

Appendix- This appendix includes additional details, examples, and tools for readers to implement in their own CEAs.

Question	‘Will an RCT with a Run-In (RI) period be <i>more cost effective</i> than an RCT with No-Run-In (NRI) period for demonstrating a <i>statistically significant</i> and <i>clinically important</i> difference in the <i>Mean Change of a Primary Outcome measured</i> at a Baseline and Final Assessment visit, between Intervention A and Placebo A on Indication X?’
1. Source Material	We develop models from data directly determined from RCTs with a Run-In Period and RCTs without a Run-In Period (NCT02954432, NCT02330315, NCT02723929, NCT01404052, NCT03625752). As our focus is on methods, we refrain from specific comparisons of interventions or indications, and primarily use the study data to inform the range of variables used in the RCT models.
2. Audience	Our CEAs are designed from the perspective of the clinical trialist (e.g., as opposed to society’s perspective).
3. Effectiveness	Given our goal of evaluating different RCT designs (as opposed to the RCT results (i.e., health benefits)), we can define Effectiveness based on metrics that characterize the trial design (as opposed to the trial health outcomes of the study intervention (e.g., ‘quality-adjusted life-years’)) ³¹ . In this light, Effectiveness could be defined in terms such as the number of patient observations completed, study power, screening criteria, levels of statistical significance, and/or their combination. For our examples, we will use the total patient sample size N_t (i.e., recruiting and maintaining a specific number of patients from enrollment through observations of the primary outcome measure) as our metric of Effectiveness- see Appendix-Table 2.
4. Comparators	One can compare multiple RCT designs, Run-In Phase designs, and/or different screening criteria. We will compare RCTs with Run-In Periods vs. RCTs without Run-In Periods, each with an Active and Sham condition (with numerous different design criteria during sensitivity analysis).
5. Result Structure	We will examine the ratio of the total discounted cost per the amount of discounted “effect” for each RCT under investigation. Secondly, we will examine incremental cost effectiveness ratios.
6. Methodology	We will implement Markov Models, Monte Carlo Simulations, and Sensitivity Analysis as part of a CEA.

Appendix-Table 1: Considerations Guided by the Research Question

Effectiveness Considerations: Dependent on available source data for RCT design			
	Example 1	Example 2	Example 3
Data Set Available:	Comprehensive data sets from: <ul style="list-style-type: none"> • an 'RCT with a Run-In Period that screened for patients with set criteria' • and a similar 'RCT without a Run-In Period'. 	Limited data sets which: <ul style="list-style-type: none"> • characterize the variability of the different RCT designs on the Primary Outcome measure. 	General knowledge of: <ul style="list-style-type: none"> • the standard deviation of the intervention on the primary outcome measure (independent of an RCT design).
Methods	<ul style="list-style-type: none"> • Identify N_i for each RCT necessary to show clinical and statistical significance, dependent on the statistical testing method chosen to assess the intervention, and a desired Type I and Type II error. 	<ul style="list-style-type: none"> • Bootstrap methods allow one to estimate the variance of the outcome measure elicited by the intervention under the different RCT designs. <ul style="list-style-type: none"> • Calculated variance can then be used to estimate N_i • Alternatively, the bootstrap method can be used to directly estimate N_i, dependent on the source data available. 	Same as Example 1, but: <ul style="list-style-type: none"> • N_i will be assumed equivalent in RCTs with and without the Run-In.
Advantages/ Disadvantages	Overall, this method requires the least amount of estimation. However, a priori analysis is not generally possible as it requires a significant amount of empirical data and the method is more generally implemented after a study's completion.	The major advantage of this method is that it allows a researcher to use limited data sets to capture the metrics of Effectiveness (for example, one could use this method to see if a particular change in variability resulting from adding a Run-In would be cost effective on a cost per patient basis).	This is the most conservative approach (i.e., considering the required N_i 's equivalent), but it also requires the greatest amount of estimation. It would be the most commonly implemented by a researcher designing an RCT and will serve as the basis of our specific examples herein.

Appendix-Table 2: Effectiveness Considerations. It should be noted that the methods that we tabulated herein are dependent on the modeling assumptions that we made and additional methods might be necessitated in situations where similar assumptions are not made (e.g., data sets with different patient characteristics in the RI and NRI cohorts, data sets with varied characteristics of patient adherence or miscalculations of adherence during RI periods (see for example <https://pubmed.ncbi.nlm.nih.gov/2289394/>), or data sets based on intention-to-treat methods for certain RCT designs (see for example <https://www.ncbi.nlm.nih.gov/pubmed/18623608>)). Future work in such areas will increase clinical trialists' toolboxes for RCT design.

State Cost Sheet

Notes:

Total cost						
Personnel						
Role	Hours Committed		Cost Per Hour		Cost per Task	
	Run in	No run in	Run in	No run in	Run in	No run in
Senior management/budgetary official	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Senior researchers	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Legal	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Nursing	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Junior Research Staff	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Admin	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Statistical consultant	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Regulatory consultant	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 9	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 10	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 11	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 12	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 13	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 14	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 15	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 16	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Labor Total	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Supplies						
Item	Units		Cost Per Item		Cost per Task	
	Run in	No run in	Run in	No run in	Run in	No run in
Computer	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Analysis Computer	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Stimulation Supplies (week)	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Experiment Disposables (week)	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Experiment Binder (week)	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Testing Materials (1 time cost)	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Non Digital Print Media (week)	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Digital Storage Media (year)	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 9	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 10	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 11	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 12	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 13	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 14	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 15	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 16	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Supplies Total	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Capital Equipment						
Item	Units		Cost Per Item		Cost per Task	
	Run in	No run in	Run in	No run in	Run in	No run in
Stimulation Hardware	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 2	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 3	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 4	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 5	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 6	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 7	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 8	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 9	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 10	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 11	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 12	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 13	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 14	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 15	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Item 16	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Equipment Total	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Travel Costs						
Role	Required Travel (0/1)		Cost as per individual		Cost per Task	
	Run in	No run in	Run in	No run in	Run in	No run in
Senior management/budgetary official	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Senior researchers	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Legal	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Nursing	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Junior Research Staff	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Admin	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Statistical consultant	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Regulatory consultant	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Reimbursed Patient Travel	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 10	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 11	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 12	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 13	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 14	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 15	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Personnel 16	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Travel Total	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Overhead Cost (assumes no payment for overhead while not actively working, nor related to travel costs)						
Overhead Cost	Weeks Committed		Cost Per Week		Cost per Task	
	Run in	No run in	Run in	No run in	Run in	No run in
	0	0	\$ 1.00	\$ 1.00	\$ -	\$ -
Time for Task						
Time	Total Weeks					
	Run in	No run in				
	0	0				

Total Time (Weeks)		Total Cost For Task	
Run in	No run in	Run in	No run in
0	0	\$ -	\$ -

Appendix-Table 3: State Cost Worksheet

		Run-In RCT Design ('RI')																			
		State #																			
State	#	1	2	3	4	5	6	7	8	9	10	11	12	13R	14	15	16	17	18	19	20
Plan and Design	1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Write IRB	2	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Submit IRB	3	0.0000	0.0000	0.0000	0.6000	0.2500	0.1500	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Minor Revision	4	0.0000	0.0000	0.0000	0.2000	0.0500	0.7500	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Major Revision	5	0.0000	0.0000	0.0000	0.6500	0.1250	0.2250	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
IRB Approval	6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Preparation	7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Contact Patient	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.1031	0.8969	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Phone Pre-Screen	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9190	0.0000	0.0810	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
In Person Consent	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2980	0.0000	0.0000	0.0000	0.7020	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Training/Prep	11	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Scheduling	12	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2917	0.7083	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Run-In	13RI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.1177	0.2941	0.5882	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Treatment Week 1	14	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Treatment Week 2	15	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.1000	0.0000	0.0000	0.0000	0.9000	0.0000	0.0000	0.0000	0.0000
Follow-up 1	16	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
Follow-up 2	17	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000
Follow-up 3	18	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
Follow-up 4	19	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
Data-Analysis	20	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
		No Run-In RCT Design ('NRI')																			
		State #																			
State	#	1	2	3	4	5	6	7	8	9	10	11	12	13NR	14	15	16	17	18	19	20
Plan and Design	1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Write IRB	2	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Submit IRB	3	0.0000	0.0000	0.0000	0.5500	0.2000	0.2500	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Minor Revision	4	0.0000	0.0000	0.0000	0.1750	0.0500	0.7750	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Major Revision	5	0.0000	0.0000	0.0000	0.6000	0.1500	0.2500	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
IRB Approval	6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Preparation	7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Contact Patient	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0631	0.9369	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Phone Pre-Screen	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9190	0.0000	0.0810	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
In Person Consent	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2980	0.0000	0.0000	0.7020	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Training/Prep	11	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Scheduling	12	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2917	0.7083	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
NRI Baseline	13NRI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.1294	0.1294	0.7412	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Treatment Week 1	14	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0476	0.0317	0.0000	0.9206	0.0000	0.0000	0.0000	0.0000	0.0000
Treatment Week 2	15	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.1035	0.0000	0.0000	0.0000	0.8966	0.0000	0.0000	0.0000	0.0000
Follow-up 1	16	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
Follow-up 2	17	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0769	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9231	0.0000
Follow-up 3	18	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
Follow-up 4	19	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
Data-Analysis	20	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

Appendix-Table 4: 'Base-Case' Model State Transition Probabilities for the No-Run-In (NRI) and the Run-In (RI) RCT Design (single patient recruiting goal basis). For our specific RCT, with $N_t > 1$, the transition probabilities of State 11 (reached after consenting patient) and

State 20 (patient completes Follow-up 4) would be similar to those of State 8 and State 12 (with stopping/transition criteria dependent on State count criteria (i.e., reaching N_t) that can be simulated during the MCS analysis). It should be noted, these transition probabilities are directly dependent on the specific indication, trial design, and Run-In screening criteria (which we directly modeled based on data from past NIBS trials). Given that, we also assess a broad range of transition probabilities during the sensitivity analysis.

