

## Objectives

To assess whether, in cohort-level models submitted to the National Institute for Health and Care Excellence (NICE), central limit theorem is used appropriately when selecting distributions for costs in probabilistic sensitivity analysis (PSA).

## Background

- The central limit theorem states that if a population is sufficiently large, the sampling mean of that population will be normally distributed regardless of its initial distribution. This is also known as assuming normality
- Probabilistic sensitivity analysis is used in cost-effectiveness models to test uncertainty; each of the model's parameters is assigned a distribution and varied over a large number of iterations based on this distribution
- The resource consumption of patients having treatment and the unit costs of these resources are often taken as averages from sources such as NHS reference costs, which come from large population samples
- Resource use and cost data are likely to be skewed at a patient level, meaning using a log-normal or gamma distribution is appropriate for individual level samples
- However, when testing the uncertainty of these parameters in a cohort model where the parameter of interest is the population mean, it is correct to follow the central limit theorem and vary parameters using the normal distribution
- Despite this, the uncertainties of costs and resource use in cohort models are often tested using the generalized gamma distribution
- This results in the uncertainty of models being measured inaccurately

## Methods

NICE technology appraisals (TAs) published between March and May 2019 were reviewed, with a focus on the distributions used to test the uncertainty of costs in the respective economic models. In addition to the distribution selected, any comments made by the Evidence Review Group about the PSA performed in the submission were recorded.

**Table 1: Targeted literature review results**

NICE TA number	Distributions used in PSA		ERG comments on distribution selections in PSA
	Costs	Resource use	
TA581 <sup>1</sup>	Gamma	NR	None
TA580 <sup>2</sup>	Gamma	NR	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter
TA579 <sup>3</sup>	Gamma	Gamma or beta	None
TA575 <sup>4</sup>	Gamma	NR	None
TA573 <sup>5</sup>	Gamma	Gamma or Dirichlet	The ERG considered that the parameters and their assigned distributions were appropriate and correctly implemented
TA569 <sup>6</sup>	<b>Adverse event costs:</b> Gamma <b>Health state costs:</b> Log-normal	NR	None
TA567 <sup>7</sup>	Gamma	NR	None
TA565 <sup>8</sup>	Gamma	NR	The ERG repeated the PSA for its base case; the distributions remained as in the company submission

**Key:** ERG, evidence review group; NR, not reported; PSA, probabilistic sensitivity analysis; TA, technology appraisal.

## Results

- 14 NICE TAs were published between March and May 2019, eight of which were suitable for review because they reported the distribution used for costs or resource use in the model's PSA
- The eight models that were reviewed were all cohort models
- Table 1** presents the results

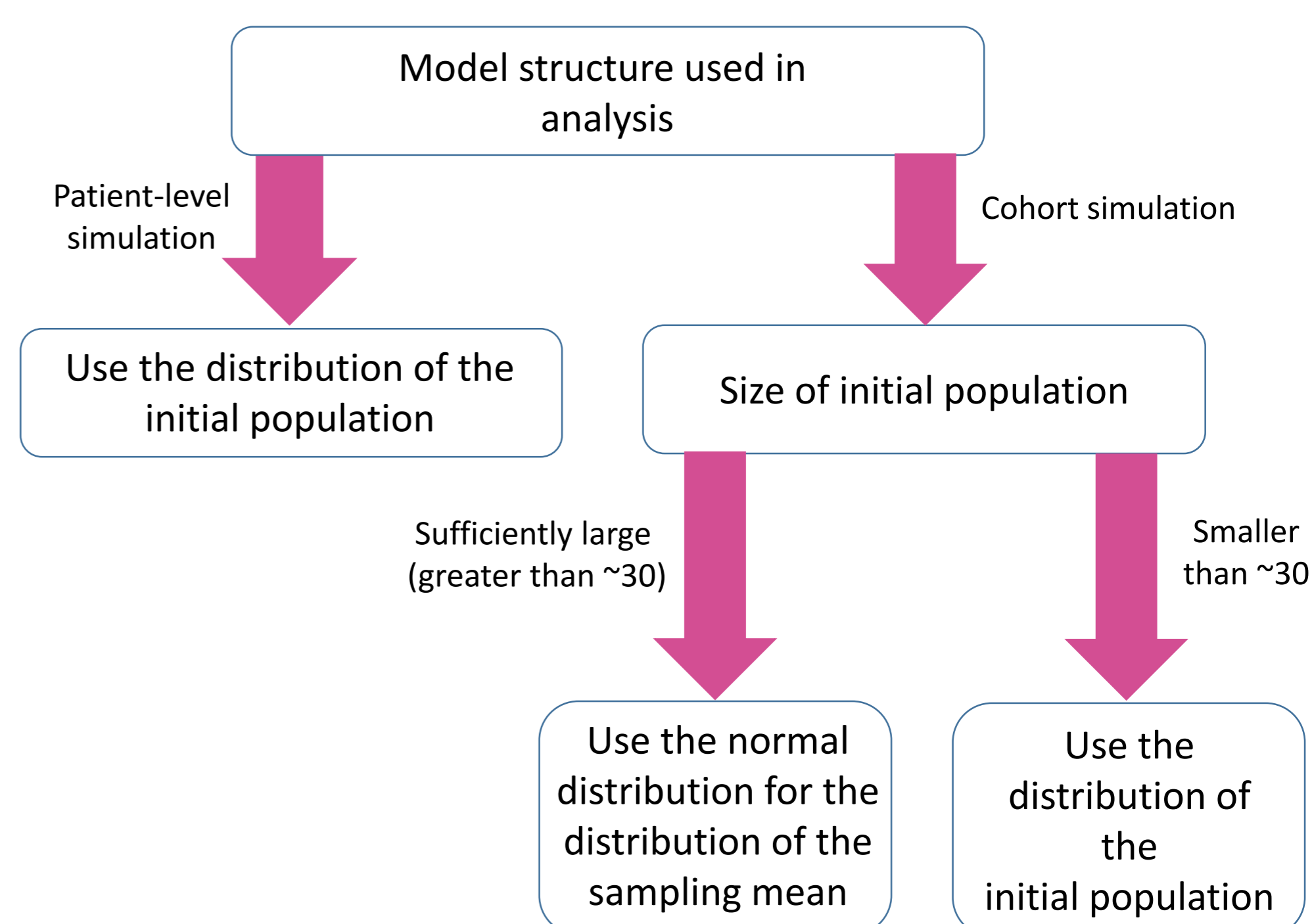
## Discussion

- In many of the TAs, the distributions used for different parameters in the PSA were not reported in the publicly available information, which creates a separate issue of making model replication more difficult
- Where this information was reported, distributions incorporating skew were consistently used incorrectly to sample uncertainty around the mean of large patient populations
- Although the central limit theorem should be applied in cohort models, they are not suitable for use in the same circumstances in a patient-level simulation model. In these models, the variation should be modelled using the distribution of the initial population

## Conclusions

- Due to a lack of guidance, central limit theorem is regularly overlooked when it is applicable in NICE TAs
- Distributions such as the log-normal or gamma should not be used to sample cohort means when data have been derived from sufficiently large data sources; in these cases, the normal distribution should be used
- There are a number of factors that dictate which distribution should be used to test the uncertainty around cost and resource use data, as shown in **Figure 1**

**Figure 1: When to use the central limit theorem**



## References

- NICE. [www.nice.org.uk/guidance/ta581](http://www.nice.org.uk/guidance/ta581). Accessed June 11, 2019.
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