Additional data on model development and parameters

Model Structure

As recommended by the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making modelling guidelines, a review of published NSTEMI/NSTEACS models was undertaken to identify the most appropriate modelling approach and structure (1). Model development was also informed by additional non-systematic reviews of models in the CVD area and a discussion with a clinical expert in the area of NSTEMI (based in the Freeman hospital, Newcastle upon Tyne).

Model Inputs

Two main approaches were used to identify parameter estimates. First, estimates reported in published literature were identified through the systematic review mentioned before. Second, additional parameter estimates were found using a targeted search approach of national routine data sources as well as peer-reviewed clinical and epidemiological papers in the cardiovascular disease area.

Baseline event rates

The two key events that could be experienced in each non-death state of the model were MI and stroke. For MI, the baseline event rates were derived from a large UK-based trial (RITA-3) (2). Further details on estimating MI rates in both control and intervention groups are explained in the “Clinical effectiveness” section.

For stroke, the average baseline event probability was calculated using a cardiovascular disease risk calculator Q-Risk®2 (3) in which average UK population characteristics, derived from Health Survey England (4) were applied. The resulting ‘Q-risks’ were presented as the cumulative 10 year age- and sex-specific incidence rates for stroke in the general population.

In order to derive the annual probability of stroke in population with heart disease, the 10-year risks were converted to annual risks and inflated by the Hazard ratio\(^1\) of stroke in ACS patients relative to the general population.

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\(^1\) Hazard ratio is a ratio whereby the incidence of event in the exposed group (in this case incidence of stroke in NSTEMI patients) is divided by the incidence of event in the unexposed group (i.e. incidence of stroke in the general population)
The model structure also allowed the possibility of recurrent events of MI and stroke (excluding the index NSTEMI event). Sex-specific rates of recurrent MI were derived from a national linked-database analysis by Smolina et al. (2012) (5). However, neither time- nor age-specific estimates were available in this study, thus, they were assumed to be constant. Similarly, the annual rate of recurrent stroke was also assumed to be constant – it was calculated based on a large national General Practice Research Database (GPRD) study (6) which reported the long-term risks of stroke recurrence in the UK setting. All clinical inputs are illustrated in Table 7 (following the “Clinical effectiveness” subsection).

Mortality

UK national life tables were used to determine the probability of all-cause death for all ages (7).

Additionally, based on the evidence from a NICE technology appraisal in a NSTEMACS population (8) it was assumed that, relative to the general population, there was an increased risk of death in ‘stable’ as well as post-event health states, therefore standardized mortality ratios (SMRs) of NSTEMACS, MI and stroke were applied to the probabilities of background mortality (i.e. all-cause death) for the ‘stable’, ‘post-MI’ and ‘post-stroke’ states respectively. For the ‘post-MI-post-stroke’ state, SMRs of the two events were summed together. All SMRs, except for stroke, were sourced from the above mentioned NICE technology appraisal (8). The SMR for stroke was obtained from a large Australian cohort study (9).

In terms of death from cardiovascular causes, short-term fatality rates were applied to both MI and stroke (first and recurrent). While age-specific fatality rates were applied to MI, the fatality rates of stroke were modelled as constant due to the unavailability of UK-based age-specific data. The source for MI fatality rates was the study by Smolina et al. (2012) (justified in the previous section). For stroke, the fatality rates of the first and recurrent events were obtained from two recent national registry analyses (6, 10).

Since all-cause and cardiovascular disease mortality were modelled separately, adjustments were made to the former in order to ensure that there was no double counting of cardiovascular disease deaths.
The model also included the possibility of operation related mortality following revascularization. Based on national registries for cardiac surgery (11, 12), it was estimated that approximately 1.1% of patients die after PCI or CABG.

**Adverse events**

Negative treatment effects such as bleeding were not modelled explicitly. This is because for all state costs and utilities average values for the patient population were used, which accounts for the proportion of patients who experienced adverse events associated with the treatment. Modelling them separately would have therefore resulted in double-counting.

**Effectiveness**

The clinical benefits of the early invasive strategy were evaluated in terms of its effects on MI and stroke. In order to estimate the difference in MIs between the two arms, we used the results of a large, most recent and nationally representative RITA-3 trial (2) comparing early invasive strategy to conservative management. The trial reported incidence of MI for one and up to five years. Having two data points (at one and five years) in both conservative and invasive arms, and given that the survival curves were not parallel (as illustrated in RITA-3 results (13)) which meant that proportional hazards did not apply, resulted in the decision to extrapolate the rates in each arm by applying Weibull survival functions (14).

RITA-3 trial estimates (2, 13) and the resulting scale and shape parameters for the Weibull survival functions for MI are presented in Table 1 below, and the curves presenting cumulative MI incidence for up to 25 years are illustrated in Figure 1.