Appendix-Table 5. CER's as a function of varying the number of institutions, number of patients that could be consented per week/institution, number of patients that could be assessed simultaneously/institution, cost discount, and effectiveness discount (with the other variables fixed at the 'Base-Case' values). We provide ACERs and ICERs for the RCT. We compared $ACER_{RI}$ to $ACER_{NRI}$ to determine cost-effectiveness per the ACERs (where an $ACER_{RI} < ACER_{NRI}$ would indicate RI cost effectiveness per the ACERs) and ICER cost-effectiveness decision criteria per ²³, similar to what would be determined by CEA plane analysis ^{23, 24}.

Trial Size	Institutions	Consent capacity	Patient Capacity	Cost Discount (i)	Effectiveness Discount (r)	RI ACER (\$/Patient)				
						Design and Approval	Recruitment	Test Period	Analysis	RCT
1	1	1	1	0.06	0.05	\$ 8,800.85	\$ 1,768.90	\$ 35,289.00	\$ 1,228.89	\$ 47,463.89
26	1	7	3	0.06	0.05	\$ 338.49	\$ 900.42	\$ 8,336.81	\$ 403.15	\$ 10,123.63
104	1	7	3	0.06	0.05	\$ 84.62	\$ 886.00	\$ 7,997.73	\$ 182.70	\$ 9,473.73
Trial Size	Institutions	Consent capacity	Patient Capacity	Cost Discount (i)	Effectiveness Discount (r)	NRI ACER (\$/Patient)				
						Design and Approval	Recruitment	Test Period	Analysis	RCT
1	1	1	1	0.06	0.05	\$ 8,070.12	\$ 1,735.00	\$ 34,716.95	\$ 1,200.76	\$ 46,087.85
26	1	7	3	0.06	0.05	\$ 310.39	\$ 888.73	\$ 7,964.79	\$ 394.38	\$ 9,703.34
104	1	7	3	0.06	0.05	\$ 77.60	\$ 875.54	\$ 7,644.01	\$ 178.69	\$ 9,112.25
Trial Size	Institutions	Consent capacity	Patient Capacity	Cost Discount (i)	Effectiveness Discount (r)	RCT ICER				
						ΔC (RI-NRI)	ΔE (RI-NRI)	ICER (\$/Patient)	CEA Decision Criteria	
1	1	1	1	0.06	0.05	\$ 1,295.96	-0.001002145	\$ (1,293,190.87)	Dominant-Reject	
26	1	7	3	0.06	0.05	\$ 10,717.24	0.078478513	\$ 136,562.73	Trade-Off	
104	1	7	3	0.06	0.05	\$ 38,847.78	1.236036456	\$ 31,429.31	Trade-Off	

Appendix-Table 5.A: CER's of the individual trial Phases and Complete RCT for the 'Base-Case', $N_i=1$ and $N_i=104$ models (with all other variables set to those levels of 'Base-Case' shown in this table). Note, the table provides ACERs for Phases assessed independently and the total RCT, assessing all the phases in total, some which occur partially in parallel (e.g., recruiting future patients simultaneously during previous patient testing)).

Trial Size	Institutions	RI ACER (\$/patient)	NRI ACER (\$/Patient)	RCT ICER			
				ΔC (RI-NRI)	ΔE (RI-NRI)	ICER (\$/Patient)	CEA Decision Criteria
1	1	\$ 47,463.89	\$ 46,087.85	\$ 1,295.96	-0.0010021	\$ (1,293,190.87)	Dominant-Reject
26	1	\$ 10,123.63	\$ 9,703.34	\$ 10,717.24	0.07847851	\$ 136,562.73	Trade-Off
	2	\$ 11,534.95	\$ 11,018.50	\$ 12,923.66	0.02359863	\$ 547,644.38	Trade-Off
	3	\$ 12,966.76	\$ 12,428.48	\$ 13,176.70	-0.0118653	\$ (1,110,521.36)	Dominant-Reject
	4	\$ 14,364.42	\$ 13,867.03	\$ 12,248.77	-0.0066071	\$ (1,853,874.04)	Dominant-Reject
104	1	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.23603646	\$ 31,429.31	Trade-Off
	2	\$ 9,241.03	\$ 8,856.26	\$ 39,556.54	0.64467521	\$ 61,358.86	Trade-Off
	3	\$ 9,438.76	\$ 9,042.48	\$ 39,690.35	0.3561805	\$ 111,433.24	Trade-Off
	4	\$ 9,720.00	\$ 9,325.56	\$ 39,810.36	0.27993607	\$ 142,212.32	Trade-Off

Appendix-Table 5.B: CERs for the RCT as a function of institution number for the 'Base-Case', $N_t=1$ and $N_t=104$ models (with all other variables set to those levels of 'Base-Case'). As this was not a primary aim of this work, when examining the impact of including multiple institutions, we made the simplifying assumption that each institution had the capacity for the same number of patients.

Patient Number	Weekly Consents	RI ACER (\$/patient)	NRI ACER (\$/Patient)	RCT ICER			
				ΔC (RI-NRI)	ΔE (RI-NRI)	ICER (\$/Patient)	CEA Decision Criteria
1	1	\$ 46,374.17	\$ 46,087.85	\$ 1,295.96	0.0219177	\$ 59,128.69	Trade-Off
26	1	\$ 10,130.16	\$ 9,740.80	\$ 10,265.82	0.15220799	\$ 67,445.98	Trade-Off
	2	\$ 10,093.63	\$ 9,686.46	\$ 10,615.97	0.11889012	\$ 89,292.31	Trade-Off
	3	\$ 10,119.47	\$ 9,695.56	\$ 10,802.21	0.07847851	\$ 137,645.45	Trade-Off
	4	\$ 10,118.07	\$ 9,696.02	\$ 10,758.25	0.07847851	\$ 137,085.35	Trade-Off
	5	\$ 10,125.18	\$ 9,698.80	\$ 10,861.15	0.07847851	\$ 138,396.46	Trade-Off
	6	\$ 10,122.27	\$ 9,702.59	\$ 10,702.81	0.07847851	\$ 136,378.89	Trade-Off
	7	\$ 10,123.63	\$ 9,703.34	\$ 10,717.24	0.07847851	\$ 136,562.73	Trade-Off
104	1	\$ 10,452.75	\$ 10,186.72	\$ 36,845.91	1.98064929	\$ 18,602.95	Trade-Off
	2	\$ 9,826.13	\$ 9,520.35	\$ 36,966.61	1.61754344	\$ 22,853.55	Trade-Off
	3	\$ 9,466.98	\$ 9,103.13	\$ 39,017.06	1.23603646	\$ 31,566.27	Trade-Off
	4	\$ 9,471.21	\$ 9,104.91	\$ 39,206.64	1.23603646	\$ 31,719.65	Trade-Off
	5	\$ 9,472.98	\$ 9,108.25	\$ 39,091.34	1.23603646	\$ 31,626.36	Trade-Off
	6	\$ 9,473.85	\$ 9,107.79	\$ 39,192.08	1.23603646	\$ 31,707.87	Trade-Off
	7	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.23603646	\$ 31,429.31	Trade-Off

Appendix-Table 5.C: CERs for the 'Base-Case' for the RCT as a function of N_t and number of simultaneous patients consented.

Trial Size	Patient Capacity	RI ACER (\$/Patient)	NRI ACER (\$/Patient)	RCT ICER			
				□ C (RI-NRI)	□ E (RI-NRI)	ICER (\$/Patient)	CEA Decision Criteria
1	1	\$ 47,463.89	\$ 46,087.85	\$ 1,376.03	-0.0010021	\$ (1,373,087.65)	Dominant-Reject
26	1	\$ 10,141.67	\$ 9,752.18	\$ 10,270.35	0.15220799	\$ 67,475.75	Trade-Off
26	2	\$ 10,094.19	\$ 9,698.96	\$ 10,340.04	0.11889012	\$ 86,971.37	Trade-Off
26	3	\$ 10,123.63	\$ 9,703.34	\$ 10,717.24	0.07847851	\$ 136,562.73	Trade-Off
26	4	\$ 10,188.50	\$ 9,724.08	\$ 11,711.61	0.05745189	\$ 203,850.74	Trade-Off
26	5	\$ 10,249.79	\$ 9,780.79	\$ 11,863.67	0.05012554	\$ 236,679.22	Trade-Off
104	1	\$ 10,462.87	\$ 10,203.71	\$ 36,449.68	1.98064929	\$ 18,402.90	Trade-Off
104	2	\$ 9,835.63	\$ 9,532.60	\$ 36,792.07	1.61754344	\$ 22,745.65	Trade-Off
104	3	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.23603646	\$ 31,429.31	Trade-Off
104	4	\$ 9,238.05	\$ 8,879.05	\$ 38,225.30	1.04570481	\$ 36,554.58	Trade-Off
104	5	\$ 9,079.78	\$ 8,701.36	\$ 39,434.47	0.88372749	\$ 44,622.88	Trade-Off

Appendix-Table 5.D: CERs as a function of Patient Testing Capacity for the 'Base-Case', N_t=1 and N_i=104 models (with all other variables set to those levels of 'Base-Case').

