A Cost-Utility Analysis of Low-Dose vs Standard-Dose IV Alteplase in the Management of Acute Non-Lacunar Ischaemic Strokes: Appendix Materials

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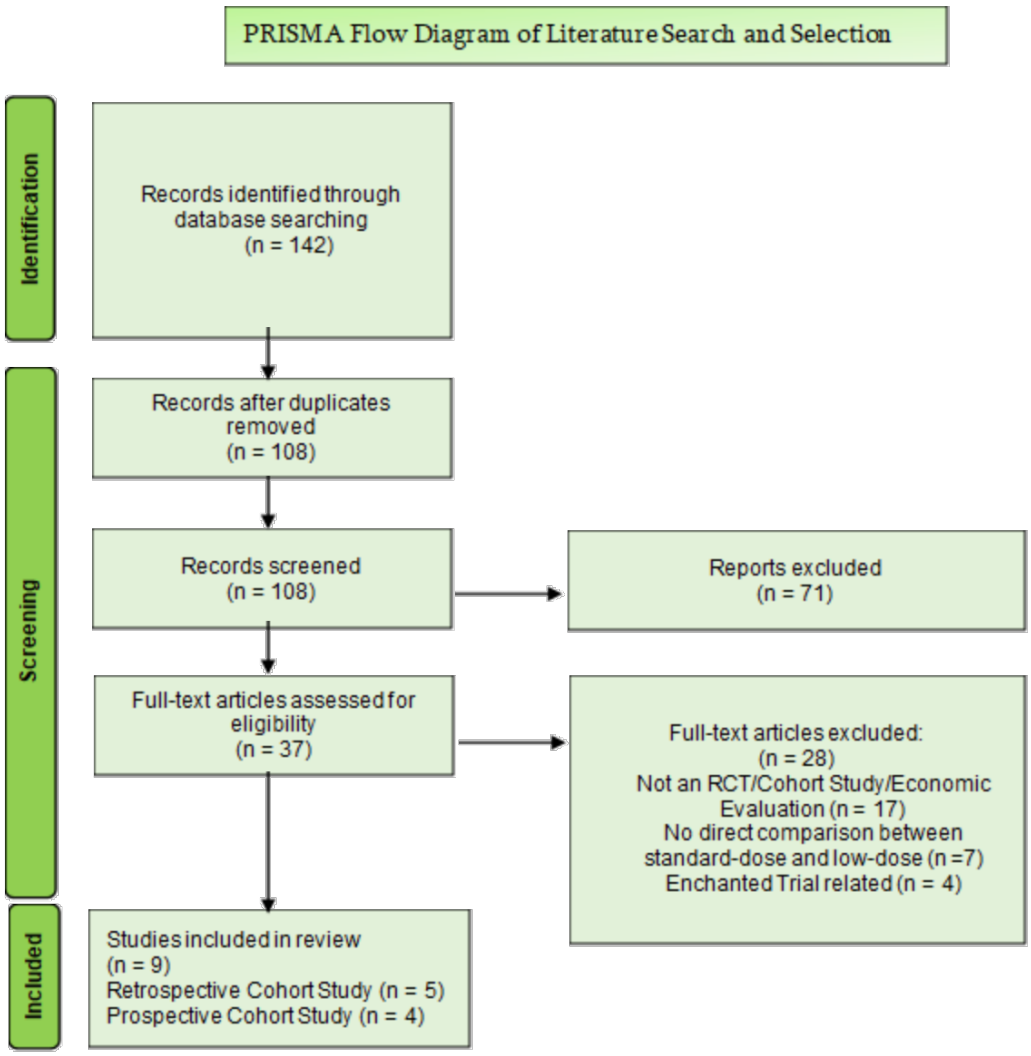
1. Appendix A: Literature Review

A.1: PRISMA flow diagram of literature search and selection process



A.2: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Trials that are based on ENCHANTED cohort	Related to ENCHANTED Trial
Direct comparison between standard-dose and low-dose	No direct comparison between standard-dose and low-dose
Alteplase usage in ischaemic stroke patients	Alteplase usage in other vascular disease
RCTs, Retrospective Cohort Studies, Prospective Cohort Studies, Economic Evaluations	Case Reports, Case Series, Reviews, Abstracts
English Language	Not in English Language