**Table 1 Parameters for extrapolating MI rates**

<table>
<thead>
<tr>
<th>MI incidence (RITA-3)</th>
<th>Mean value (control)</th>
<th>Mean value (intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 1 year</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>At 5 years</td>
<td>0.11</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Weibull Parameter</strong></td>
<td><strong>Control</strong></td>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Lambda (scale)</td>
<td>0.4807121</td>
<td>0.486302</td>
</tr>
<tr>
<td>Gamma (shape)</td>
<td>0.051503527</td>
<td>0.040289844</td>
</tr>
</tbody>
</table>
Since stroke was not a reported outcome in the RITA-3 trial (2), we obtained an estimate of the relative risk of 0.83 from a Cochrane review (15).

We applied the relative risk of stroke to the baseline probability in patients who underwent revascularization (in either arm). The relative risk had to be adjusted for baseline revascularization rates in NSTEMI in order to fully reflect the clinical benefit of the invasive procedure. As a sensitivity analysis, we used the same source and method to derive the benefit of revascularization in terms of MI.

**Resource use and costs**

Annual costs were obtained for each state in the Markov model. Where appropriate, the annual costs also included the acute event costs of MI and stroke as well as the costs of fatal events. The main sources of data were national routine sources, such as the NHS reference costs 2016-17 (16), British National Formulary (BNF) (17) and Personal Social Services Unit (PSSRU) (18), and previous economic evaluations. Where necessary, in order to have a constant valuation year, the costs were inflated to 2017 price level. The inflation was carried out using the Bank of England inflation calculator (19). All sources for calculating the state costs are explained in Table 2.
### Table 2 Costs included in the model

<table>
<thead>
<tr>
<th>State/Event</th>
<th>Cost (£)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>220</td>
<td>NICE guideline CG94, 2017 (20) BNF, 2017 (17) PSSRU, 2017 (18)</td>
</tr>
<tr>
<td>Post-MI</td>
<td>280</td>
<td>NICE guideline CG94, 2017 (20)</td>
</tr>
<tr>
<td>Post-stroke</td>
<td>5,800</td>
<td>SSNAP, 2016 (21)</td>
</tr>
<tr>
<td>Post-MI post-stroke</td>
<td>6,080</td>
<td>NICE guideline CG94, 2017 (20) SSNAP, 2016 (21)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>6,000</td>
<td>Palmer, 2005 (22)</td>
</tr>
<tr>
<td>Acute stroke</td>
<td>22,000</td>
<td>SSNAP, 2016 (21)</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>1,200</td>
<td>Greenhalgh, 2010 (23)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>2,200</td>
<td>Greenhalgh, 2010 (23)</td>
</tr>
</tbody>
</table>

In terms of intervention costs, these included the cost of angiogram and the cost of revascularization. Since the unit cost of angiogram was not available in the NHS reference costs (16), a value was obtained from the RITA-2 trial (UK-based) (24). The unit cost of revascularization was the weighted average of PCI and CABG.

Baseline estimates of the intervention-related resource use were based on the relative proportions of patients undergoing revascularization in the UK in 2012-2013, as reported by a national database study on NSTEMI patient care (25). Table 3 below illustrates both the unit costs and associated proportions of these interventions in each arm.

### Table 3 Intervention costing

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost (£)</th>
<th>Resource use (proportion of patients undergoing the procedure)</th>
<th>Source of unit costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogram</td>
<td>1,053</td>
<td>0.72</td>
<td>1</td>
</tr>
<tr>
<td>PCI</td>
<td>1,992*</td>
<td>0.33</td>
<td>0.47</td>
</tr>
<tr>
<td>CABG</td>
<td>9,752*</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Revascularization (PCI/CABG) 4,033 0.36 0.51 NHS reference costs, 2017 (16)

*Weighted average of all procedure costs in the appropriate category

**For assumptions behind deriving these proportions, see "Assumptions related to cost"

Utilities

In order to calculate QALYs, each of the health states included in the Markov model had a utility value associated with it, as shown in Table 4. The utility values for ‘stable’ and ‘post-MI’ states were sourced from a NICE Technology appraisal in ACS area (8). The reported utilities were 0.842 and 0.821 for ‘stable’ and ‘post-MI’ states respectively. While an estimate for the ‘post-stroke’ state (i.e. 0.703) was also reported, the value was largely based on authors’ assumptions due to the lack of evidence.

Therefore, the following steps were taken to calculate a utility value for the ‘post-stroke’ state. First, we identified a utility mapping study\(^2\) (26) which reported values for each level of stroke severity, as captured by modified-ranking scale (ranging from 1 to 5). Then, based on data from a UK-based randomised controlled trial (27), we defined a distribution of different severity levels. Finally, we combined each value of severity with its frequency and this allowed me to calculate the average utility score for stroke. The calculated value was equal to 0.702 which was almost identical to the value reported above (0.703). Reportedly, the instrument used to elicit utilities for all of the states was EQ-5D-3L to which UK tariff values were applied, as recommended by NICE (28).

Table 4 Utility values used in the model

<table>
<thead>
<tr>
<th>State/Event</th>
<th>Utility</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>0.842</td>
<td>NICE, 2011 (8)</td>
</tr>
<tr>
<td>Post-MI</td>
<td>0.821</td>
<td>NICE, 2011 (8)</td>
</tr>
</tbody>
</table>
| Post-stroke             | 0.702   | Whynes, 2013 (26)   
|                         |         | Kalra, 2000 (27)    |
| Post-MI and Post-stroke | 0.576   | NICE, 2011 (8)      
|                         |         | Whynes, 2013 (26)   
|                         |         | Kalra, 2000 (27)    |

\(^2\) The study was based on a multi-national randomised controlled trial which included more than 150 hospitals in 16 different countries but majority patients were recruited from the UK sites. The sample size was 1462 patients.
Model Assumptions

Assumptions related to patient cohort, model structure and treatment pathways

1. The age and gender mix modelled is applicable to the UK.
2. The model structure is a valid representation of clinical pathways in the area of NSTEMI.
3. Findings related to NSTEACS patients are transferable to NSTEMI patients.
4. Patients can experience no more than one cardiac event in a year.
5. All post-index event MIs and strokes have the same degree of severity.
6. Probability of recurrent events is constant (i.e. independent of the number or time of previous events).

Assumptions related to effectiveness

1. Clinical benefits of the intervention in terms of reductions in MI are solely based on the clinical effectiveness estimates from the RITA-3 trial. A simplifying assumption has been made that these effects are independent of current revascularization rates in the UK.
2. The intervention has no direct effect on the all-cause mortality. Its effects on mortality are generated by reductions in MI and stroke, and by an increased risk of operative mortality.
3. The benefit of revascularization in terms of stroke is constant.
4. Mortality rates are higher than those of the general population in both ‘stable’ and in the post event health states due to the cardiac event history.

Assumptions related to utilities

1. Utilities are not treatment-dependent – i.e. the model did not differentiate utilities based on the treatment strategy. This decision was based on RITA-3 trial analysis (29) which reported very similar utilities at one year (0.74 and 0.75) for interventional and conservative arms respectively.
2. Utilities are not age-dependent. Age-related utility decrements have been considered in the sensitivity analysis. This is consistent with NICE guidance for the conduct of Technology Appraisals (28)
Assumptions related to cost

1. All patients in the intervention arm incur the cost of angiography.
2. The frequency and therefore the cost of revascularization in the intervention arm is proportional to the frequency of revascularization in the control arm (i.e. 72% of patients had an angiogram in the control arm (as per current clinical practice) and around half of them had revascularization (36%), the same relative difference was assumed in the intervention arm whereby the rate of angiogram was 100% and that of revascularization was therefore equal to 51%).

By repeatedly checking the model, we were able to identify the key drivers of the results and therefore only the parameters that were found to be critical were tested in the sensitivity analyses which are described in the paper.

Model validation

In addition to conducting sensitivity analyses, the NICE guidance for cost-effectiveness states that all cost-effectiveness models should be validated (30). Model validation can be defined by three key processes: face or descriptive validity, internal validity and external validity (31).

In terms of establishing face validity, the model structure was informed by a consultation with a clinical expert, systematic review of NSTEMI (NSTEACS) modelling studies as well as by a more focused review of other models in heart disease area. Furthermore, the structure was consistent with those of the previous models.

As far as internal validation was concerned, several tests were performed to check for errors in programming and incorporation of data into the model. In the simplest of these tests, no difference between the interventions (i.e. same rates of angiography and revascularization in both arms) and no treatment effect were applied in the model, i.e. the relative risk was set to one for stroke and, for MI, the probability in the invasive arm was set equal to probability of MI in the control arm. This yielded the expected results of no difference in life-expectancy between the treatment strategies, indicating that the model was internally valid. In addition, considerable modelling checking was used to identify the model parameters the results of the model were most sensitive to. This helped to ensure that the model was responsive to
changes in the key parameters and also informed the choice of variables for the deterministic sensitivity analyses. All model inputs were quality-checked by an external modeller.

External validation was carried out by comparing the life expectancy that the model predicted with the life expectancy in the UK life table. This was done by setting CVD-related mortality risks to zero and setting standardized mortality ratios to one in order to remove the additional mortality from heart disease. It was reassuring that the predicted survival of the model (11.94) was shown to fit well with the real experience of an external cohort (11.33 for males and 13.05 for females aged 75 in the general population). Although the predicted estimate was very similar, it was not identical due to some of the model assumptions regarding the patient population.

An additional and a more rigorous way of establishing external validity could have been a comparison of the model outcomes with the real world data for NSTEMI patients. However, due to the current unavailability of these data, such analysis was not feasible.
References

20. NICE. Early management of unstable angina and NSTEMI. 2017.