Trial Size	Cost Discount (i)	RI ACER (\$/Patient)	NRI ACER (\$/Patient)	RCT ICER			
				□ C (RI-NRI)	□ E (RI-NRI)	ICER (\$/Patient)	CEA Decision Criteria
1	0	\$ 47,995.05	\$ 46,811.34	\$ 1,183.71	-0.0004089	\$ (2,894,645.35)	Dominant-Reject
1	0.01	\$ 47,915.12	\$ 46,589.05	\$ 1,326.07	-0.0007326	\$ (1,809,983.03)	Dominant-Reject
1	0.02	\$ 47,826.82	\$ 46,595.15	\$ 1,231.67	-0.000607	\$ (2,029,111.69)	Dominant-Reject
1	0.03	\$ 47,721.99	\$ 46,422.35	\$ 1,299.64	-0.0007848	\$ (1,656,102.37)	Dominant-Reject
1	0.04	\$ 47,680.52	\$ 46,385.60	\$ 1,294.92	-0.0006666	\$ (1,942,491.27)	Dominant-Reject
1	0.05	\$ 47,575.59	\$ 46,247.71	\$ 1,327.88	-0.0008214	\$ (1,616,550.44)	Dominant-Reject
1	0.06	\$ 47,463.89	\$ 46,087.85	\$ 1,376.03	-0.0010021	\$ (1,373,087.65)	Dominant-Reject
1	0.07	\$ 47,214.30	\$ 45,994.81	\$ 1,219.49	-0.0005056	\$ (2,411,838.27)	Dominant-Reject
1	0.08	\$ 47,190.72	\$ 46,056.14	\$ 1,134.58	-0.000514	\$ (2,207,313.16)	Dominant-Reject
1	0.09	\$ 47,061.76	\$ 45,911.45	\$ 1,150.32	-0.0005713	\$ (2,013,353.03)	Dominant-Reject
1	0.1	\$ 47,041.15	\$ 45,887.07	\$ 1,154.08	-0.0005964	\$ (1,935,232.73)	Dominant-Reject
26	0	\$ 10,639.78	\$ 10,183.82	\$ 11,855.15	0.08767885	\$ 135,211.04	Trade-Off
26	0.01	\$ 10,547.46	\$ 10,147.65	\$ 10,395.10	0.09326308	\$ 111,460.01	Trade-Off
26	0.02	\$ 10,491.37	\$ 10,039.15	\$ 11,757.68	0.08158002	\$ 144,124.47	Trade-Off
26	0.03	\$ 10,396.13	\$ 9,965.93	\$ 11,185.34	0.08482652	\$ 131,861.40	Trade-Off
26	0.04	\$ 10,316.19	\$ 9,841.11	\$ 12,351.97	0.06544771	\$ 188,730.40	Trade-Off
26	0.05	\$ 10,218.41	\$ 9,774.31	\$ 11,546.55	0.08304943	\$ 139,032.31	Trade-Off
26	0.06	\$ 10,123.63	\$ 9,703.34	\$ 10,927.54	0.07847851	\$ 139,242.50	Trade-Off
26	0.07	\$ 10,051.82	\$ 9,581.57	\$ 12,226.51	0.07851752	\$ 155,716.97	Trade-Off
26	0.08	\$ 9,944.78	\$ 9,551.02	\$ 10,237.66	0.10813378	\$ 94,675.86	Trade-Off
26	0.09	\$ 9,874.23	\$ 9,427.83	\$ 11,606.24	0.07591129	\$ 152,892.17	Trade-Off
26	0.1	\$ 9,782.29	\$ 9,397.34	\$ 10,008.63	0.09624608	\$ 103,990.01	Trade-Off
104	0	\$ 11,204.55	\$ 10,862.93	\$ 35,528.67	1.24949371	\$ 28,434.46	Trade-Off
104	0.01	\$ 10,874.07	\$ 10,502.30	\$ 38,663.47	1.25987591	\$ 30,688.31	Trade-Off
104	0.02	\$ 10,566.14	\$ 10,241.18	\$ 33,795.79	1.37628066	\$ 24,555.89	Trade-Off
104	0.03	\$ 10,283.04	\$ 9,935.42	\$ 36,151.55	1.30714523	\$ 27,656.87	Trade-Off
104	0.04	\$ 9,985.17	\$ 9,642.55	\$ 35,632.68	1.35314629	\$ 26,333.20	Trade-Off
104	0.05	\$ 9,734.97	\$ 9,363.76	\$ 38,605.95	1.17876818	\$ 32,751.10	Trade-Off
104	0.06	\$ 9,473.73	\$ 9,112.25	\$ 37,593.68	1.23603646	\$ 30,414.70	Trade-Off
104	0.07	\$ 9,231.89	\$ 8,889.66	\$ 35,591.48	1.2607563	\$ 28,230.27	Trade-Off
104	0.08	\$ 8,971.51	\$ 8,637.39	\$ 34,747.94	1.31101238	\$ 26,504.66	Trade-Off
104	0.09	\$ 8,772.50	\$ 8,410.63	\$ 37,633.99	1.24711109	\$ 30,176.93	Trade-Off
104	0.1	\$ 8,548.10	\$ 8,204.96	\$ 35,686.40	1.31181833	\$ 27,203.77	Trade-Off

Appendix-Table 5.E: CERs as a function of Cost Discount for the 'Base-Case', N_t=1 and N_i=104 models (with all other variables set to those levels of 'Base-Case').

Trial Size	Effectiveness Discount(r)	RI ACER (\$/Patient)	NRI ACER (\$/Patient)	RCT ICER			CEA Decision Criteria
				ΔC (RI-NRI)	ΔE (RI-NRI)	ICER (\$/Patient)	
1	0	\$ 46,295.21	\$ 44,999.24	\$ 1,295.96	0	Infinity	Always Reject
1	0.05	\$ 47,463.89	\$ 46,087.85	\$ 1,295.96	-0.0010021	\$ (1,293,190.87)	Always Reject
1	0.1	\$ 48,661.91	\$ 47,202.65	\$ 1,295.96	-0.0019558	\$ (662,620.95)	Always Reject
1	0.15	\$ 49,889.99	\$ 48,344.25	\$ 1,295.96	-0.0028628	\$ (452,694.21)	Always Reject
1	0.2	\$ 51,148.90	\$ 49,513.30	\$ 1,295.96	-0.0037248	\$ (347,933.10)	Always Reject
1	0.25	\$ 52,439.39	\$ 50,710.46	\$ 1,295.96	-0.0045434	\$ (285,242.21)	Always Reject
1	0.3	\$ 53,762.26	\$ 51,936.38	\$ 1,295.96	-0.0053203	\$ (243,589.80)	Always Reject
1	0.35	\$ 55,118.31	\$ 53,191.78	\$ 1,295.96	-0.006057	\$ (213,962.36)	Always Reject
1	0.4	\$ 56,508.38	\$ 54,477.34	\$ 1,295.96	-0.006755	\$ (191,853.18)	Always Reject
1	0.45	\$ 57,933.30	\$ 55,793.78	\$ 1,295.96	-0.0074157	\$ (174,758.60)	Always Reject
1	0.5	\$ 59,393.96	\$ 57,141.85	\$ 1,295.96	-0.0080407	\$ (161,176.48)	Always Reject
26	0	\$ 9,223.31	\$ 8,811.11	\$ 10,717.24	0	Infinity	Dominant-Reject
26	0.05	\$ 10,123.63	\$ 9,703.34	\$ 10,717.24	0.07847851	\$ 136,562.73	Trade-Off
26	0.1	\$ 11,111.68	\$ 10,685.77	\$ 10,717.24	0.14275372	\$ 75,075.03	Trade-Off
26	0.15	\$ 12,196.02	\$ 11,767.52	\$ 10,717.24	0.19475626	\$ 55,028.99	Trade-Off
26	0.2	\$ 13,385.99	\$ 12,958.60	\$ 10,717.24	0.23618315	\$ 45,376.82	Trade-Off
26	0.25	\$ 14,691.89	\$ 14,270.05	\$ 10,717.24	0.26852438	\$ 39,911.61	Trade-Off
26	0.3	\$ 16,124.98	\$ 15,714.02	\$ 10,717.24	0.29308649	\$ 36,566.82	Trade-Off
26	0.35	\$ 17,697.63	\$ 17,303.87	\$ 10,717.24	0.31101364	\$ 34,459.07	Trade-Off
26	0.4	\$ 19,423.42	\$ 19,054.33	\$ 10,717.24	0.32330638	\$ 33,148.87	Trade-Off
26	0.45	\$ 21,317.22	\$ 20,981.58	\$ 10,717.24	0.33083825	\$ 32,394.20	Trade-Off
26	0.5	\$ 23,395.37	\$ 23,103.46	\$ 10,717.24	0.33437065	\$ 32,051.98	Trade-Off
104	0	\$ 6,951.43	\$ 6,577.90	\$ 38,847.78	0	Infinity	Dominant-Reject
104	0.05	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.23603646	\$ 31,429.31	Trade-Off
104	0.1	\$ 12,910.67	\$ 12,622.48	\$ 38,847.78	1.79917099	\$ 21,592.04	Trade-Off
104	0.15	\$ 17,593.75	\$ 17,484.14	\$ 38,847.78	1.96428003	\$ 19,777.11	Trade-Off
104	0.2	\$ 23,974.51	\$ 24,217.24	\$ 38,847.78	1.90638396	\$ 20,377.73	Trade-Off
104	0.25	\$ 32,668.00	\$ 33,541.75	\$ 38,847.78	1.73467111	\$ 22,394.90	Trade-Off
104	0.3	\$ 44,511.99	\$ 46,454.45	\$ 38,847.78	1.51538736	\$ 25,635.54	Trade-Off
104	0.35	\$ 60,647.53	\$ 64,335.33	\$ 38,847.78	1.28713535	\$ 30,181.58	Trade-Off
104	0.4	\$ 82,628.67	\$ 89,094.82	\$ 38,847.78	1.07102208	\$ 36,271.69	Trade-Off
104	0.45	\$ 112,571.92	\$ 123,377.51	\$ 38,847.78	0.87732738	\$ 44,279.68	Trade-Off
104	0.5	\$ 153,256.94	\$ 170,844.19	\$ 38,847.78	0.70983659	\$ 54,727.78	Trade-Off

Appendix-Table 5.F: CERs as a function of Effectiveness Discount for the 'Base-Case', $N_t=1$ and $N_t=104$ models (with all other variables set to those levels of 'Base-Case'). When $N=104$ the RCT RI design became cost effective, per the ACERs, compared to the NRI RCT when r_d reached ~16%, with lowest ICER at $r_d=15\%$ (for the $N_t=26$ case, the ACER inflection point would be found at $r_d\sim 69\%$). For our examples, as $C_{RI} > C_{NRI}$, when the RI RCT duration is shorter than the NRI RCT duration and the effectiveness discount is raised then $ACER_{NRI} > ACER_{RI}$ (seen with the increased sample sizes), but as incremental differences in effectiveness become lower the ICERs can become quite high.