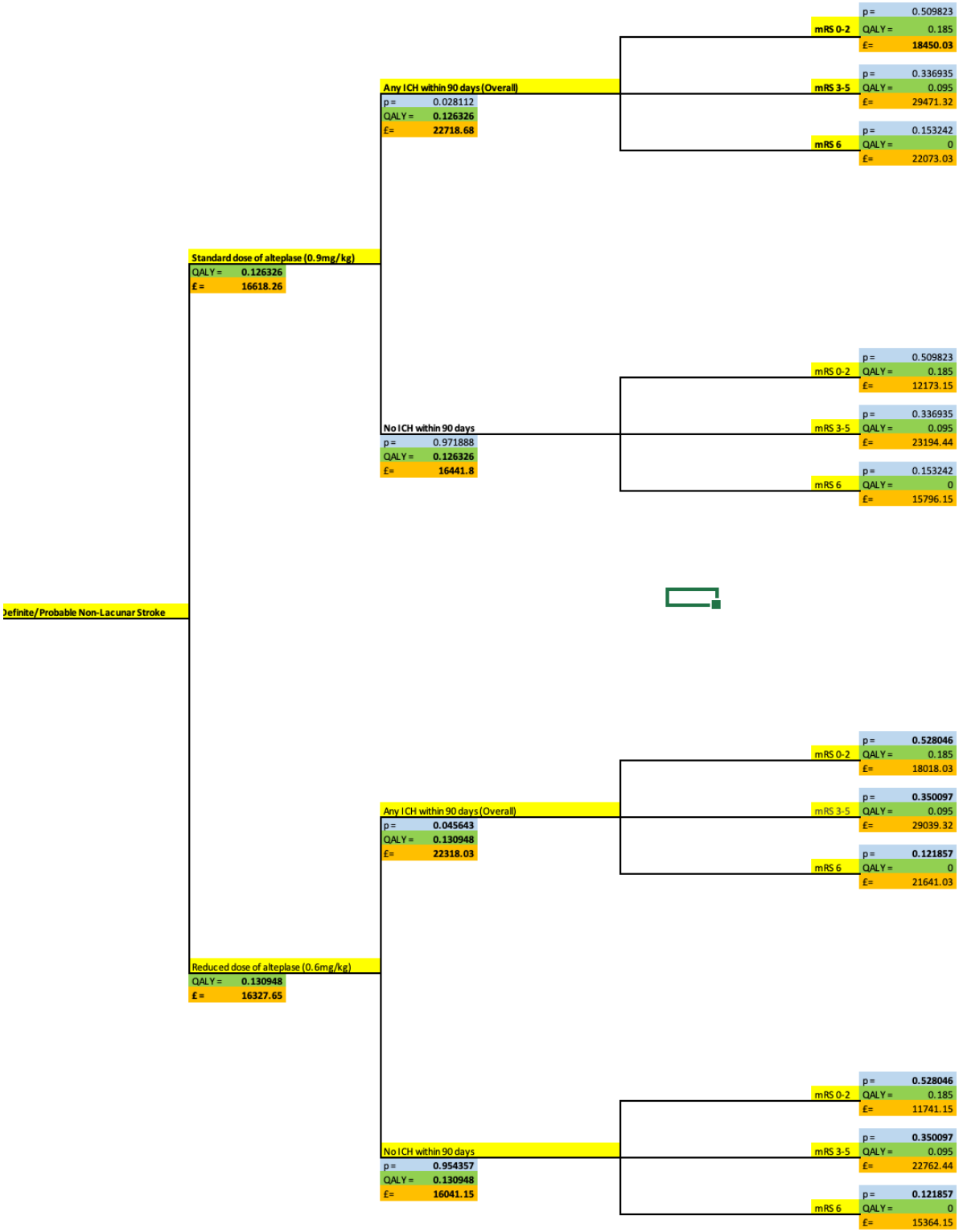
A.3: Study characteristics

Title	Author	Country	Sample Size	mRS Functional Outcome (0-2) success rate	ICH complication rate	Mortality Rate	Type of Study
Low versus standard dose intravenous alteplase in the treatment of acute ischemic stroke in Egyptian patients	Afifi, K. Elsheikh, W. El-Shanawany, B. Salem, G.	Egypt	80	Low-Dose: 67.5%. Standard-Dose (62.5%)	Low-dose: 2.5% Standard-Dose: 12.5%		Prospective Cohort Study
Low-dose versus standard-dose intravenous alteplase for octogenerian acute ischemic stroke patients: A multicenter prospective cohort study	Chao, A. C. Han, K. Lin, S. F. Lin, R. T. Chen, C. H. Chan, L. Lin, H. J. Sun, Y. Lin, Y. Y. Chen, P. L. Lin, S. K. Wei, C. Y. Lin, Y. T. Lee, J. T. Hu, H. H. Bai, C. H.	Taiwan	249	Low-Dose: 22.2%. Standard-Dose 34.8%	Low-dose: 3.7% Standard-dose: 3.6%		Prospective Cohort Study
Intravenous Thrombolysis Administration 3–4.5 h After Acute Ischemic Stroke: A Retrospective, Multicenter Study	Chen, Y. W. Sung, S. F. Chen, C. H. Tang, S. C. Tsai, L. K. Lin, H. J. Huang, H. Y. Po, H. L. Sun, Y. Chen, P. L. Chan, L. Wei, C. Y. Lee, J. T. Hsieh, C. Y. Lin, Y. Y. Yeh, S. J. Lien, L. M. Jeng, J. S.	Taiwan	748	Low-Dose: 31.8%. Standard-Dose 36.3%	Low-dose: 18.8% Standard-dose: 15.9%	Low-dose: 8.3% Standard-dose: 7.1%	Retrospective Cohort Study
Standard-dose intravenous tissue-type plasminogen activator for stroke is better than low doses	Liao, X. Wang, Y. Pan, Y. Zhao, X. Wang, D. Z. Wang, C. Liu, L	China	919	Low-dose 56.76% Standard-dose 64.51%	Low-dose: 0% Standard-dose: 1.62%	Low-dose: 5.41% Standard-dose: 7.36%	Retrospective Cohort Study
