Will Delays in Treatment Jeopardize the Population Benefit From Extending the Time Window for Stroke Thrombolysis?

Martin Pitt, EngD; Thomas Monks, PhD; Paritosh Agarwal, MSc; David Worthington, PhD; Gary A. Ford, MB; Kennedy R. Lees, MD; Ken Stein, MD; Martin A. James, MD

**Background and Purpose**—Pooled analyses show benefits of intravenous alteplase (recombinant tissue-type plasminogen activator) treatment for acute ischemic stroke up to 4.5 hours after onset despite marketing approval for up to 3 hours. However, the benefit from thrombolysis is critically time-dependent and if extending the time window reduces treatment urgency, this could reduce the population benefit from any extension.

**Methods**—Based on 3830 UK patients registered between 2005 to 2010 in the Safe Implementation of Treatments in Stroke—International Stroke Thrombolysis Registry (SITS-ISTR), a Monte Carlo simulation was used to model recombinant tissue-type plasminogen activator treatment up to 4-5 hours from onset and assess the impact (numbers surviving with little or no disability) from changes in hospital treatment times associated with this extended time window.

**Results**—We observed a significant relation between time remaining to treat and time taken to treat in the UK SITS-ISTR data set after adjustment for censoring. Simulation showed that as this “deadline effect” increases, an extended treatment time window entails that an increasing number of patients are treated at a progressively lower absolute benefit to a point where the population benefit from extending the time window is entirely negated.

**Conclusions**—Despite the benefit for individual patients treated up to 4.5 hours after onset, the population benefit may be reduced or lost altogether if extending the time window results in more patients being treated but at a lower absolute benefit. A universally applied reduction in hospital arrival to treatment times of 8 minutes would confer a population benefit as large as the time window extension. ([Stroke. 2012;43:2992-2997.])

**Key Words:** emergency care ■ simulation ■ thrombolysis

The only treatment currently licensed for acute ischemic stroke is thrombolysis with intravenous recombinant tissue-type plasminogen activator (rtPA) originally approved for use within 3 hours of onset. A recent updated pooled analysis of 8 randomized controlled trials (RCTs) of rtPA treatment up to 6 hours after onset demonstrated efficacy up to 4.5 hours without a corresponding increase in hazard of intracerebral hemorrhage.1 Even before this, results from the third European Cooperative Acute Stroke Study (ECASS III)2 prompted expert groups in North America, Australia, Europe, and the United Kingdom to recommend rtPA treatment for eligible patients between 3 and 4.5 hours after onset.3,5 Since then there has been a substantial increase in the number of patients treated beyond 3 hours in Europe.6

Nonetheless, the benefit from rtPA remains critically dependent on the time to treatment with an exponential decay in the odds of a favorable outcome from one 90-minute interval to the next up to 4.5 hours.7 This has led to concern that extension of the time window may result in treatment being delayed by the perception that more time remains in which to treat.7,8 This concern may be justified; several studies have reported that patients arriving earlier in the existing 3-hour time window are subject to delays in treatment, presumably resulting from less urgency when more time remains.9-11 The latest large-scale US and European data sets confirm a strong correlation between time remaining to treat and time taken to treat with considerably shorter hospital arrival-to-treatment (ATT) times as the treatment deadline approaches.6,13 What is more, the United Kingdom has a median onset-to-treatment (OTT) time of approximately 155 minutes14 compared with close to 90 minutes in the original RCT.15 With over half of all patients being treated in the last...
Do Delays Jeopardize the Benefits of Thrombolysis?

Methods

We constructed a Monte Carlo simulation in Microsoft Excel from prospective data from 3830 UK patients treated with rtPA registered in SITS-ISTR between January 2005 and February 2010. We excluded 191 patients from a small number of centers before 2005 because of large variability in the data in this period. In the model, a notional cohort of 1000 patients progresses along a pathway consisting of 3 phases: onset to hospital arrival (OTA), arrival to scan (ATS), and scan to treatment. A Monte Carlo simulation was used to sample from a representative probabilistic density function based on the respective population distribution of times for each phase of treatment. Further probabilistic sampling was then used to assign outcomes to each patient based on (1) whether or not they received rtPA; and (2) their individual OTT time. The model encompassed potential interactions between the different phases of treatment such as the effect of reductions in ATS and scan to treatment associated with later OTA times—the deadline effect. The model consisted of patients diagnosed with acute ischemic stroke and eligible for thrombolysis who arrived at hospital within 270 minutes of stroke onset (see online-Only Data Supplement). Because our analysis was concerned only with the incremental outcomes between the 180- and 270-minute scenarios, patients with hemorrhagic stroke or other contraindications to thrombolysis were excluded because they had identical outcomes in both scenarios.