Trial Size	Start-Up Cost Multiplier	RI ACER (\$/Patient)	NRI ACER (\$/Patient)	RCTICER			CEA Decision Criterion
				□ C (RI-NRI)	□ E (RI-NRI)	ICER (\$/Patient)	
1	0.5	\$ 43,993.12	\$ 40,922.44	\$ 2,944.92	-0.001149821	\$ (2,561,200.99)	Dominant-Reject
1	1	\$ 47,463.89	\$ 46,087.85	\$ 1,295.96	-0.001002145	\$ (1,293,190.87)	Dominant-Reject
1	1.5	\$ 72,701.40	\$ 69,545.92	\$ 2,992.35	-0.001184476	\$ (2,526,302.61)	Dominant-Reject
1	2	\$ 87,125.53	\$ 83,706.95	\$ 3,226.85	-0.001243348	\$ (2,595,292.43)	Dominant-Reject
1	2.5	\$ 101,349.50	\$ 97,949.96	\$ 3,190.88	-0.00123958	\$ (2,574,163.17)	Dominant-Reject
1	3	\$ 115,799.58	\$ 112,246.24	\$ 3,315.16	-0.001309743	\$ (2,531,148.85)	Dominant-Reject
26	0.5	\$ 9,534.22	\$ 9,095.66	\$ 11,042.20	0.071846518	\$ 153,691.53	Trade-Off
26	1	\$ 10,123.63	\$ 9,703.34	\$ 10,717.24	0.078478513	\$ 136,562.73	Trade-Off
26	1.5	\$ 10,713.53	\$ 10,250.91	\$ 11,637.86	0.066231437	\$ 175,715.04	Trade-Off
26	2	\$ 11,298.78	\$ 10,857.42	\$ 11,300.19	0.077573264	\$ 145,671.14	Trade-Off
26	2.5	\$ 11,879.81	\$ 11,471.96	\$ 10,718.51	0.091885194	\$ 116,651.15	Trade-Off
26	3	\$ 12,494.52	\$ 12,020.22	\$ 12,117.84	0.073198641	\$ 165,547.39	Trade-Off
104	0.5	\$ 9,282.60	\$ 8,929.81	\$ 37,724.59	1.209514513	\$ 31,189.86	Trade-Off
104	1	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.236036456	\$ 31,429.31	Trade-Off
104	1.5	\$ 9,648.95	\$ 9,309.34	\$ 37,718.09	1.266846293	\$ 29,773.22	Trade-Off
104	2	\$ 9,856.95	\$ 9,501.28	\$ 39,075.82	1.256744529	\$ 31,092.89	Trade-Off
104	2.5	\$ 10,016.09	\$ 9,653.64	\$ 39,043.69	1.178851802	\$ 33,120.10	Trade-Off
104	3	\$ 10,204.89	\$ 9,875.42	\$ 38,034.92	1.305310813	\$ 29,138.59	Trade-Off

Appendix-Table 5.G: CERs as a function of Testing Phase Start-Up Costs for the 'Base-Case', Nt=1 and Ni=104 models (with all other variables set to those levels of 'Base-Case').

Trial Size	Baseline Cost Multiplier	RI ACER (\$/Patient)	NRI ACER (\$/Patient)	RCTICER			CEA Decision Criterion
				□ C (RI-NRI)	□ E (RI-NRI)	ICER (\$/Patient)	
1	0.5	\$46,692.80	\$ 45,697.70	\$ 921.94	-0.001063895	\$ (866,573.41)	Dominant-Reject
1	1	\$47,463.89	\$ 46,087.85	\$ 1,295.96	-0.001002145	\$ (1,293,190.87)	Dominant-Reject
1	1.5	\$48,338.14	\$ 46,674.93	\$ 1,581.78	-0.000866385	\$ (1,825,719.71)	Dominant-Reject
1	2	\$48,926.21	\$ 46,903.99	\$ 1,935.66	-0.000789764	\$ (2,450,939.60)	Dominant-Reject
1	2.5	\$50,025.60	\$ 47,251.31	\$ 2,656.30	-0.00104891	\$ (2,532,440.69)	Dominant-Reject
1	3	\$50,875.09	\$ 47,585.42	\$ 3,154.25	-0.001136849	\$ (2,774,552.83)	Dominant-Reject
26	0.5	\$ 9,229.12	\$ 9,285.99	\$ (585.56)	0.082026685	\$ (7,138.70)	Dominant-Accept
26	1	\$10,123.63	\$ 9,703.34	\$ 10,717.24	0.078478513	\$ 136,562.73	Trade-Off
26	1.5	\$11,002.72	\$ 10,124.10	\$ 21,658.33	0.08289513	\$ 261,273.90	Trade-Off
26	2	\$11,910.40	\$ 10,500.39	\$ 34,270.96	0.082077157	\$ 417,545.60	Trade-Off
26	2.5	\$12,787.17	\$ 10,938.14	\$ 44,758.38	0.086249943	\$ 518,938.03	Trade-Off
26	3	\$13,646.53	\$ 11,305.12	\$ 56,424.68	0.082015687	\$ 687,974.22	Trade-Off
104	0.5	\$ 8,536.90	\$ 8,687.97	\$ (861.95)	1.227073798	\$ (702.44)	Dominant-Accept
104	1	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.236036456	\$ 31,429.31	Trade-Off
104	1.5	\$10,419.31	\$ 9,558.49	\$ 77,662.80	1.252709829	\$ 61,995.84	Trade-Off
104	2	\$11,358.46	\$ 10,010.46	\$ 115,600.27	1.276108404	\$ 90,588.12	Trade-Off
104	2.5	\$12,300.98	\$ 10,418.01	\$ 156,180.03	1.200993139	\$ 130,042.40	Trade-Off
104	3	\$13,239.05	\$ 10,872.86	\$ 193,960.87	1.235687191	\$ 156,966.00	Trade-Off

Appendix-Table 5.H: CERs as a function of Testing Phase Baseline Costs for the 'Base-Case', Nt=1 and Ni=104 models (with all other variables set to those levels of 'Base-Case').

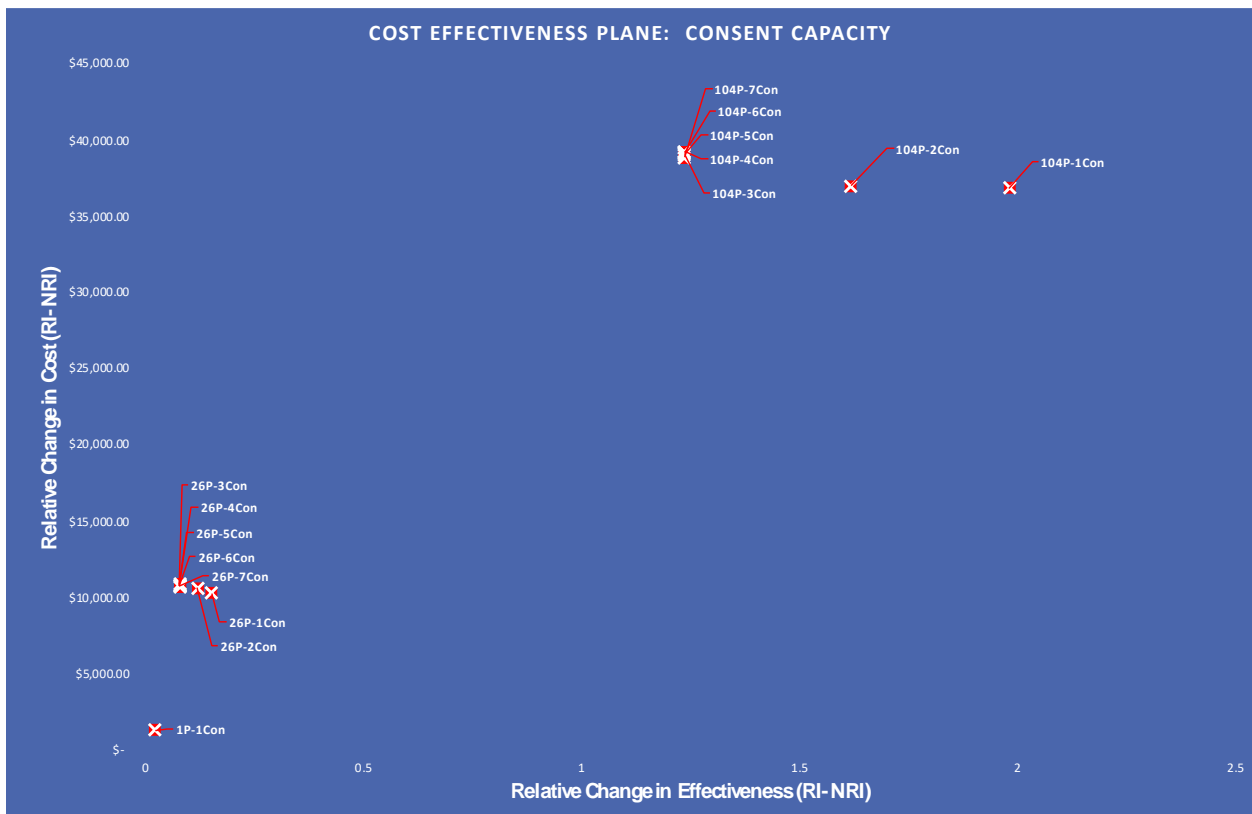
Trial Size	Treatment Cost Multiplier	RI ACER (\$/Patient)	NRI ACER (\$/Patient)	RCT ICER			
				□ C (RI-NRI)	□ E (RI-NRI)	ICER (\$/Patient)	CEA Decision Criter
1	0.5	\$45,642.90	\$ 44,101.88	\$ 1,459.94	-0.000982614	\$ (1,485,766.61)	Dominant-Reject
1	1	\$47,463.89	\$ 46,087.85	\$ 1,295.96	-0.001002145	\$ (1,293,190.87)	Dominant-Reject
1	1.5	\$49,197.26	\$ 47,957.43	\$ 1,153.13	-0.001168673	\$ (986,698.84)	Dominant-Reject
1	2	\$50,884.28	\$ 49,846.51	\$ 954.68	-0.001152794	\$ (828,141.23)	Dominant-Reject
1	2.5	\$52,643.19	\$ 51,864.38	\$ 701.30	-0.001123777	\$ (624,055.21)	Dominant-Reject
1	3	\$54,349.43	\$ 54,035.73	\$ 252.21	-0.000994623	\$ (253,575.07)	Dominant-Reject
26	0.5	\$ 8,304.25	\$ 7,621.56	\$ 16,765.35	0.077804452	\$ 215,480.60	Trade-Off
26	1	\$10,123.63	\$ 9,703.34	\$ 10,717.24	0.078478513	\$ 136,562.73	Trade-Off
26	1.5	\$11,956.49	\$ 11,808.61	\$ 4,552.74	0.088873058	\$ 51,227.47	Trade-Off
26	2	\$13,760.72	\$ 13,854.86	\$ (1,203.51)	0.074126555	\$ (16,235.82)	Dominant-Accept
26	2.5	\$15,568.59	\$ 15,853.70	\$ (5,500.05)	0.079370025	\$ (69,296.32)	Dominant-Accept
26	3	\$17,437.64	\$ 17,978.60	\$ (11,467.11)	0.075025944	\$ (152,841.97)	Dominant-Accept
104	0.5	\$ 7,543.27	\$ 6,903.34	\$ 56,979.69	1.187288217	\$ 47,991.46	Trade-Off
104	1	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.236036456	\$ 31,429.31	Trade-Off
104	1.5	\$11,419.96	\$ 11,341.03	\$ 20,034.26	1.235451373	\$ 16,216.15	Trade-Off
104	2	\$13,375.59	\$ 13,563.17	\$ 1,858.50	1.19210724	\$ 1,559.00	Trade-Off
104	2.5	\$15,310.61	\$ 15,844.37	\$ (19,558.82)	1.337063958	\$ (14,628.19)	Dominant-Accept
104	3	\$17,268.36	\$ 18,067.16	\$ (37,725.72)	1.284666767	\$ (29,366.15)	Dominant-Accept