Recombinant tissue Plasminogen activator in acute ischemic stroke patients receiving thrombectomy: Standard or low dose therapy?	Lin, C. H. Liu, C. H. Wang, A. Y. Wu, Y. M. Chen, C. C. Tsai, Y. H. Chang, T. Y. Huang, K. L. Wu, H. C. Lee, T. H. Chang, Y. J. Lin, C. M. Cheng, C. K. Chang, C. H.	Taiwan	42	Low-dose: 33.3% Standard-dose: 44.8%	Low-dose: 0% Standard-dose: 6.9%		Retrospective Cohort Study
Low-Dose vs. Standard-Dose Intravenous Alteplase in Bridging Therapy Among Patients With Acute Ischemic Stroke: Experience From a Stroke Center in Vietnam	Mai, D. T. Dao, V. P. Nguyen, V. C. Vu, D. L. Nguyen, T. D. Vuong, X. T. Bui, Q. V. Phan, H. Q. Pham, Q. T. Le, H. K. Tran, A. T. Nguyen, Q. A. Dang, P. D. Nguyen, H. Phan, H. T.	Vietnam	107	Low-dose: 68.5% Standard-dose: 64.8%	Low-dose: 26% Standard-dose: 32.4%	Low-dose: 2.7% Standard-dose: 8.8%	Prospective Cohort Study
Efficacy and safety of low-dose versus standard-dose alteplase regimens in patients with acute ischaemic stroke	Skrbiu, R. Vujkoviu, Z. Stojilijkoviu, M. P. Gajanin, R. Bokonjiu, D. Komiu, J.	Bosnia and Herzegovina	210	Low-dose: 53.33% Standard-dose: 64.24%	Low-dose: 13.3% Standard-dose: 21.2%	Low-dose: 0% Standard-dose: 6.1%	Retrospective Cohort Study
Comparative Analysis on Low- and Standard-Dose Regimes of Alteplase Thrombolytic Therapy for Acute Ischemic Stroke: Efficacy and Safety	Zhao, G. Huang, T. Zheng, M. Cui, Y. Liu, Y. Cheng, Z. Wang, Z.	Taiwan	1487	Low-dose: 36.1% Standard-dose: 37.6%	Low-dose: 2.2% Standard-dose:5.9%	Low-dose: 5.5% Standard-dose: 7.3%	Retrospective Cohort Study
Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT)	Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y	Japan	100	Low-dose 36.9% Standard-dose 39%	Low-dose: 5.8% Standard-dose: 6.4%	Low-dose: 9.7% Standard-dose: 17%	Prospective Cohort Study

