1 Pseudo-code for clinical outcome estimation

Estimation of clinical outcome uses a modification of a method described by Holodinsky et al.[9].

The model calculates probability of good outcome. A good outcome is taken as patient with a Modified Rankin Score of 0-1 at 3-6 months (this is effecively disability-free, and may also be considered an *excellent* clinical outcome).

The code below is presented as pseudo-code and describes all the essential steps used in calculating clinical outcome (the actual code is adjusted to make use of NumPy arrays for faster calculation).

1.1 Stroke types

Breakdown of stroke types were as described by de la Ossa[4].

The breakdown is as follows:

- 51.7% non-large vessel occlusions (nLVO)
- 31.7% large vessel occlusions (LVO)
- 16.6% Intracerebral haemorrhage (ICH)

Of ischaemic strokes, this is equivalent to 62% nLVO and 38% LVO.

Though our model allows for stroke mimics, we model based just on confirmed strokes in the results described here.

1.2 Baseline good outcomes for nLVO and LVO

The baseline good outcomes (outcome if given no treatment) come from the placebo controlled meta-analysis of the effectiveness of thrombolysis[6]. An NIHSS of 0-10 is taken as a surrogate for a nLVO, and a NHSS over 11 or more is taken as a surrogate for a LVO. Baseline good outcomes are:

- baseline_good_outcomes_nLVO = 0.4622
- baseline_good_outcomes_LVO = 0.1328

1.3 Calculate additional good outcomes for nLVO (for those eligible for treatment)

Outcomes for nLVO are based on treatment with thrombolysis (IVT) only.

The decay of effect of IVT (alteplase) was taken from the meta-analysis by Emberson et al.[6]. Log odds ratio was used to approximate a linear relationship between time and effect, and this gives a time-effect relationship shown in equation 1:

$$log\ Odds\ Ratio = 0.746\ \ (0.12\ *hours\ from\ onset\ to\ treatment) \tag{1}$$

Baseline good outcomes of 46.2% are set based on the the probability of a good outcome given no treatment and a NIHSS of 0-10 (taken as a surrogate for nLVO)[6]. Maximum theoretical probability of good outcome (if treatment given at time of stroke onset) was calculated by extrapolation of treatment effect back to t=0 after stroke onset (and is 64.4%).

Pseudocode:

```
# Set time where all effect of thrombolysis is lost (6.3 hrs)

thrombolysis_time_no_effect = 6.3 * 60

# Set maximum permitted time for thrombolysis (4.5 hrs)

maximum_permitted_time_to_ thrombolysis = 4.5 * 60
```

```
# Set limits of max/min probability of good outcomes*
p_good_max = 0.6444 # at t=0 after stroke onset
p_good_min = 0.4622 # at time of no effect of IVT
# Convert proportion of good outcomes to odds ratios
odds_good_max = p_good_max / (1 - p_good_max)
odds_good_min = p_good_min / (1  p_good_min)
# Calculate fraction of time to no-effect at time of treatment
fraction_max_effect_time_used =
      onset_to_needle / thrombolysis_time_no_effect
# Calculate odds of good outcome based on time to treatment
odds_good = exp(log(odds_good_max) -
      ((log(odds_good_max) - log(odds_good_min)) *
      fraction_max_effect_time_used)
# Convert odds of good outcome to probability of good outcomes
prob_good = odds_good / (1 + odds_good)
# Set to min good outcome probability if >max permitted time
if onset_to_needle >maximum_permitted_time_to_thrombolysis:
      p_good = p_good_min
# Ensure all patients have at least minimum of good probability
if p_good <p_good_min:
      p_good = p_good_min
# Calculate additional probability of good outcome due to IVT
p_good_add = p_good - p_good_min
```

1.4 Calculate additional good outcomes for LVO (for those eligible for treatment)

Baseline good outcomes of 13.3% are set based on the the probability of a good outcome given no treatment and a NIHSS of 11+ (taken as a surrogate for LVO)[6].

Pseudocode

```
good_outcomes_for_LVO = p_additional_good_given_IVT +
      (1  p_additional_good_given_IVT)
p_good_given_ET
```

1.4.1 Calculate additional good outcomes for LVO given thrombolysis (IVT)

As with the treatment of nVLO with IVT, the decay of effect of IVT (alteplase) was taken from the meta-analysis by Emberson et al.[6]. Log odds ratio was used to approximate a linear relationship between time and effect, and this gives a time-effect relationship shown in equation 2:

$$log\ Odds\ Ratio = 0.746\ \ (0.12\ *hours\ from\ onset\ to\ treatment) \tag{2}$$

Maximum theoretical probability of good outcome (if treatment given at time of stroke onset) was calculated by extrapolation of treatment effect back to t=0 after stroke onset (and is 24.4%). The benefit reduces to no clinical effect at 6.3 hours.

The probability of an *additional* good outcome given IVT is calculated. Good outcomes due to baseline rate of good outcomes are not included. We assume that only those responding to IVT will not progress to ET.

Pseudocode:

```
# Set time where all effect of thrombolysis is lost (6.3 hrs)
thrombolysis_time_no_effect = 6.3 * 60
# Set maximum permitted time for thrombolysis (4.5 hrs)
maximum_permitted_time_to_ thrombolysis = 4.5 * 60
# Set limits of max/min probability of good outcomes
p_good_max = 0.2441 # at t=0 after stroke onset
p_good_min = 0.1328 # at time of no effect of ET
# Convert proportion of good outcomes to odds ratios
odds_good_max = p_good_max / (1 - p_good_max)
odds_good_min = p_good_min / (1  p_good_min)
# Calculate fraction of time to no-effect at time of treatment
fraction_max_effect_time_used =
      onset_to_needle / thrombolysis_time_no_effect
# Calculate odds of good outcome based on time to treatment
odds_good = exp(log(odds_good_max) -
      ((log(odds_good_max) - log(odds_good_min)) *
      fraction_max_effect_time_used)
# Convert odds of good outcome to probability of good outcomes
prob_good = odds_good / (1 + odds_good)
# Set to min good outcome probability >max permitted time
if onset_to_needle >maximum_permitted_time_to_thrombolysis:
      p_good = p_good_min
# Ensure all patients have at least minimum of good probability
if p_good <p_good_min:
      p_good = p_good_min
# Calculate additional probability of good outcome due to ET
p_good_add = p_good - p_good_min
```

1.4.2 Calculate additional good outcomes for LVO given thrombectomy (ET)

Those patients with LVO who do not respond to IVT progress to EVT. The probability of good outcome after ET includes both the baseline probability of a good outcome, and the additional probability of a good outcome due to ET.

The decay of effect of ET was taken from the Mr CLEAN multicentre trial analysis[7]. This does not include patients who may be selected at later times with advanced imagine techniques. Log odds ratio was

used to approximate a linear relationship between time and effect, and this gives a time-effect relationship as shown in equation 3.

$$log\ Odds\ Ratio = 1.96(0.255\ * hours\ from\ onset\ to\ treatment) \tag{3}$$

Maximum theoretical probability of good outcome (if treatment given at time of stroke onset) was calculated by extrapolation of treatment effect back to t=0 after stroke onset (and is 52.1%). The benefit reduces to no clinical effect at 12 hours.