Data Sources

Data to populate the model were drawn from 3830 UK patients treated with rtPA in SITS-ISTR. We excluded 284 patients with an OTA time of zero (assumed to be strokes occurring in the hospital) and 59 patients with OTT times >300 minutes. We also excluded a further 319 patients treated 2 months either side of the publication of ECASS III in September 2008 to minimize contamination from prospective data from 3830 UK patients treated with rtPA registered in SITS-ISTR. We excluded 284 patients with an OTA time of zero (assumed to be strokes occurring in the hospital) and 59 patients with OTT times >300 minutes. We also excluded a further 319 patients treated 2 months either side of the publication of ECASS III in September 2008 to minimize contamination from the study results and only included patients from centers with records in both periods to minimize bias from a learning effect (excluding 290 patients). From the remaining 2878 patients (1378 before August 1, 2008, and 1500 after November 30, 2008), we derived population time distributions for the 3 phases of treatment (OTA, ATS, scan to treatment).

Outcome Measures

We described disability outcomes for the 2 periods before and after the publication of ECASS III using the modified Rankin Scale (mRS) at 90 days after treatment, dichotomized between an mRS of 0 to 1 (a favorable outcome indicating survival with minimal or no disability) and an mRS of 2 to 6 (an unfavorable outcome indicating survival with significant disability or death). We used the pooled analysis from Lees et al to estimate the benefit from thrombolysis treatment. In the model, we used these probabilities to sample a mRS outcome for each simulated patient.

Role of the Funding Source

This work was funded by the UK National Institute of Health Research through the Peninsula Collaboration for Leadership in Applied Health Research and Care. The authors had access to all data and analyses in the study and have sole responsibility for the content of the report and the decision to submit for publication.

Results

For 2878 patients, we identified the following median (inter-quartile range) times from onset to treatment: OTA: 75 (54) minutes, ATS: 31 (30) minutes, scan to treatment: 25 (26) minutes, ATT: 63 (42) minutes, and OTT: 150 (59) minutes. Figure 1 shows the distribution of OTT times before and after publication of ECASS III and shows a marked increase in the annual rate of treated patients in keeping with the steep growth elsewhere in Europe. A greater proportion of patients were treated between 120 and 180 minutes in the pre-ECASS III data set with an increase in the number of patients treated >3 hours post-ECASS III.

Table 1 shows the times for the main treatment phases before and after publication of ECASS III.

We examined the relationship between OTA time and reductions in the ATS and scan to treatment phases as the treatment deadline approaches (the deadline effect). To eliminate the effect of censoring at 3 hours, we limited the analyses to patients treated within 180 minutes of onset before (n=1187) and after (n=1104) the publication of ECASS III. Figure 2 shows the mean ATT time against OTA time for patients pre- and post-ECASS III and identifies 2 features. First, as observed in previous studies, ATT times for patients treated within 3 hours reduce as OTA times increase, although because of the censoring in the data, the extent to which the reduction is due to a deadline effect cannot be definitively established. Second, after ECASS III there is an acceleration of treatment of 8 minutes (95% CI, 5.5–10.5 minutes) for earlier patients with an OTA time between 10 and 90 minutes, that is, those for whom the deadline is not imminent, probably representing improved processes. However, when OTA time is beyond 90 minutes, that is, when pre-ECASS III deadlines were imminent but post-ECASS III deadlines were not imminent, the 8-minute improvement is not seen.

This loss of the improvement effect for post-ECASS III patients arriving after 90 minutes suggests a relaxation of treatment urgency associated with the deadline extension, which corresponds to an average reduction in ATT time of
20% (95% CI, 14.5%–25.5%) for this OTA range. This confirms a significant reduction in ATT times as OTA times increase even after adjustment for censoring in line with other studies describing a correlation between time remaining to treat and time taken to treat in unadjusted data.6,9–13