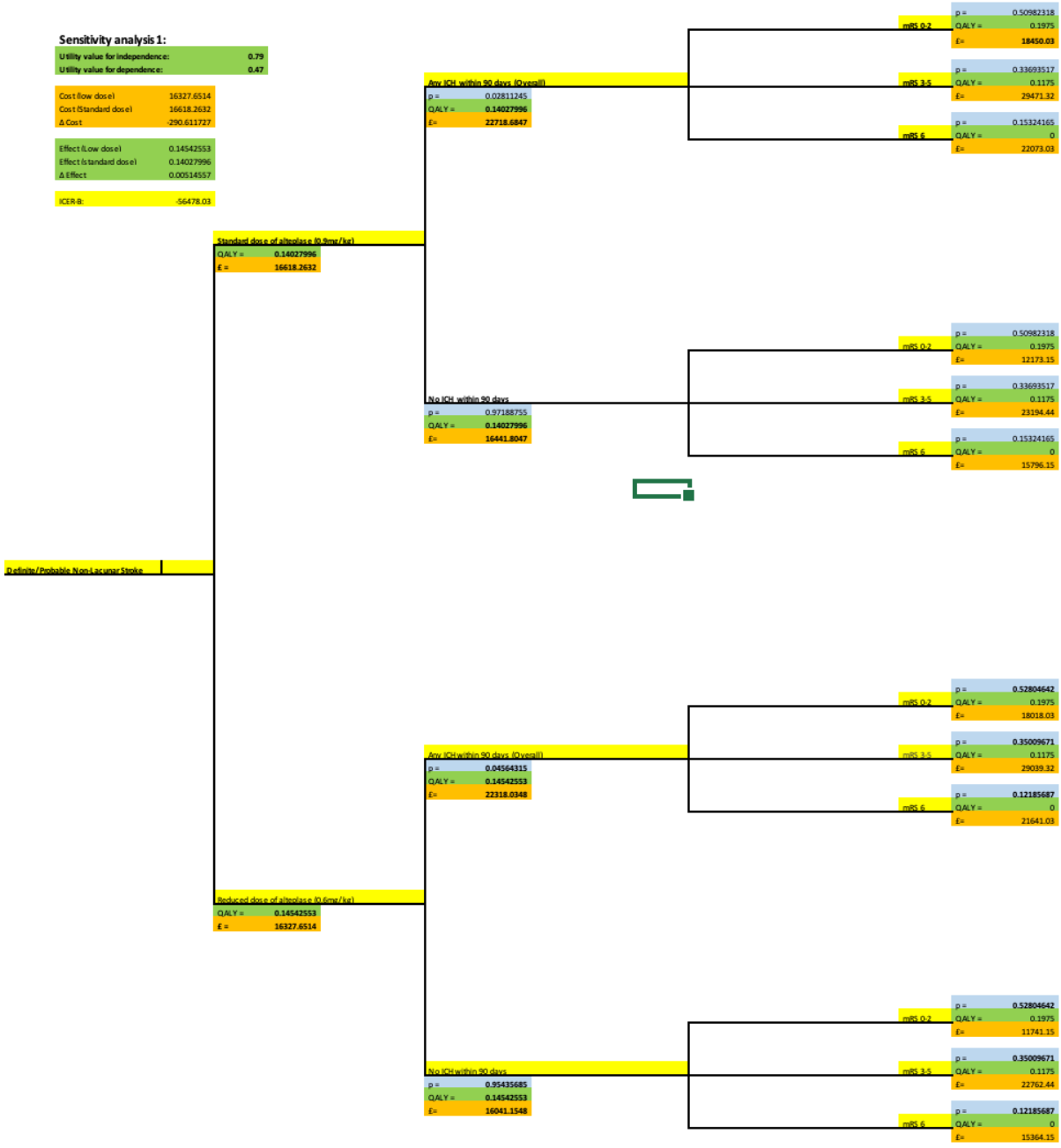
2. Appendix B: Decision Trees

Probabilities and QALYs have been rounded to 5DP where applicable

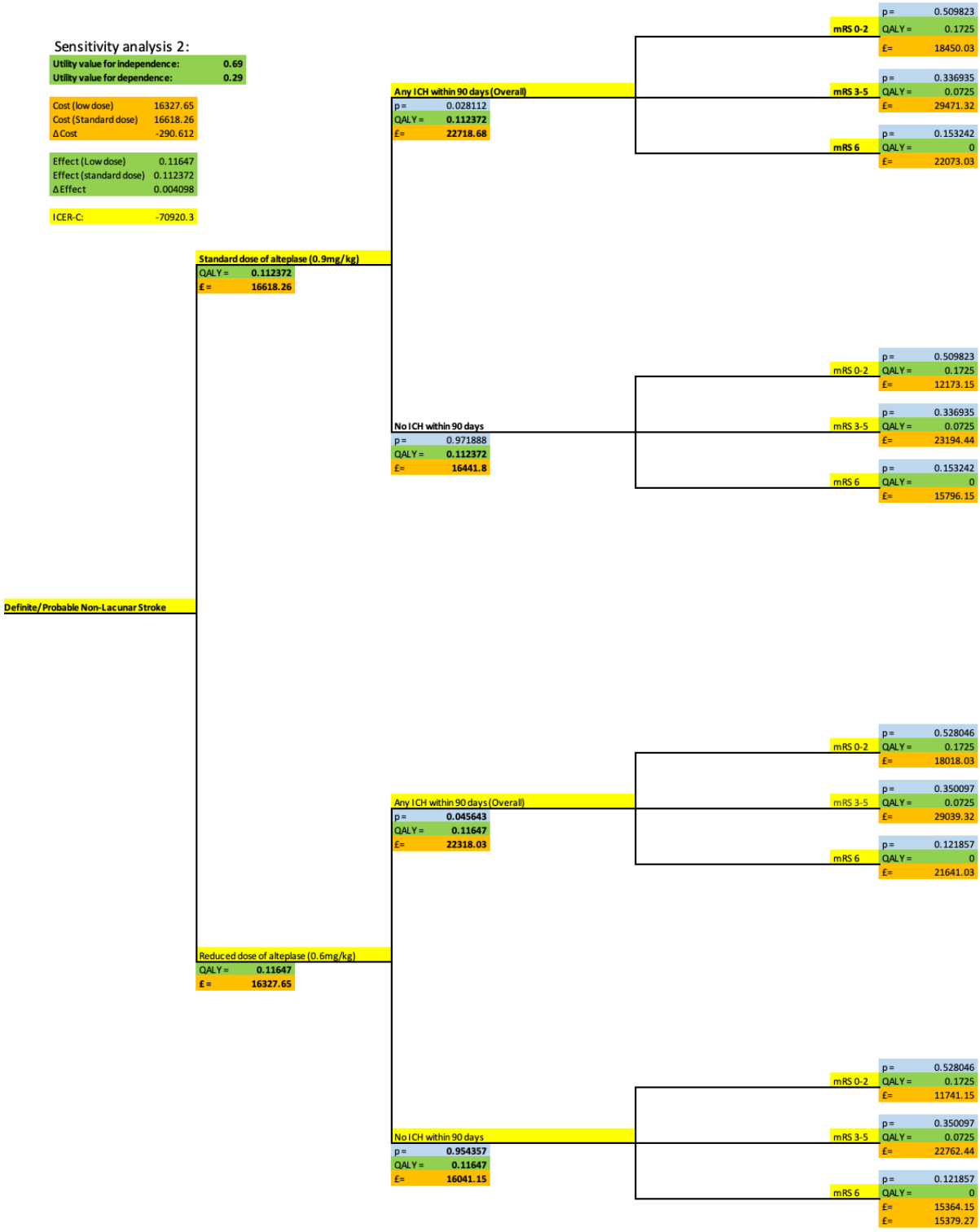
