta) \qquad \textit{Equation 4}$$

The next step was to estimate the EVSI for a future study with a sample size *n* that will provide additional information *D* for θ_I. Assuming that θ_I and θ_C are a priori independent, the expected optimal NB given *D* is found by taking the expectation over the posterior distribution of θ_I given *D* and the prior distribution of θ_C, which is $max\, E_{\theta_C,(\theta_I|D)}\, NB(i,\theta_I,\theta_C)$. As *D* is unknown, we average over the distribution of *D*, which gives $E_D max_i\, E_{\theta_C,(\theta_I|D)}\, NB(i,\theta_I,\theta_C)$. The EVSI is the difference between this, and the expected NB with current information:

$$EVSI_n = E_D max_i\, E_{\theta_C,\theta_I|\,D}\, NB(i,\theta_I,\theta_C)\; -\; max_i\, E_\theta NB(i,\theta) \qquad \textit{Equation 5}$$

The first term in Equation 5 has a two-level Monte Carlo solution. The inner expectation requires a Bayes update of θ_I given data *D*, and the averaging of the NB function over this posterior distribution combined with the prior distribution of θ_C. This is made assuming that the likelihood for the proposed data *D* is conjugate with prior parameter distributions, which means that the parameters for posterior distributions can be estimated using closed forms and to scalar priors with no correlations. The nested simulation can be avoided in linear models with no parameter correlation.

$$EVSI_n = E_D max_i\, NB(i,E(\theta_I|D),E(\theta_C))\; -\; max_i\, E_\theta NB(i,\theta) \qquad \textit{Equation 6}$$