Appendix-Table 5.I: CERs as a function of Testing Phase Treatment Costs for the 'Base-Case', Nt=1 and Nt=104 models (with all other variables set to those levels of 'Base-Case').

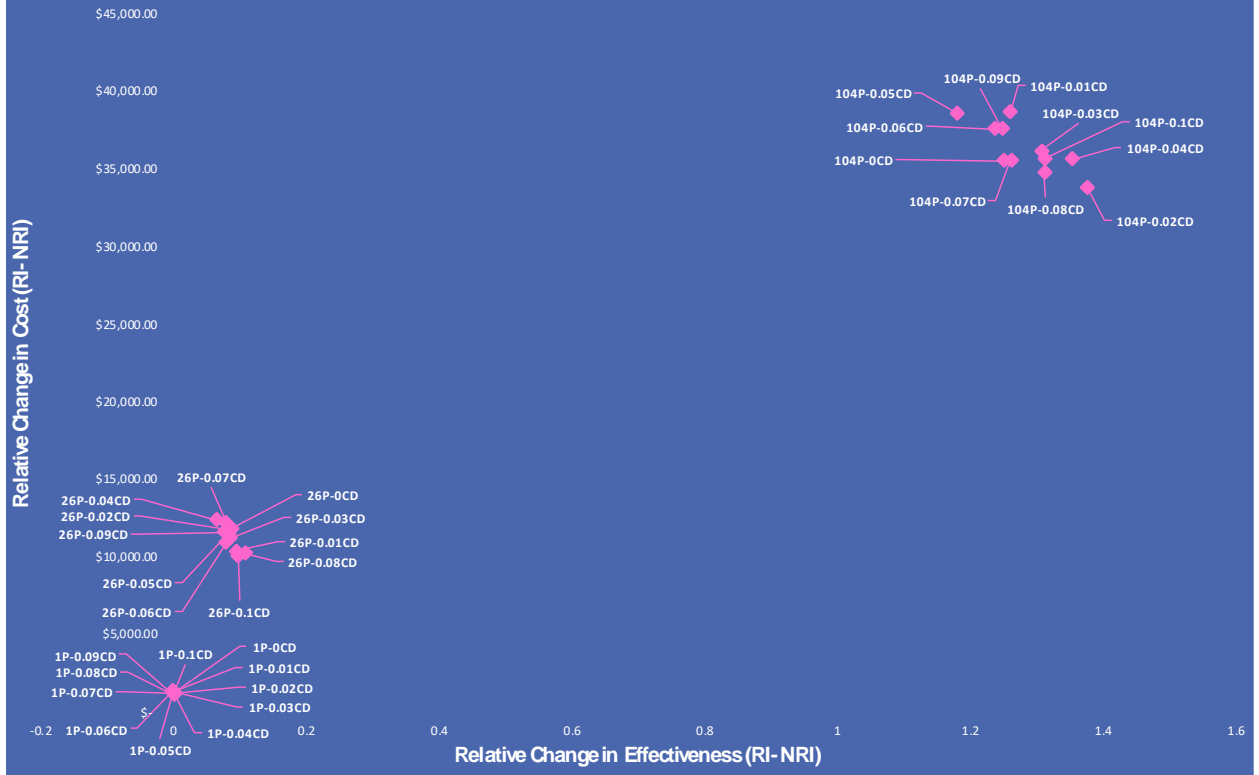
Trial Size	Follow-up Cost Multiplier	RI ACER (\$/Patient)	NRI ACER (\$/Patient)	RCT ICER			
				□ C (RI-NRI)	□ E (RI-NRI)	ICER (\$/Patient)	CEA Decision Criter
1	0.5	\$56,812.29	\$ 53,660.67	\$ 3,003.95	-0.001244248	\$ (2,414,271.25)	Dominant-Reject
1	1	\$47,463.89	\$ 46,087.85	\$ 1,295.96	-0.001002145	\$ (1,293,190.87)	Dominant-Reject
1	1.5	\$60,154.03	\$ 56,916.28	\$ 3,081.62	-0.00127972	\$ (2,408,042.02)	Dominant-Reject
1	2	\$61,599.34	\$ 58,588.23	\$ 2,865.40	-0.001172331	\$ (2,444,191.92)	Dominant-Reject
1	2.5	\$63,356.22	\$ 60,130.16	\$ 3,063.47	-0.001326562	\$ (2,309,329.83)	Dominant-Reject
1	3	\$64,859.03	\$ 61,788.18	\$ 2,917.26	-0.001210586	\$ (2,409,786.92)	Dominant-Reject
26	0.5	\$ 9,283.99	\$ 8,840.10	\$ 11,345.07	0.093515035	\$ 121,318.16	Trade-Off
26	1	\$10,123.63	\$ 9,703.34	\$ 10,717.24	0.078478513	\$ 136,562.73	Trade-Off
26	1.5	\$10,944.07	\$ 10,560.86	\$ 10,051.27	0.091764092	\$ 109,533.78	Trade-Off
26	2	\$11,783.94	\$ 11,409.59	\$ 9,816.15	0.082813621	\$ 118,532.99	Trade-Off
26	2.5	\$12,625.95	\$ 12,298.09	\$ 8,881.06	0.090356185	\$ 98,289.47	Trade-Off
26	3	\$13,430.96	\$ 13,184.21	\$ 7,032.82	0.089883917	\$ 78,243.40	Trade-Off
104	0.5	\$ 8,574.71	\$ 8,174.91	\$ 40,886.71	1.269222442	\$ 32,213.98	Trade-Off
104	1	\$ 9,473.73	\$ 9,112.25	\$ 38,847.78	1.236036456	\$ 31,429.31	Trade-Off
104	1.5	\$10,394.20	\$ 10,071.23	\$ 37,154.12	1.243376823	\$ 29,881.63	Trade-Off
104	2	\$11,297.23	\$ 11,028.92	\$ 33,968.23	1.224526247	\$ 27,739.89	Trade-Off
104	2.5	\$12,200.86	\$ 11,957.29	\$ 32,704.21	1.181137992	\$ 27,688.73	Trade-Off
104	3	\$13,093.24	\$ 12,929.50	\$ 29,080.07	1.282492771	\$ 22,674.65	Trade-Off

Appendix-Table 5.I: CERs as a function of Testing Phase Follow-up Costs for the 'Base-Case', Nt=1 and Nt=104 models (with all other variables set to those levels of 'Base-Case').