Modeled Disability Outcomes

Our simulation modeled the number of patients from a notional sample of 1000 who could be expected to benefit from thrombolysis before and after the time window extension. Dichotomized scores for 90-day mRS were derived to estimate disability outcomes in each scenario. Based on our observations from the SITS-ISTR data set, the model took account of patients whose treatment is delayed, even to a small extent, by shifting the treatment deadline. In a sensitivity analysis, we investigated the impact of varying the deadline effect, described by the percentage reduction in ATT time for patients arriving in the 90 minutes before the treatment deadline (either 180 or 270 minutes). Table 2 shows the outputs for a range of deadline effects either side of the observed 20% value. With no deadline effect, 40.5% more patients are treated after extension with no cost in terms of delays for those treated within 180 minutes. However, with the observed deadline effect of 20%, extension results in the treatment of an additional 244 patients at a mean OTT of approximately 219 minutes, but 212 patients have their treatment delayed by a mean of 7.8 minutes.

Figure 3 shows the frequency distributions of OTT times pre- and postextension for 2 levels of deadline effect (20% [8 minutes] and 50% [23 minutes]). As the deadline effect increases, the shaded area before the 180-minute point increases, representing those patients treated later postextension (ie, the “cost” of extending the treatment window). The equivalent-sized shaded area beyond the 180-minute point shows when these delayed patients are treated postextension. The area beneath the pale line represents those additional patients who are treated postextension (ie, the benefit of extending the treatment window). Thus, as the deadline effect increases, the effective cost of extending the treatment deadline (the number of patients whose treatment is delayed) also increases.

Projected Outcomes

We used the simulation to derive the population disability benefit (projected number of patients achieving a favorable outcome, mRS 0–1) pre- and postextension for different levels of deadline effect (Figure 4; bold lines). At the observed deadline effect of 20%, an additional 5 patients per 1000 achieve a favorable outcome postextension. At greater levels of deadline effect, the difference between the projected outcomes pre- and postextension narrows to a point beyond 45% (equivalent to a mean delay for patients arriving within 90 minutes of the treatment deadline of approximately 20 minutes) where no additional population benefit accrues from the extension of the treatment window.

By contrast, Figure 4 also illustrates (narrow lines) the impact of a general reduction in ATT times if the deadline effect applied for patients at all values of OTA time, that is, if all patients were treated with the same urgency as a patient arriving within 90 minutes of the treatment deadline. In both the pre- and postextension simulations and with a deadline effect of ≥20%, delivering treatment more rapidly in all patients (by at least 8 minutes across all OTA times) yields a greater population benefit than the extension of the time window.

Table 1. Median (IQR) Times (Min) for Hospital Treatment Phases by OTA Time Before (Pre) and After (Post) the Publication of ECASS III

<table>
<thead>
<tr>
<th>Onset to Arrival Time</th>
<th>No. of Patients</th>
<th>Arrival-to-Scan Time</th>
<th>Scan-to-Treatment Time</th>
<th>Arrival-to-Treatment Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>1–30</td>
<td>90</td>
<td>77</td>
<td>45</td>
<td>34</td>
</tr>
<tr>
<td>31–60</td>
<td>429</td>
<td>422</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>61–90</td>
<td>361</td>
<td>433</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>91–120</td>
<td>258</td>
<td>250</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>121–150</td>
<td>141</td>
<td>132</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>151–180</td>
<td>89</td>
<td>110</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>181–300</td>
<td>10</td>
<td>76</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>1378</td>
<td>1500</td>
<td>33</td>
<td>31</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; OTA, onset-to-arrival; ECASS, European Cooperative Acute Stroke Study.

Figure 2. Onset-to-hospital arrival (OTA) and arrival-to-treatment (ATT) times before and after publication of European Cooperative Acute Stroke Study (ECASS) III.
Our study used data from a large prospective registry of stroke thrombolysis in the United Kingdom to build a simulation model of the impact of extension of the treatment window after the publication of ECASS III.\textsuperscript{2–5} Extending the window could be expected to result in treatment of a further 4.7% of people with stroke\textsuperscript{6} but at a lower absolute benefit.\textsuperscript{1} Our study is the first to take account of the effect on clinical behavior of shifting the 180-minute deadline for patients presenting during the latter part of the treatment window and the first to quantify how finely balanced the benefits and disbenefits may be. These consequences are not theoretical: data for >100,000 patients with acute ischemic stroke in the US Get with the Guidelines (GWTG) data set have shown a strong correlation between the time remaining to treat and the time taken to treat in unadjusted data.\textsuperscript{13} After adjustment for the effect of censoring, we estimate that for patients arriving in the final 90 minutes before the deadline, ATT times are reduced by 20% compared with patients arriving earlier. Furthermore, we believe that our adjusted estimate of this deadline effect is conservative. The GWTG data set identified that patients arriving at the hospital in the second and third hours after known stroke onset had an ATT time 30% lower than patients arriving in the first hour.\textsuperscript{13} In the updated analysis of the European SITS registry,\textsuperscript{6} patients arriving within 30 minutes of onset took an average of 61 minutes longer to be treated than those arriving in the last 30 minutes of the 3-hour time window. After the publication of ECASS III, mean ATT times for patients arriving in the last 30-minute period lengthened from 24 to 45 minutes.\textsuperscript{6} Our sensitivity analysis suggests that if the loss of urgency is pronounced, then a point may be reached where the extension of the time window from 3 to 4.5 hours confers no additional population disability benefit. Although our estimate of 20% for the deadline effect is below this “tipping point” (see Figure 4), the unadjusted data from the updated European SITS-ISTR (which includes the UK data) suggest that this tipping point may be exceeded.