Pseudo-code:

```
# Set time where all effect of thrombectomy is lost*
thrombectomy_time_no_effect = 8.3 * 60
# Set maximum permitted time for thrombectomy (6 hrs)
maximum_permitted_time_to_thrombolysis = 6 * 60
# Set limits of max/min probability of good outcomes
p_good_max = 0.5208 # at t=0 after stroke onset
p_good_min = 0.1328 # at time of no effect of ET
# Convert proportion of good outcomes to odds ratios
odds_good_max = p_good_max / (1 - p_good_max)
odds_good_min = p_good_min / (1  p_good_min)
# Calculate fraction of time to no-effect at time of treatment
fraction_max_effect_time_used =
      onset_to_puncture / thrombectomy_time_no_effect
# Calculate odds of good outcome based on time to treatment
odds_good = exp(log(odds_good_max) -
      ((log(odds_good_max) - log(odds_good_min)) *
      fraction_max_effect_time_used)
# Convert odds of good outcome to probability of good outcomes
prob_good = odds_good / (1 + odds_good)
# Set to min good outcome probability if >max permitted time
if onset_to_needle >maximum_permitted_time_to_thrombectomy:
      p_good = p_good_min
# Ensure all patients have at least minimum of good probability
if p_good <p_good_min:
      p_good = p_good_min
# Calculate additional probability of good outcome due to ET
p_good_IVT = p_good  p_good_min
```

1.4.3 Alternative ET decay

An alternative decay of effect of ET may taken from the HERMES meta-analysis analysis[?] , using the common odds ratio of improved outcome. This includes patients who may be selected at later times with advanced imagine techniques, which may over-estimate the overall effect of ET at longer onset-to-treatment

times. Log odds ratio was used to approximate a linear relationship between time and effect, and this gives a time-effect relationship as shown in equation 4.

$$log\ Odds\ Ratio = 1.38(0.115\ * hours\ from\ onset\ to\ treatment) \tag{4}$$

Maximum theoretical probability of good outcome (if treatment given at time of stroke onset) was calculated by extrapolation of treatment effect back to t=0 after stroke onset (and is 37.8%).

Note: though the theoretical t=0 effect of Mr CLEAN vs. HERMES appears significantly different (52.1% vs 37.8%), the effect at realistic onset-to-treatment times are more similar, for example at 3 hours the predicted proportion of good outcomes for Mr CLEAN and HERMES are 33.6% and 30.1%.

1.5 Calculate good outcomes for ICH

All patients with ICH have a fixed 24% probability of a good outcome[?]

1.6 Calculate good outcomes for mimic

In this model all mimics will have a good outcome (that is there are no stroke-related bad outcomes).

1.7 Calculate overall number of good outcomes

After calculation of baseline and treated outcomes, the number of good outcomes are adjusted in accordance with the proportion of each stroke type and the proportion of nLVO and LVO eligible for treatment.

Pseudocode:

```
good_outcomes_mimic = proportion_mimic * p_good_outcome_mimic

good_outcomes_ICH = proportion_ICH * p_good_outcome_ICH

good_outcomes_nLVO_base = proportion_nLVO * p_good_outcome_nLVO_base

good_outcomes_nLVO_IVT = proportion_nLVO *
      nLVO_eligible_for_treatment *
      p_good_outcome_nLVO_IVT

good_outcomes_LVO_base = proportion_LVO *
      p_good_outcome_nLVO_base

good_outcomes_LVO_IVT = proportion_LVO *
      LVO_eligible_for_treatment *
p_good_outcome_LVO_IVT

For thrombectomy treatment of LVO, the number of LVO patients treated with thrombectomy
is reduced by the number of LVO patients who would have good response to thrombolysis
(to avoid double-counting good outcomes from thrombolysis + thrombectomy).

good_outcomes_LVO_ET = ((proportion_LVO *
      LVO_eligible_for_treatment) -
      good_outcomes_LVO_IVT) *
      p_good_outcome_LVO_ET
```

1.8 Proportion of patients eligible for treatment

We have taken a pragmatic approach to the estimation of the proportion of patients eligible for treatment. For LVO, McMeekin et al.[?] have estimated that 10% of the total emergency stroke admissions may be suitable for thrombectomy. For thrombolysis we note from SSNAP that there appears to be an upper bound of proportion of patients who receive thrombolysis, and this occurs at 20%[?] . Back-calculating from those figures, and the assumed breakdown of stroke types, produces figures of a maximum of 19.4% and 31.3% of nLVO and LVO being suitable for treatment.

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