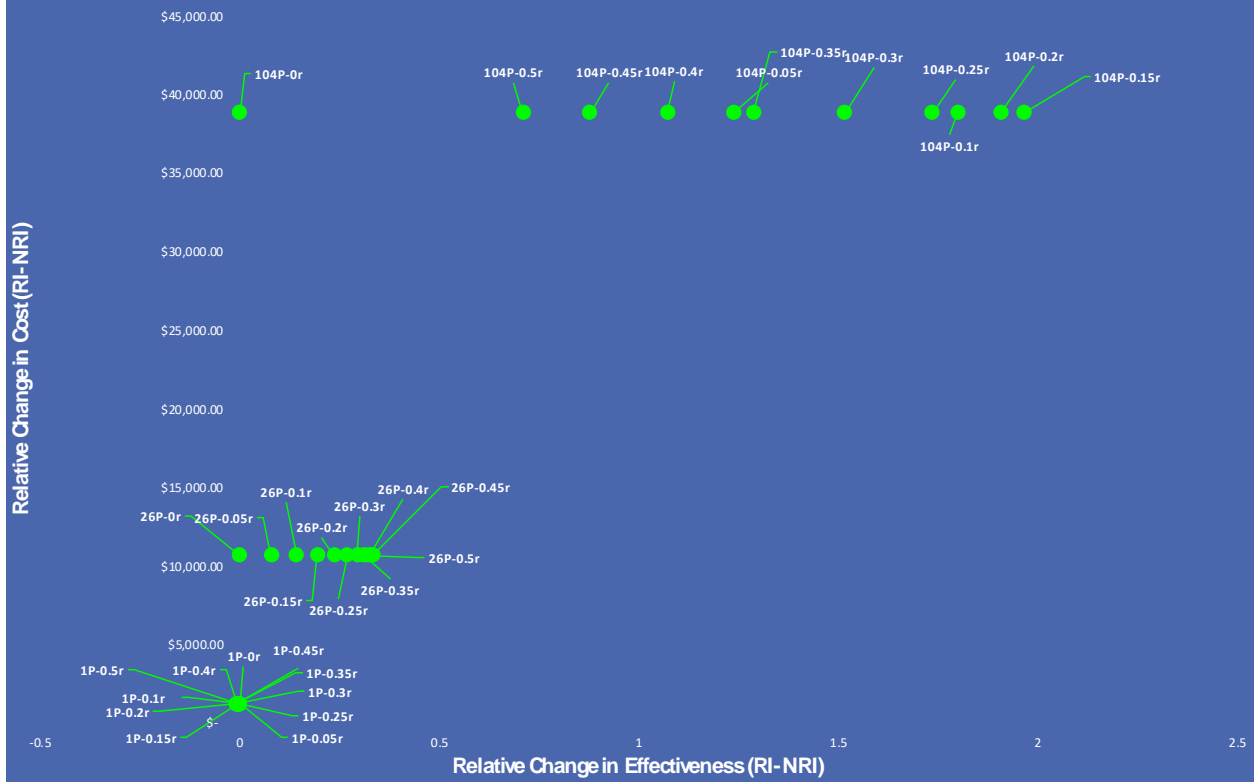
Appendix-Figure 1A- Cost-Effectiveness (CE) Planes for designs when varying the number of institutions, number of patients that could be consented per week/institution, number of patients that could be assessed simultaneously/institution, and/or cost discount (with the other variables fixed at the 'Base-Case' values). We depict the CE planes relative to the RI-NRI results for each RCT Design condition.

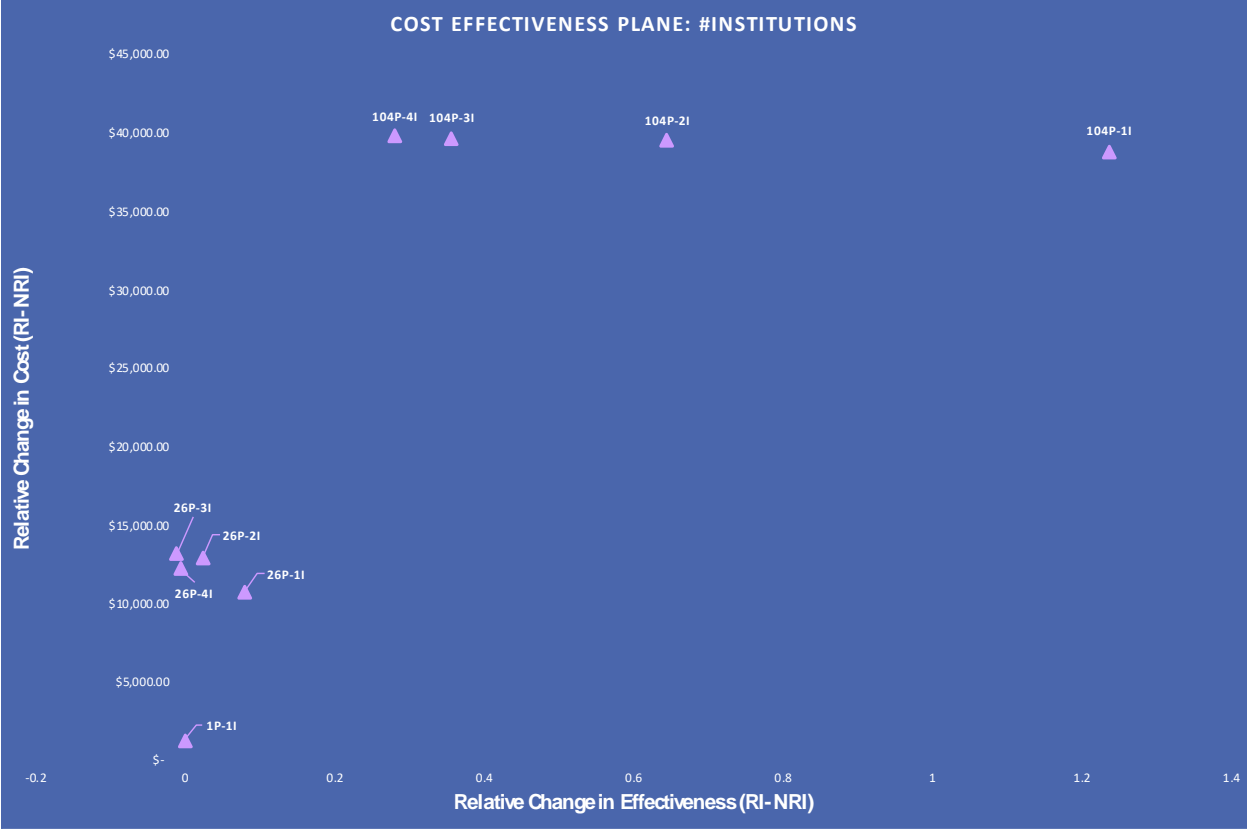
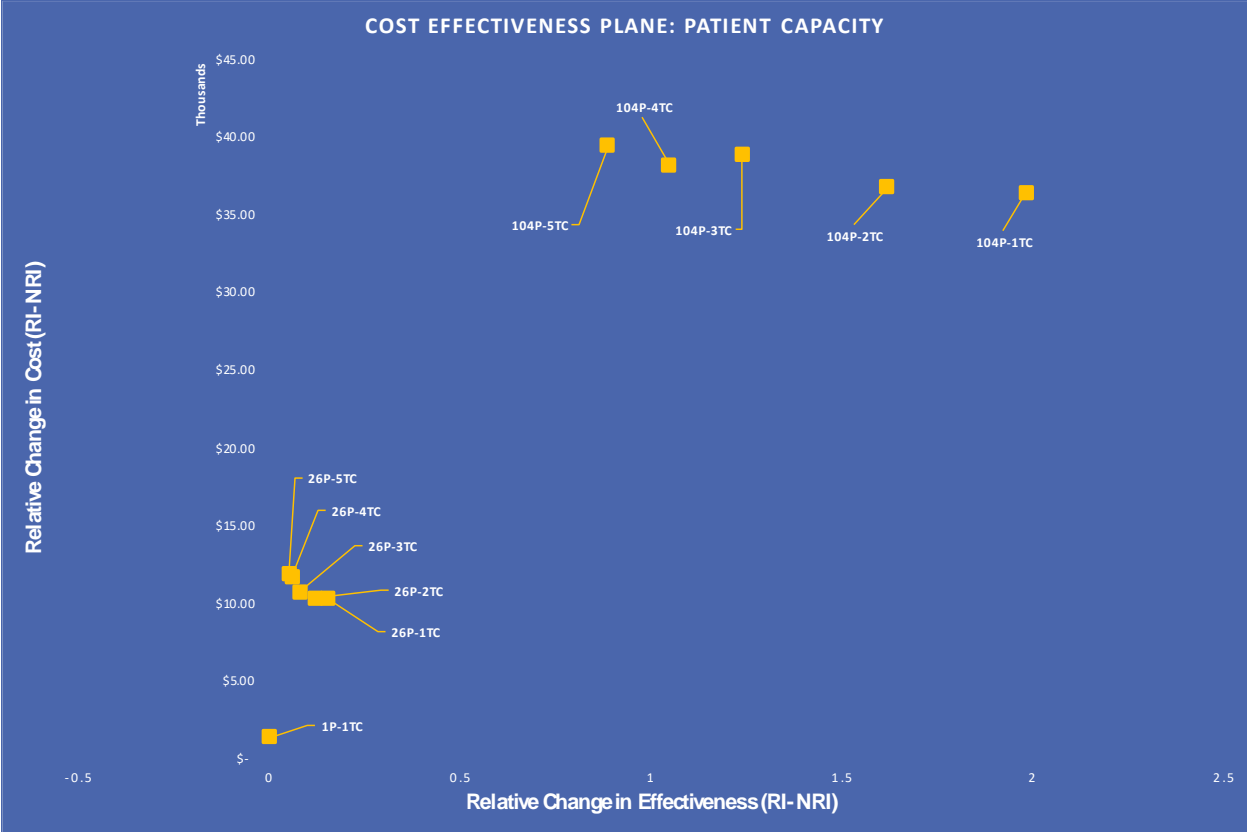