It might be argued that improvements in the emergency response will counteract the effect of delays in treatment after extension of the time window. Indeed, our analysis indicates, for patients arriving early in the treatment window, a reduction in ATT times between 2005 and 2010 of 8 minutes, probably as participating centers gained experience as described elsewhere.\textsuperscript{13} However, it remains that a relatively small proportion of patients arrive in this early period even as overall numbers treated have markedly increased, and no similar reduction in ATT time is seen for the majority of patients who arrive later in the treatment window. This observation is an example of the second gap of research translation\textsuperscript{6}: a failure to deliver in clinical practice the benefits for individuals and healthcare systems that should result from the full implementation of the primary research. Whereas in the original RCT of treatment within 3 hours the median OTT time was, by design, close to 90 minutes,\textsuperscript{3} the latest figure for median OTT time from the UK SITS-ISTR is 150 minutes, an hour later, representing a substantial reduction in the absolute benefit compared with that promised by
the primary research.7 In the latest Swedish data,19 all the
growth in thrombolysis since the publication of ECASS III
has come in the >3-hour category with the number of
patients treated before 3 hours actually declining by 4.4% per
year since that point. As the European SITS-ISTR database
shows, it is the preponderance of patients close to the
3-hour time point that is most at risk of a delay in treatment
after extension, possibly by as much as 21 minutes.6

Importantly, we do not interpret our findings as supporting
any case against extending the window for rtPA treat-
ment up to 4.5 hours, and we consider the efficacy of rtPA to
be proved for individual patients treated between 3 and 4.5
hours.1 However, our study highlights the pitfalls of real-life
implementation of research evidence, which cannot be suc-
cessfully implemented without considering all the factors
that may diminish the anticipated benefit. In so doing, our
findings send out a significant warning to those involved with
the emergency response for stroke. Patients arriving early in
the time window should be treated with the same urgency as if
time were imminently running out, and every patient should
be treated as quickly as is compatible with safe practice.
Healthcare systems need to ensure the delivery of thromboly-
sis at a median OTT time as close as possible to that seen in
the original trial,13 which may involve revising current guid-
ance regarding timescales for assessment and treatment after
hospital arrival.20 If the same coordinated effort and resources
were directed to this target as were directed to the conduct of
the major commercial RCT of rtPA between 3 and 4.5 hours,2
our study indicates that at least as much further population
benefit could accrue.

We recognize the limitations of our study: the adjusted esti-
mate of the deadline effect may be too conservative, although
as shown in our sensitivity analysis, this would underscore
both the adverse impact of shifting the treatment deadline
and the benefits of faster treatment. Our study has not mod-
eled variation in OTA times, which has been the focus of a
recent public education campaign in the United Kingdom.
The latest UK audit suggests this campaign has not had a sig-
nificant impact on OTA times with the proportion of people
with stroke arriving at the hospital within 3 hours unchanged
between 2008 and 2010.21 However, in the United States, the
GWTG data set showed a steady if small increase in the pro-
portion of patients arriving within the first hour after onset.13

Another limitation is the voluntary nature of the SITS registry,
which may introduce reporting bias. There may be those who
suggest there is no purpose in monitoring rtPA use now that
the regulatory authorities in Europe have been reassured that
the use of rtPA in clinical practice is, if anything, safer than
in the original RCTs.6 Our study indicates that continuous
monitoring for unintended effects should be mandatory if the
anticipated benefits from extension of the window are not to
be jeopardized.