B.1: Diagram of full decision tree



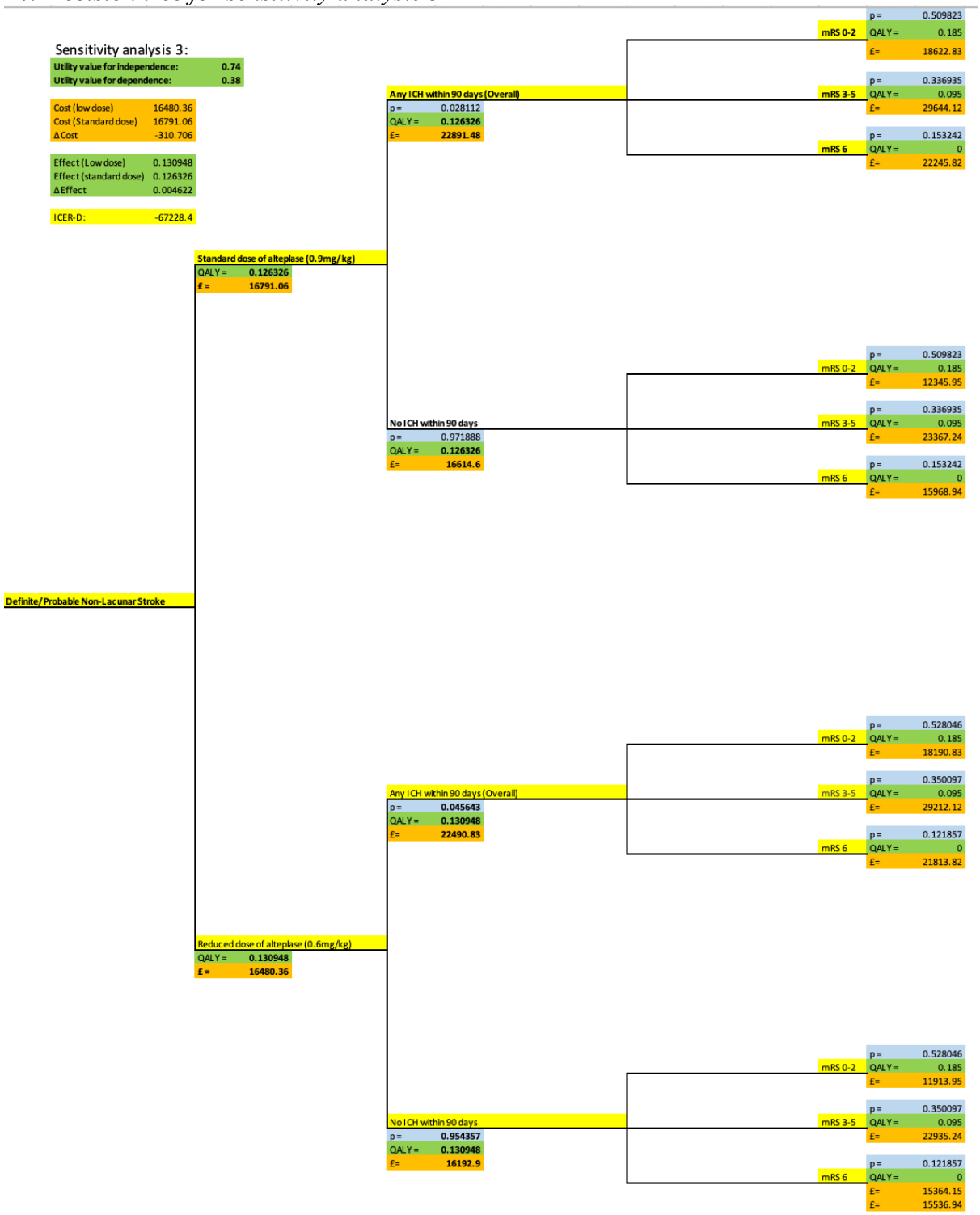
B2: Decision tree for sensitivity analysis 1



B3: Decision tree for sensitivity analysis 2



B4: Decision tree for sensitivity analysis 3



3. Appendix C: Unit costs, costing resource use items and sources

C1: QALYs of each mRS (using base case values for utility and 0.25 years for Length of Life)

MRS range	QALY
0-2	0.185
3-5	0.095
6	0

C2: Probabilities of each mRS score range for standard or low-dose alteplase

mRS range	Standard-dose Alteplase (0.9mg/kg)	Low-dose Alteplase (0.6mg/kg)
0-2	0.509823	0.528046
3-5	0.336935	0.350097
6	0.153242	0.121857

C3: The comprehensive dissection of all costs within the management of acute non-lacunar ischaemic stroke

Treatment Component	Description of cost calculation	Cost per hour (£)	Unit Cost (£)	Year	Discounted at 3.5% (£)	Source
Cost of Alteplase (0.9mg/kg, average weight of 76 kg)	Actilyse: 2 x 50mg powder and solvent for solution for infusion vials		864	2022	864.00	(NICE, 2022)
Cost of Alteplase (0.6mg/kg, average weight of 76 kg)	Actilyse: 1 x 50mg powder and solvent for solution for infusion vials		432	2022	432.00	(NICE, 2022)
Administration Costs (NB: Resource Levels provided by Sandercock et al (2002))	50 min consultant time	123	102.5	2021	106.09	(PSSRU, 2021)
	190 min registrar time	52	164.7	2021	170.46	(PSSRU, 2021)
	5 min additional nurse time	97	8	2011	11.68	(PSSRU, 2011)
	5 min routine observation by senior nurse in place of more junior nurse	25	2.08	2011	3.04	(PSSRU, 2011)
	12 additional sets of observations at each 5 min each	142	142	2011	207.32	(PSSRU, 2011)
	5 hours 1:1 senior nurse care	142	710	2011	1036.58	(PSSRU, 2011)
	10 min overnight junior staff review	31	5.17	2021	5.35	(PSSRU, 2021)
Total administration cost					1540.51	
3 months acute costs independent mRS 0-1-2	3-month cost of acute event + ongoing care		6854.28	2012	9668.64	(Davis et al, 2012) + (Youman et al, 2004)
3 months acute costs Dependent mRS 3-4-5	3-month cost of acute event + ongoing care		14667.48	2012	20689.93	(Davis et al, 2012) + (Youman et al, 2004)
Cost of acute event fatal stroke mRS 6			9422.69	2012	13291.63	(Davis et al, 2012) + (Youman et al, 2004)
Any ICH within 90 days	AA23D HRG name		5968	2021	6176.88	(NHS National Tariff Payment System, 2021)
CT Scan	Patient experiencing SICH requires an additional CT scan (£100)		100	2022	100.00	

C4: Costs at each terminal node for low-dose and standard-dose alteplase

Treatment Component used in Cost Calculation	Cost
Cost of Alteplase (0.9mg/kg) + Administration costs + cost of any ICH within 90 days + 3 months acute costs in an independent state MRS 0-1-2	18450.03
Cost of Alteplase (0.9mg/kg) + Administration costs + cost of any ICH within 90 days + 3 months acute costs in a dependent state MRS 3-4-5	29471.32
Cost of Alteplase (0.9mg/kg) + Administration costs + cost of any ICH within 90 days + cost of an acute event fatal stroke MRS 6	22073.03
Cost of Alteplase (0.9mg/kg) + Administration costs + 3 months acute costs in an independent state MRS 0-1-2	12173.15
Cost of Alteplase (0.9mg/kg) + Administration costs + 3 months acute costs in an independent state MRS 3-4-5	23194.44
Cost of Alteplase (0.9mg/kg) + Administration costs + cost of an acute event fatal stroke	15796.15
Cost of Alteplase (0.6mg/kg) + Administration costs + cost of any ICH within 90 days + 3 months acute costs in an independent state MRS 0-1-2	18018.03
Cost of Alteplase (0.6mg/kg) + Administration costs + cost of any ICH within 90 days + 3 months acute costs in a dependent state MRS 3-4-5	29039.32
Cost of Alteplase (0.6mg/kg) + Administration costs + cost of any ICH within 90 days + cost of an acute event fatal stroke MRS 6	21641.03
Cost of Alteplase (0.6mg/kg) + Administration costs + 3 months acute costs in an independent state MRS 0-1-2	11741.15
Cost of Alteplase (0.6mg/kg) + Administration costs + 3 months acute costs in an independent state MRS 3-4-5	22762.44
Cost of Alteplase (0.6mg/kg) + Administration costs + cost of an acute event fatal stroke	15364.15