COST EFFECTIVENESS PLANE: COST DISCOUNT

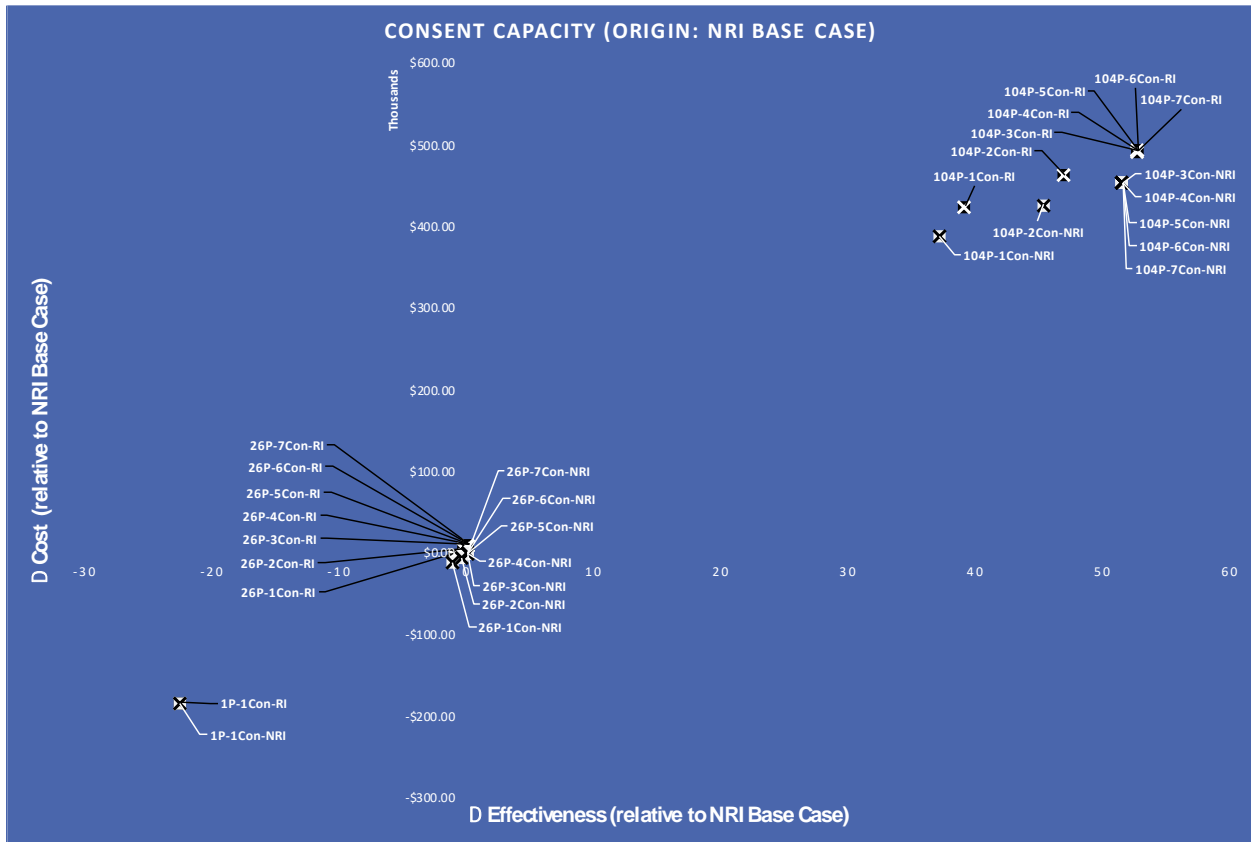


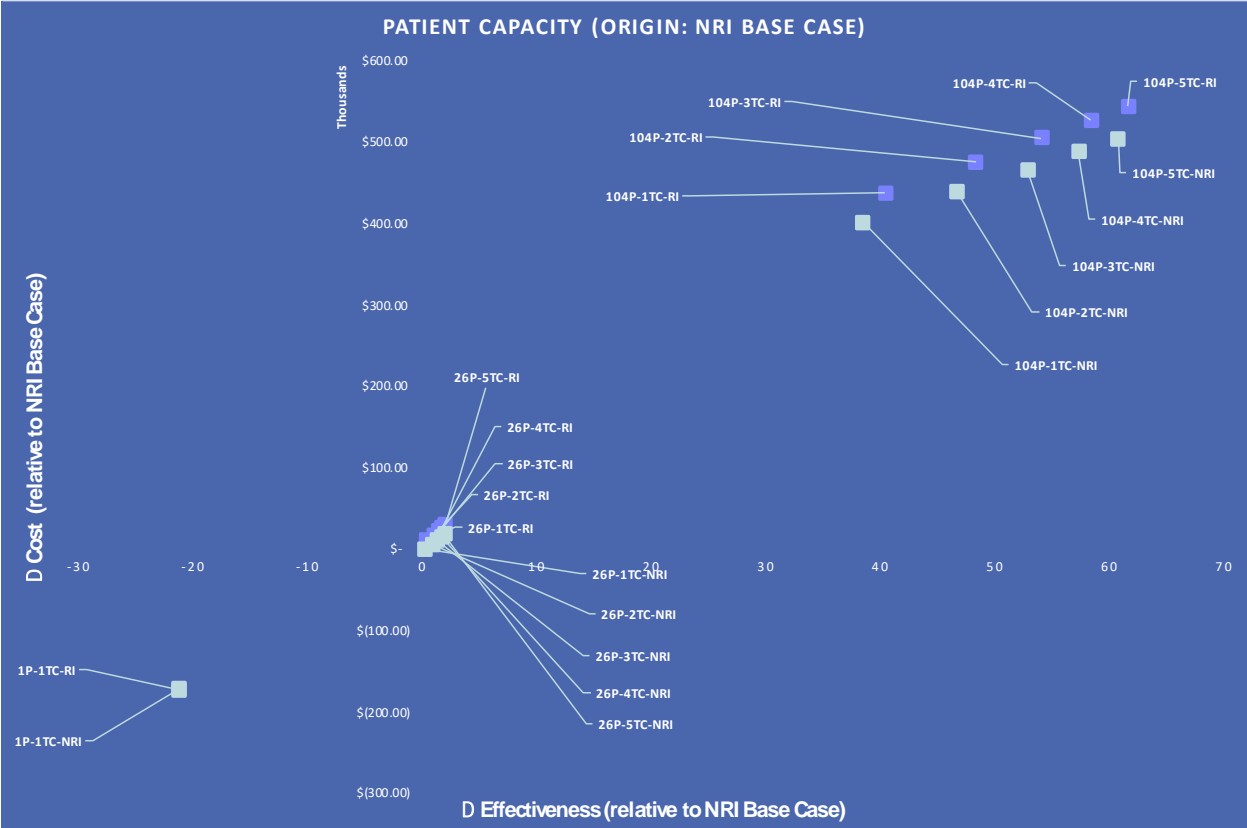
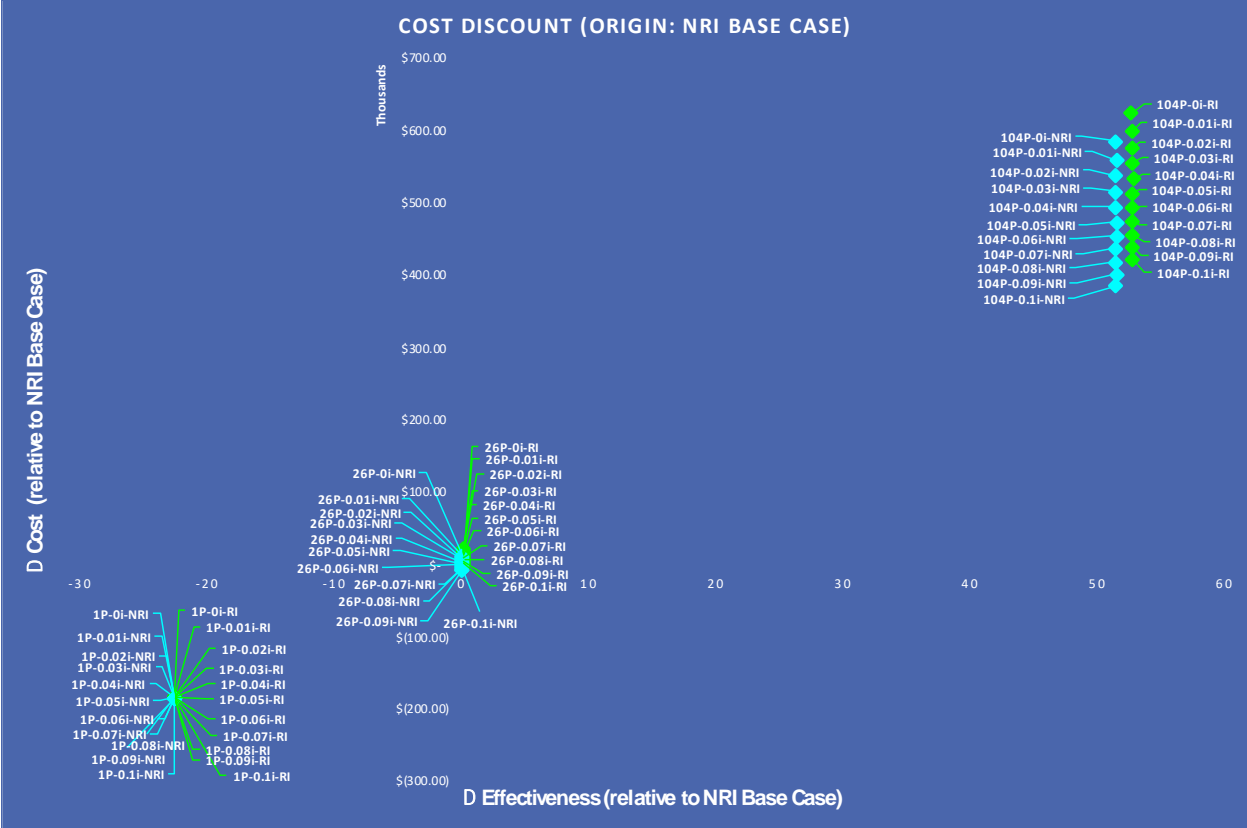
COST EFFECTIVENESS PLANE: EFFECTIVENESS DISCOUNT

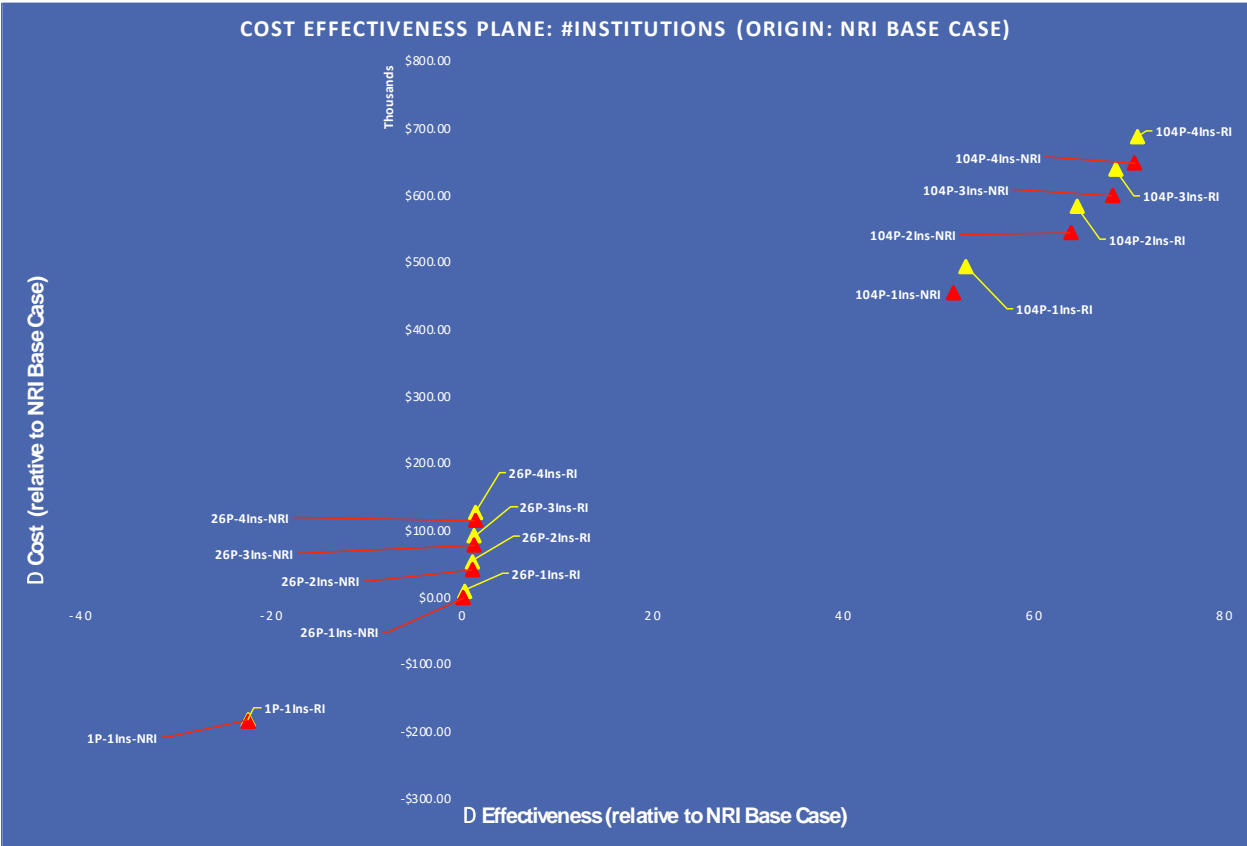
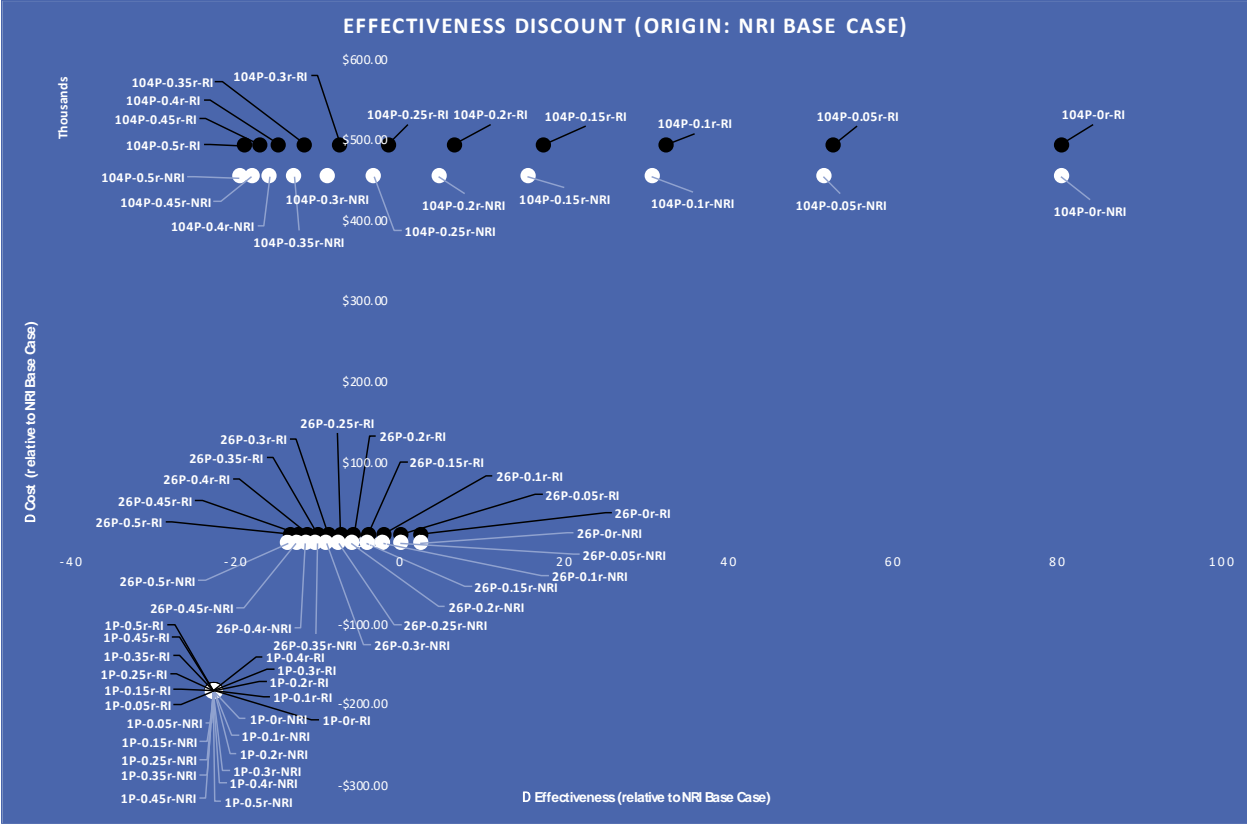




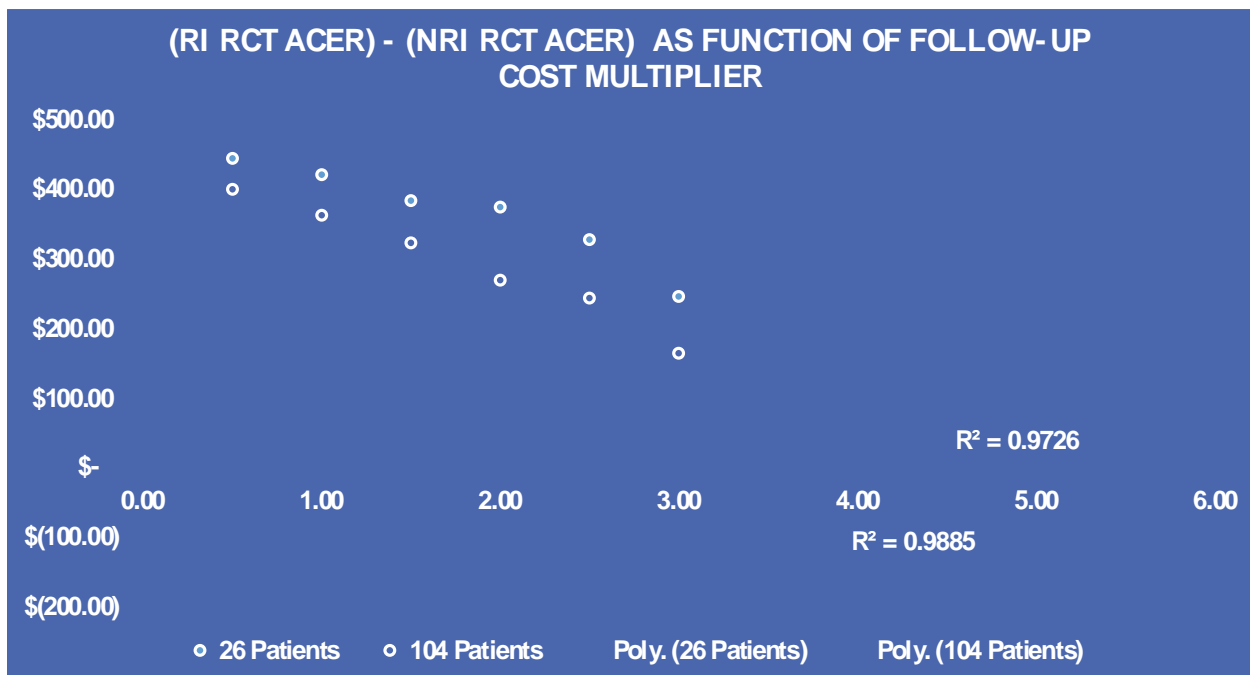
Appendix-Figure 1B- Cost-Effectiveness (CE) Planes for designs when varying the number of institutions, number of patients that could be consented per week/institution, number of patients that could be assessed simultaneously/institution, and/or cost discount (with the other variables fixed at the 'Base-Case' values). We depict the CE planes relative to the 26 patient NRI 'Base-Case'.







Appendix-Figure 2- The cost effectiveness of the RI was never greater than the NRI when altering the Follow-up Phase costs between 0.5-3x. However, curve fitting (Polynomial Curve fits, abbreviated Poly. in figure legend) demonstrates that a RI design would become more cost effective than an NRI design with a Follow-up cost multiplier of ~4.5 and ~4.4 respectively. Similarly, ICER analysis shows a trend of decreasing Cost differentials between the NRI and RI cases with increasing Follow-up costs, with limited changes in Effectiveness differentials (see Appendix-Table 5.I).



Appendix-Figure 3

Impact of Varying State Transition Probabilities and Effectiveness Discount: Testing Period Focus