In summary, our simulation study of the effect of exten-
sion of the time window for the treatment of acute isch-
emic stroke has for the first time quantified the risk of
treating larger numbers of patients but at a lower absolute
benefit and the benefit from making comparatively mod-
est but universally applied reductions in hospital delays.

It sends a clear message to those delivering the emergency
response to suspected stroke. Progress in shortening OTT
times for all patients has not occurred as might have been
expected, and renewed effort is needed to minimize delays
at every stage from onset to treatment and in particular
radical steps to eliminate in-hospital delays in treatment
combined with continued monitoring. These elements are
essential if the population benefit from thrombolysis for
acute ischemic stroke promised by the original RCTs is
not to be unwittingly jeopardized but instead realized in
clinical practice.

Disclosures

None.

References

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References


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SUPPLEMENTAL MATERIAL:

Will delays in treatment jeopardise the population benefit from extending the time window for stroke thrombolysis?


Introduction
This on-line supplement provides technical details specific to the simulation model and analysis reported in the paper reference above.

Model Structure
In order to model the impact of treatment delays for stoke patients receiving rt-PA (i.e. thrombolysis), a Monte-Carlo simulation model was constructed using Microsoft Excel. The modelled pathway is shown in Figure S1 below. Since the focus of our study was to compare populations of stroke patients who are eligible for thrombolysis, it was not necessary to include contra-indications and ineligible patients in our model or to factor in patients arriving with an Onset to Arrival time (OTA) greater than 270 minutes since the pathway and outcome for these patients would not vary between the compared scenarios (and would hence be cancelled out in the incremental analysis). Within our model, therefore, the only reason for a patient not to receive rt-PA is when their Onset-to-Treatment time (OTT) exceeds the time threshold defined by the modelled scenario conditions.

Figure S1. Diagram of model structure
Data Sources and Methods
In our model the key time intervals for each patient were determined by sampling from a series of representative empirical distribution functions (edfs). These edfs are the observed distribution functions presented by the SITS-ISTR data as describe in the paper and summarised in Table S1 below. Differences between mean and median values in Table S1 demonstrate the positively skewed nature of these distributions.

<table>
<thead>
<tr>
<th>Data Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Median</th>
<th>Inter Quartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to Arrival (OTA) mins</td>
<td>85.63</td>
<td>44.87</td>
<td>75</td>
<td>54</td>
</tr>
<tr>
<td>Arrival to Scan (ATS) mins</td>
<td>42.42</td>
<td>31.87</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Scan to Thrombolysis (STT) mins</td>
<td>32.52</td>
<td>24.56</td>
<td>25</td>
<td>26</td>
</tr>
</tbody>
</table>

Table S1. Summary of probability distributions used to model time delays before treatment

The deadline effect was included in our model by applying a scale factor to sampled ATS and STT times corresponding to the level of deadline effect modelled in the sensitivity analyses. A deadline effect of x% was therefore modelled by scaling the sampled ATS and STT times for an individual patient by multiplying the sampled time value by (100-x)%. Application of the deadline effect within the model was dependant on how close the patient’s current delay from onset time was to the defined treatment threshold time of the modelled scenario. The deadline effect was applied only for those patients whose current delay from onset was within 90 minutes of the treatment deadline and a stepped system was used whereby those patients whose current delay from onset was within an hour of the modelled treatment deadline experienced the full deadline effect whilst patients whose current delay from onset was between 60 and 90 minutes of the treatment deadline experienced half the overall deadline effect.

In order to model patient outcomes within the simulation, a modified Rankin Score (mRS) after 90 days was assigned to each modelled patient. This was determined by a probability function and affected by two key factors, firstly whether the patient had received rt-PA and secondly, for those patients who receive rt-PA, the OTT of the patient. The probabilistic relationship between these two factors and likelihood of an outcome mRS < 2 (after 90 days) is described in detail by the pooled analysis given in Lees et al.² and shown below in Table S2. Within our model, simulated patients were assigned to one of these three groups dependant on their OTT. The probability of achieving an MRS < 2 was then calculated for each patient group based on the Lees et al data. These probabilities (shown in Table S2) were assumed to apply to the mid-point of the referenced OTT interval and linear interpolation was used, where an OTT of 270 minutes was assumed to have a probability of an mRS < 2 outcome equivalent to an untreated patient, to obtain a continuous probability function to represent the likelihood of patients attaining an mRS < 2 for all relevant values of OTT for each simulated patient in each of the separate groups.
<table>
<thead>
<tr>
<th>OTT treatment period</th>
<th>Odds Ratio of favourable outcome (rt-PA vs Placebo (95% CI))</th>
<th>Estimated number of patients needed to treat to attain an additional mRS &lt; 2</th>
<th>Probability of mRS &lt; 2 after for treated patients</th>
<th>Probability of mRS &lt; 2 for untreated patients &amp; patients with OTT = 270 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-90 minutes</td>
<td>2.55 (1.44-4.52)</td>
<td>4.5</td>
<td>51.2%</td>
<td>29.2%</td>
</tr>
<tr>
<td>91-180 minutes</td>
<td>1.64 (1.12-2.40)</td>
<td>9.0</td>
<td>40.0%</td>
<td>28.9%</td>
</tr>
<tr>
<td>181-270 minutes</td>
<td>1.34 (1.06-1.68)</td>
<td>14.1</td>
<td>44.8%</td>
<td>37.7%</td>
</tr>
</tbody>
</table>

Table S2. Relationship of time from onset to treatment and probability of a favourable outcome (taken from Lees et al)²

Model Outputs
The simulation was primarily used to compare two scenarios 1) ’Pre-ECASS III’ treatment where the OTT deadline for rt-PA treatment was 180 minutes and (2) ’Post-ECASS III’ treatment where the rt-PA deadline was extended to patients with an OTT up to 270 minutes. The key sensitivity parameter of interest in this analysis was the level of ‘deadline effect’ as defined in our paper and these outputs are presented in the main text.

In each trial run of the model a notional population of 1000 patients were simulated for each arm of the simulation. The mean outputs from a total of 1000 replications of the model (each with a 1000 patient population) were recorded for each separate analysis to mitigate the effects of any within-sample variability.

The primary results from our simulation are presented in the main paper. We did however conduct a range of sensitivity analyses by varying individual input parameters in the model to explore the impact of changes. These outputs are presented in Table S3 below and for each analysis show:

- firstly, the additional patients treated in the post-ECASS III scenario versus the pre-ECASS III scenario which represents the effective benefit of increasing the treatment deadline.
- secondly, the number of patients who experienced treatment delay (and the average delay accrued by these patients) due to the deadline effect within the extended deadline scenario which represents the effective cost to patient population of the post-ECASS III extension given the assumed deadline effect.

In order to vary the sampled distributions for OTA, ATS and STT in our model we used parameterised log-normal distributions.

These analyses demonstrate that the impact of the deadline effect level applies relatively consistently across a range of OTA, ATS and STT values.
<table>
<thead>
<tr>
<th>Varied Parameter (mean, SD) mins</th>
<th>Deadline Effect</th>
<th>No of Patients</th>
<th>Time (minutes)</th>
<th>Extra patients treated post extension</th>
<th>Mean delay for patients post-extension</th>
<th>Mean OTT for extra patients treated post-extension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deadline Effect Level</td>
<td>Treated pre-extension</td>
<td>Treated post-extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base Case 0%</td>
<td>680</td>
<td>956</td>
<td>276</td>
<td>0</td>
<td>214.6</td>
<td></td>
</tr>
<tr>
<td>Base Case 20%</td>
<td>717</td>
<td>961</td>
<td>244</td>
<td>7.8</td>
<td>216.7</td>
<td></td>
</tr>
<tr>
<td>Base Case 40%</td>
<td>762</td>
<td>965</td>
<td>203</td>
<td>17.7</td>
<td>223.0</td>
<td></td>
</tr>
<tr>
<td>OTA (50,25) 0%</td>
<td>842</td>
<td>990</td>
<td>148</td>
<td>0</td>
<td>212.3</td>
<td></td>
</tr>
<tr>
<td>OTA (50,25) 20%</td>
<td>862</td>
<td>996</td>
<td>134</td>
<td>8.7</td>
<td>214.4</td>
<td></td>
</tr>
<tr>
<td>OTA (50,25) 40%</td>
<td>880</td>
<td>999</td>
<td>119</td>
<td>19.0</td>
<td>215.9</td>
<td></td>
</tr>
<tr>
<td>OTA (100,50) 0%</td>
<td>560</td>
<td>907</td>
<td>347</td>
<td>0</td>
<td>214.8</td>
<td></td>
</tr>
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<td>OTA (100,50) 20%</td>
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Table S3. Summary outputs for modelled sensitivity analyses

References: