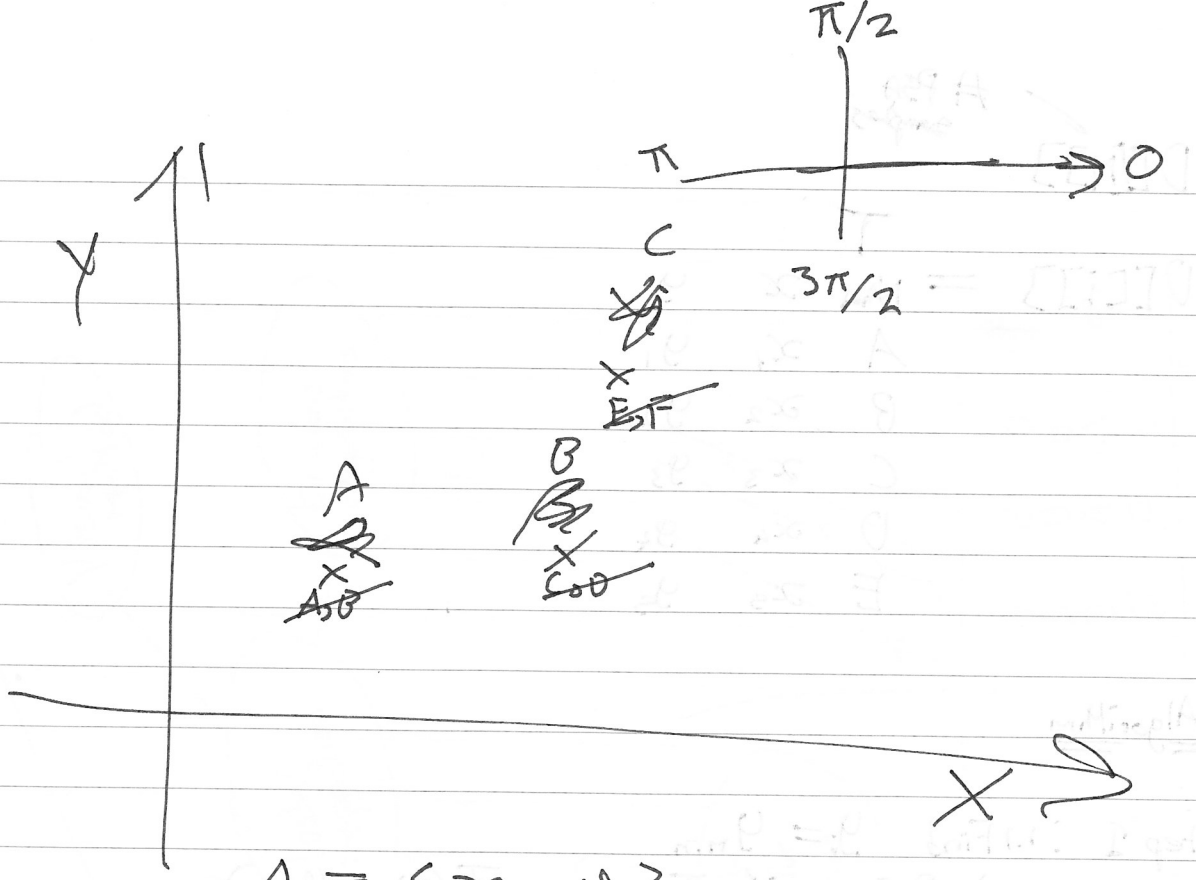


$A \equiv \{x_1, y_1\}$

$B \equiv \{x_2, y_2\}$

$C \equiv \{x_3, y_3\}$

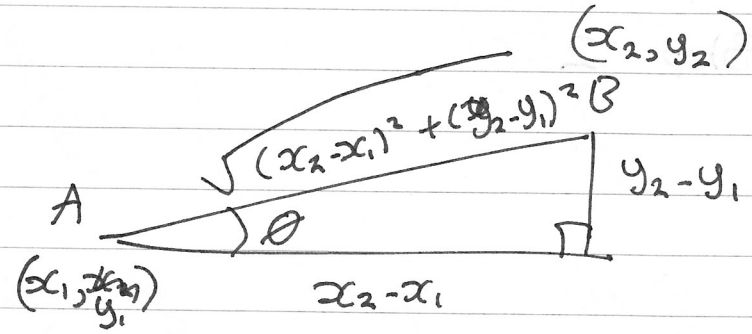
$\emptyset(A, B)$

Which

Min $\{\theta_{AB}, \theta_{AC}\}$?

THIS

repeat cont.? all $\theta > 90°$ $(\frac{\pi}{2})$



$$\sqrt{(x_2-x_1)^2 + (y_2-y_1)^2}\,\cos\theta = x_2 - x_1$$

$$\cos\theta = \frac{x_2 - x_1}{\sqrt{(x_2-x_1)^2 + (y_2-y_1)^2}}$$

$$\theta = \cos^{-1}\left(\frac{x_2 - x_1}{\sqrt{(x_2-x_1)^2 + (y_2-y_1)^2}}\right.$$

D[[M]] (# PSA samples)

D[[i]] = T

Name	x	y
A	x_1	y_1
B	x_2	y_2
C	x_3	y_3
D	x_4	y_4
E	x_5	y_5

Algorithm

Step 1 : 1.1 Find $y_i = y_{min}$

1.2) Define $T_{min1} \equiv T(y = y_{min})$

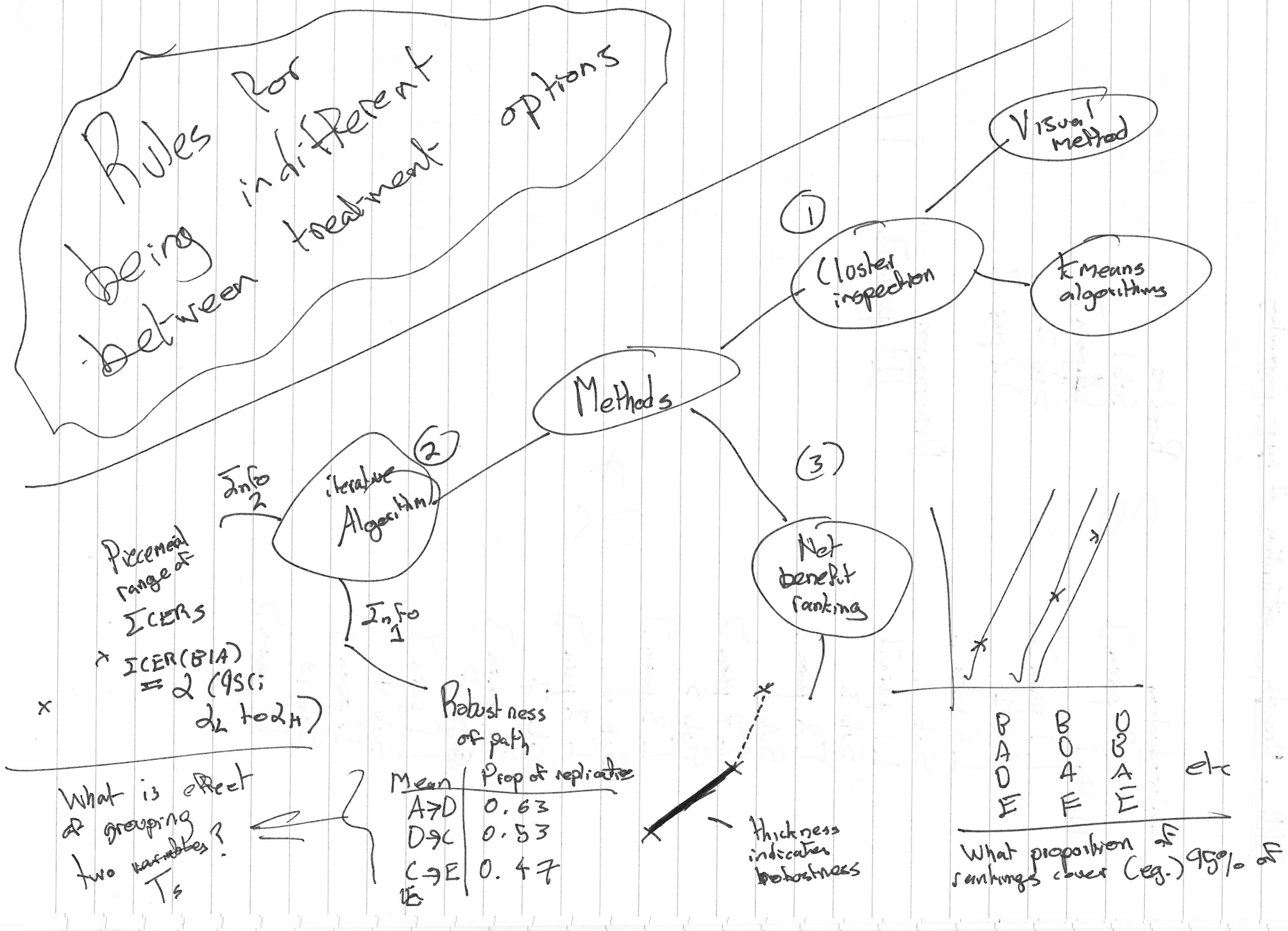
Step 2 : Find

2.1 Find all $\Theta_{T1}, {}'_{T1}$

2.2 Define $T_{i+1} = T(\Theta_{Ti}, {}'_{Ti} = Min(\theta))$

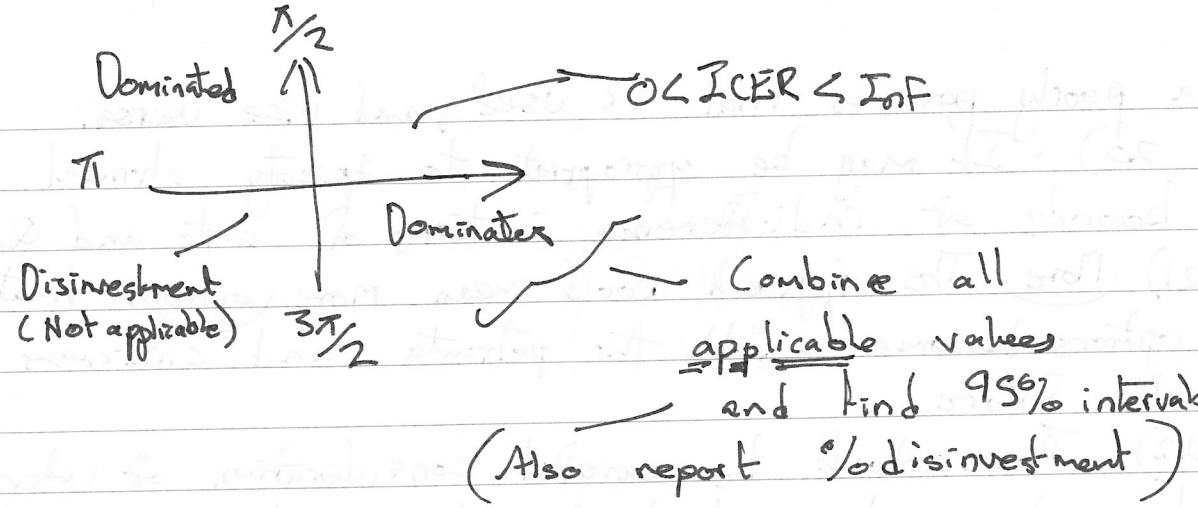
Step 3 : 3.1 Stop if all $\Theta_{T1}, {}'_{T1} > \frac{\pi}{2}$

Step 4 : 4.1 Go to Step 2


Rules for being indifferent between treatment options
Methods
(1)
Cluster inspection
Visual method
k means algorithms
(2)
Iterative Algorithm
Info 2
Info 1
Piecemeal range of ΣCERs
ICER(B|A) = Δ(QSC; Δ2 to Δ2H)
Robustness of path
Mean | Prop of replications
A→D | 0.63
D→C | 0.53
C→E | 0.47
What is effect of grouping two variables? Ts
(3)
Net benefit ranking
thickness indicates robustness
B A D E
B D A E
U B A E
etc
What proportion of rankings cover (eg.) 95% of

Chuck Norris Facts

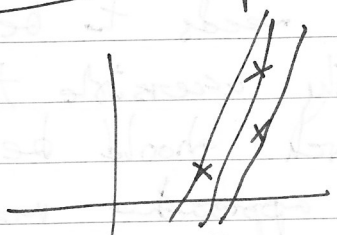
1) If two treatments are identical, one will dominate the other
2) Just using mean values means uncertainty about these values of treatments is ignored.
3) Many treatments that are very similar to those that have been accepted may have been rejected for this reason
4) It is important to decide in an accountable way when to be indifferent between two or more options
5) Three types of approach to consider are cluster analysis, algorithmic procedures, and net benefit ranking.
6) We can do informal cluster analysis by looking at PSA scatter by ignoring after removing identifier information
7) Algorithms exist to determine how the best number of clusters to assume a scatter is composed of.
8) The advantages of a formal algorithm are consistency and fairness
9) The algorithm for automating the process of calculating CE frontiers may benefit could be based on trigonometry
10) Two pieces of info the path robustness algorithm could produce are ICER ranges and robustness of each path component
11) ICER ranges are formulated by forcing the same treatment sequence be used each time, then looking at angles between points
12) There is a relationship between angles and ICERs



12) Path robustness is found by calculating the proportion of treatment sequences in each PSA run that involve are also in the Mean run.

13) From bootstrapping algorithm approach, propose whether to combine te terms should be combined if combining them substantively increases path robustness.

14) Paulson has suggested that rankings of treatment options be considered from produced using a net value perspective



15) The net value perspective produces a mean rank, for an and whi-

16) The rank could be produced for each PSA run

17) Density plots and/or histograms for each treatment option could be produced using this framework

18) Options could be combined if this leads to substantial reduction in switching

19) An issue with the approach is that less well powered trials may an inferior treatment will gain have a better chance of appearing cost of equivalent of

a poorly powered trial is used, and vice versa.

20) It may be appropriate to specify clinical boards of indifference in terms of costs and QALYs

21) More The approach could mean more options treatment options become available for patients and clinicians in the future

22) There should be careful consideration of when to comb combine treatments within analyses and consider them to be equivalent.

23) It is possible to perform a full incremental analysis using a pinboard, some differently [illegible] coloured string, and a long piece of string.

24) The pinboard approach can be useful for learning an intuition about the approach, and teaching it.

25) The pinboard approach is also the basis for the algorithm.

26) The algorithm needs to be developed and made available in an easily accessible format.

27) Further research should be conducted to see where the suggested approaches may have changed NICE recommendations or similar.

28) This 4 is not an issue in many cases if there is only one treatment and a comparator.

29) This is an issue where there are many new treatments for the same population

30) This is also an issue where there are many sequences need to be considered.

I

R (findings)

M

Visual

Informal

Formal

Algorithmic

Pinboard

Algorithm

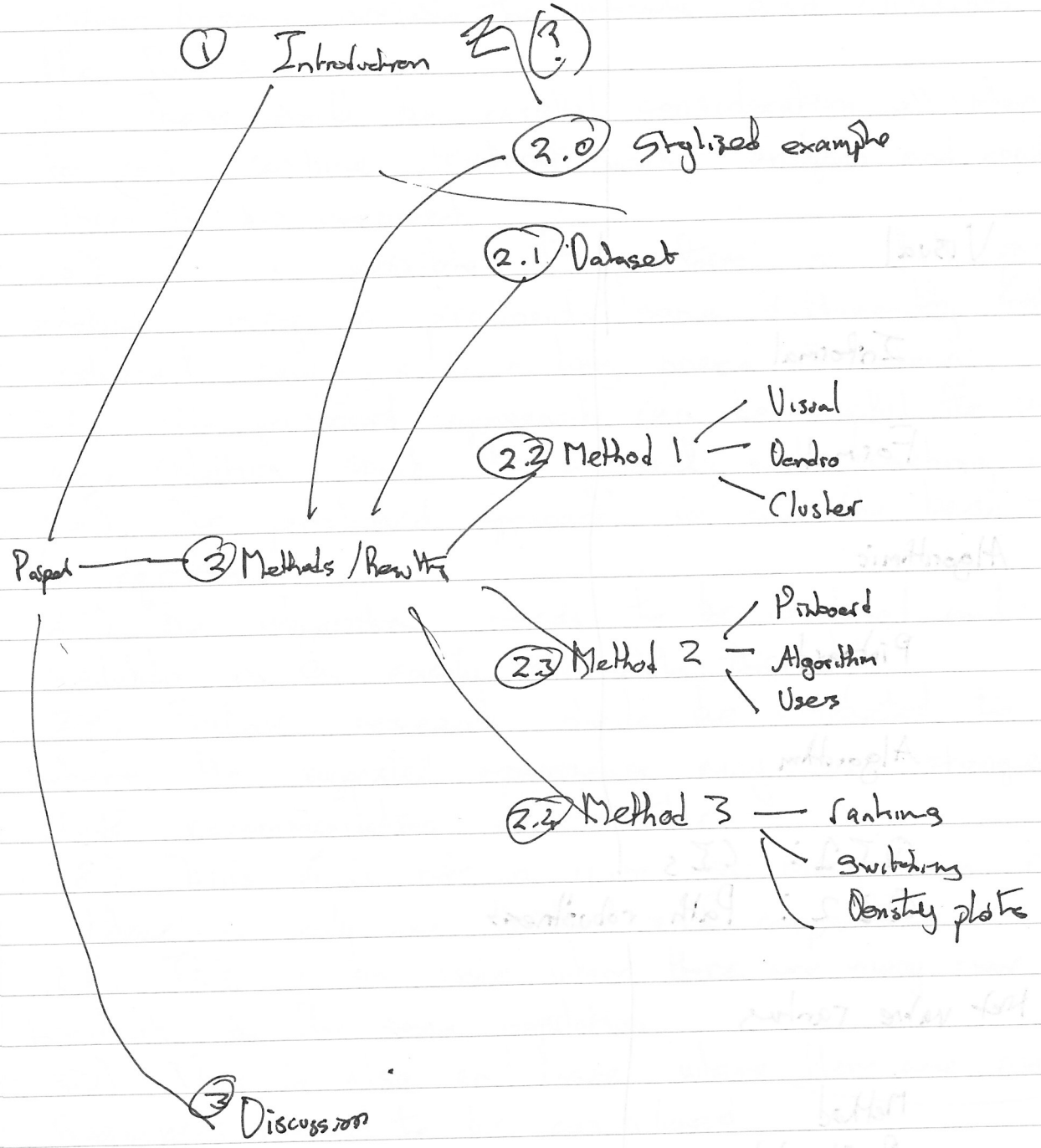
QI1: CIs

QI2: Path robustness

Net value ranking

Method

Density plots


1 Introduction
2.0 Stylized example
2.1 Dataset
2.2 Method 1
Visual
Dendro
Cluster
Paper
3 Methods / Results
2.3 Method 2
Pinboard
Algorithm
Users
2.4 Method 3
ranking
switching
Density plots
3 Discussion

Paragraph structure (1) Introduction

1) Why did we start?
   i) When constructing/performing full incremental analyses, uncertainty about the true costs and QALYs of each treatment option are not currently considered.

2) Not doing this we may reject options that are as good as those we accept, reducing patient and clinician choice without good reason.
3) This is more of an issue recently due to the introduction of multiple new treatment options for some conditions.
4) This is also a big issue when we need to consider different treatment sequences as different options.
5) In HTA, PSA are almost always produced.

WHAT DID WE DO?

6) In this paper, we explore three types of approach that use PSA to better inform decision makers about whether how different any two options are in terms of costs and QALYs.

2.0 Styled example

1) Fig X below presents a simplified and stylised example of the problem.

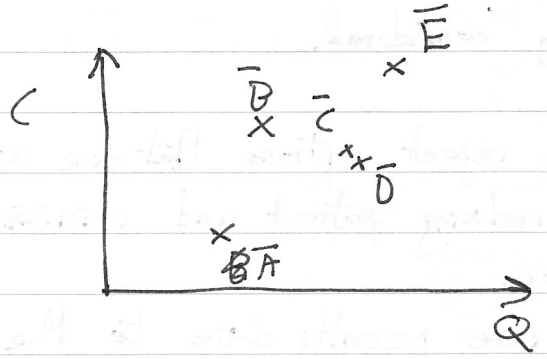


Fig X

2) The Efficiency Frontier is $\bar{A} \rightarrow \bar{D} \rightarrow \bar{E}$.

3) $\bar{C}$ is ruled out ~~along with $\bar{B}$~~ by extended dom (~~due to~~ along with $\bar{D}$.

4) This means $\bar{C}$ will not be recommended by a reimbursement organisation such as NICE.

5) Imagine now that in reviewing the evidence for $\bar{D}$, it is found that the QoL estimates are very slightly incorrect, by approx 0.05 QALYs.

6) Following correction, the Results now look like

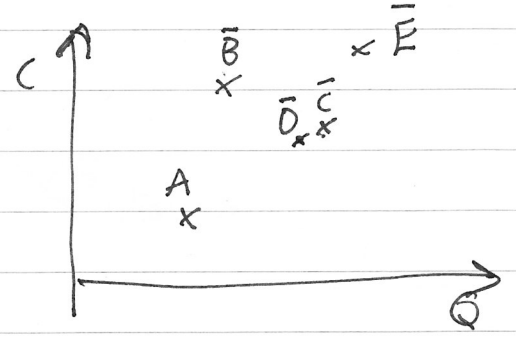


Fig X

7) The efficiency frontier is now $\bar{A} \rightarrow \bar{C} \rightarrow \bar{E}$.

8) $\bar{D}$ is now ruled out by extended dominance, meaning it is less likely to be available to

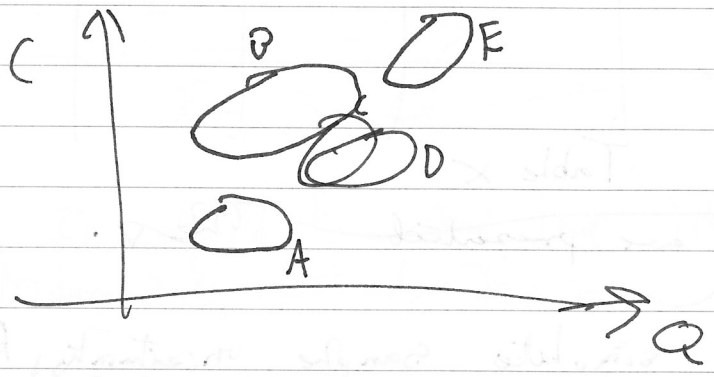
patients and clinicians as an option.

8) Even though the diffs in Q estimates were tiny in clinical terms, they led to different recommendations

9) The problem emerges because $\overline{C}$ and $\overline{D}$ are very similar, but NICE does not currently allow people a decision of indifference between two or more options.

10) The problem is starkest when the two treatments are effectively identical in every way. As people

11) In the stylised example being able to get a sense of how similar/tapering are by looking at how much PSA results overlap each other.



12) This shows that the confidence ellipses for C and D overlap substantially.

13) It is also seen that there is a lot of uncertainty about the true mean value of A, the starting point in the analysis.

14) None of this uncertainty is currently (regret incorporated or formally represented.

(2.1) Dataset

1) In order to provide a common test for all the approaches, a fictitious dataset was constructed ~~comprising 1000 p~~

2) The dataset ~~used~~ involves nine distinct treatments labelled A to I. ~~1000 PSA run~~ Ra

3) The characteristics of the data generating process for each of the treatments is/are shown in table X below.

	TrtName	Mean Cost	Mean QALY	Var Cost	Var QALY	Covar(cost) (cost, QALY)
~						
~						
~						

Table X

4) ~~There values are presented~~ The v.

~~5) V 5)~~ 1000

5) In order to simulate sample uncertainty, for each treatment was assumed to be based on a trial of a different sample size. ~~This meant~~ ~~This meant samp~~ As the Sample The means, vars, ~~xoxa~~ covars available to the BRS are then sample values ~~as~~ shown in X below

Trt Name	Sample Size	Sample Mean C	Sample Mean C	Sample Var / Covar

Table X

6) The sample means and covars /produced were then used to form the basis of 1,000 PSA runs, as shown below.

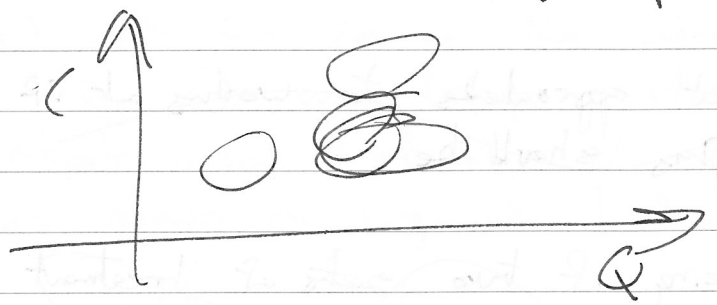
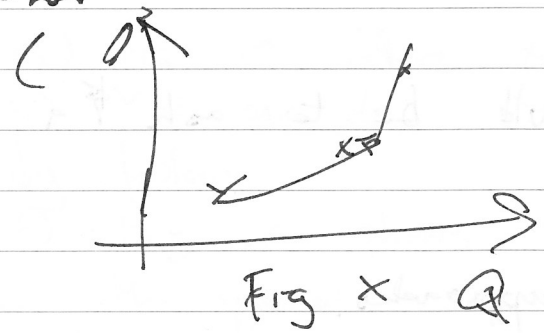


Fig X

7) Given these data, the ~~Wasserstein~~ mean values ICERs and thresholds are shown in Fig X and Tab X below



Trt	Q	C	Rank	ICER
Trt			2	
			-	

two X

8) It should be noted that the X and Y are fundamentally identical. The on

9) ~~Within all~~ / For all methods, the ~~individuals~~ BRGs/ decision makers will have access to summary stats and PSA. The aim of the analysis is to ~~compare~~ (~~treatment~~) see how the methods (~~decision~~) (rape w) use these data (~~given~~) when the true values are known.

2.2 Method One: Visual inspection, dendrograms and cluster analysis

1) One (appro) Some of approaches to working out if two (s) treatment options should be

1) One way of seeing if two sets of treatment options are identical is to

2) One way of figuring out if two treatment options is to look. we should be indifferent between

2) A related approach would be to ask for a computer to look.

3) These are all top down approaches.

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3) These are all top down approaches.

2.2.1 Informal

1) If we remove the colour from the PSA results (Fig X), we remove information (looking broad) about which (treatment) dot came from which treatment, as shown in Fig X. below

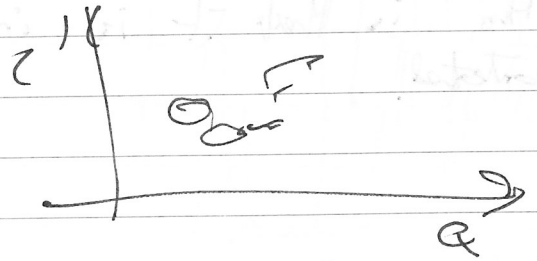
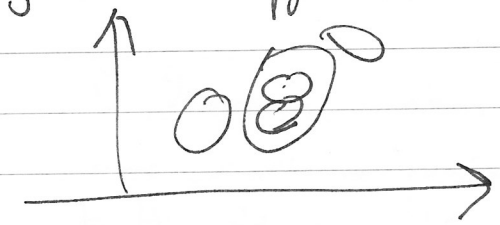


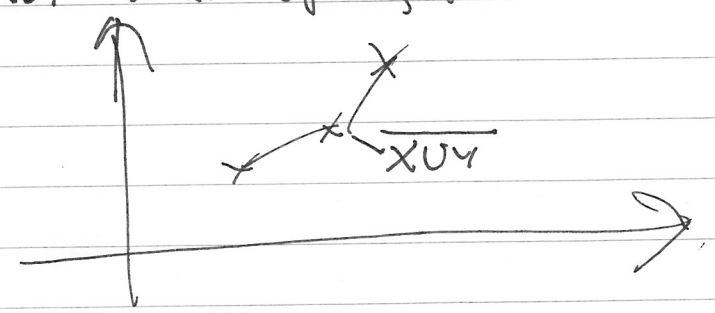
Fig X

2) Fig X offers anonymised scatter
3) We can do informal cluster analysis just by looking.
4) Fig X shows X clusters that appear present given the approach



5) If we then compare these clusters with the treatments, we can see that treatment X and Y are in cluster Z, (providing) indicating that in evaluating we should (run) be indifferent between these options.
6) If we recalculate the (means) ICERs using XUY as an option, the results now look like.. (table X

Fig X.

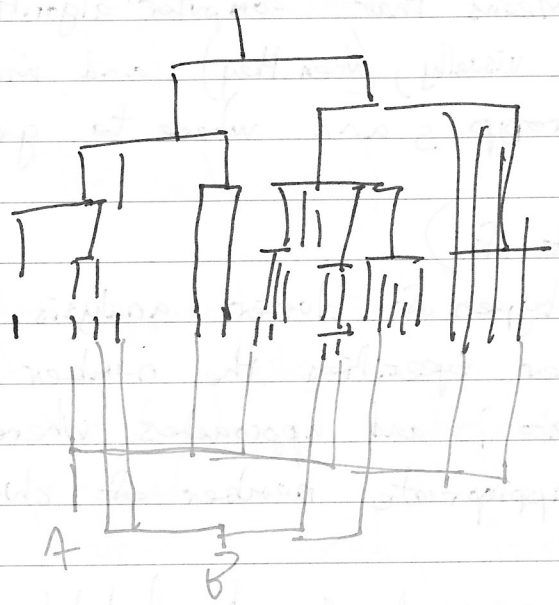


(7) The problem w)

7) One problem with this approach is that we cannot easily (org) de anonymise the scatter, given that it is often the people who make the PSA who produce the Incrementals.

8) Another problem with this is that it is inherently subjective, so can be contested.

2.2.2 Semi formal : Dendrograms



Assumed Membership

True Membership (indicated by colour)

Could also do for means

1) Dendrograms show what happens as people move from (the) one extreme position - all items are completely different to the other position - all items are the same.
(k = n groups ⇒ k = one groups)

2) Help people make judgement about k

intermediate #

To go back to and complete later

2.2.3 Cluster analysis

1) Cluster analysis means that computer algorithms can do what people do visually, when they and make decisions about how to group s and where to group data.

2) (Within the context of)
2) Two alternative types of cluster analysis algorithm exist: one where the user specifies the number of clusters to divide the data into; and approaches where the computer also estimates the appropriate number of clusters.

3) Both types of approach can be helpful for making better use) informing the decision whether to be indifferent between options, but in different ways.

4) One approach with the that could be adopted would be, if the user for the user. to tell the computer that A) the number of treatments to be compared, and for the computer algorithm to then try to identify which data belong to which group.

5) Results could then be cross tabulated, as shown in table X below Treatment

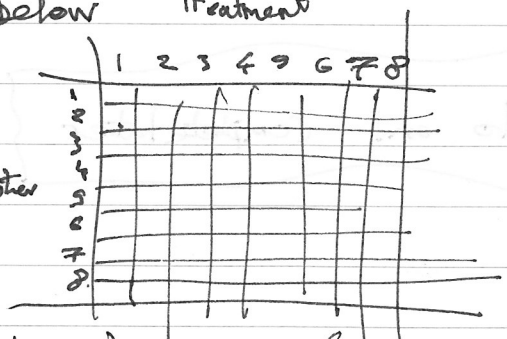


table X

6) If (a high) each (treatment) cluster is comprised primarily of data drawn from a single treatment, then this indicates that the treatments are different.

7) If there is a lot of cross membership between treatments and clusters, (such) then this indicates that two or more treatments are difficult to tell apart (and so).

~~(8) If two treatments are~~

8) An iterative approach could be adopted: (If specifying a lot) If nine clusters with nine treatments produces a lot of cross (contamin) membership, then the algorithm could be reapplied (to eight) with eight clusters and eight treatments, including two treatments which have been applied.

9) (No) (A) If combining two or more treatments leads to a great reduction in cross membership then this is strong evidence that it was correct to combine these treatments in the analysis.

10) (Th) It is important to try the (results) analyses multiple times due to the effect of different starting values and other stochastic elements. Different algorithms exist and so the robustness of these findings to the choice of algorithm should also be explored

---

11) Rather than using an iterative approach (or using K means algorithms), a number of computationally intensive algorithms exist which attempt to determine how many groups there are, as well as (how) where each point belongs to.

2.3 Frontiers using pinboards

1) It is possible to determine the efficiency frontier using a pinboard, some differently coloured or labelled pins) visual method, and understanding this is key to developing an (frontier) algorithm for (identifying the) finding the frontier automatically.

2) The visual method can be performed using a pinboard, some differently (identified) or labelled or coloured pins, and a piece of string. (Drawing on (an) (exce) a scatterplot) (Alternatively, a). Equivalently, the graphical features of software like Excel could be used.

3) Each of the pins / dots is the cost / risk where of a particular treatment.

4) The frontier can now be identified as follows:

1) Find the treatment with the lowest cost. Attach one end of the line to this pin.

2) Pull the string to the right, so it forms a horizontal line. Now move the string upwards, in an anti clockwise direction.

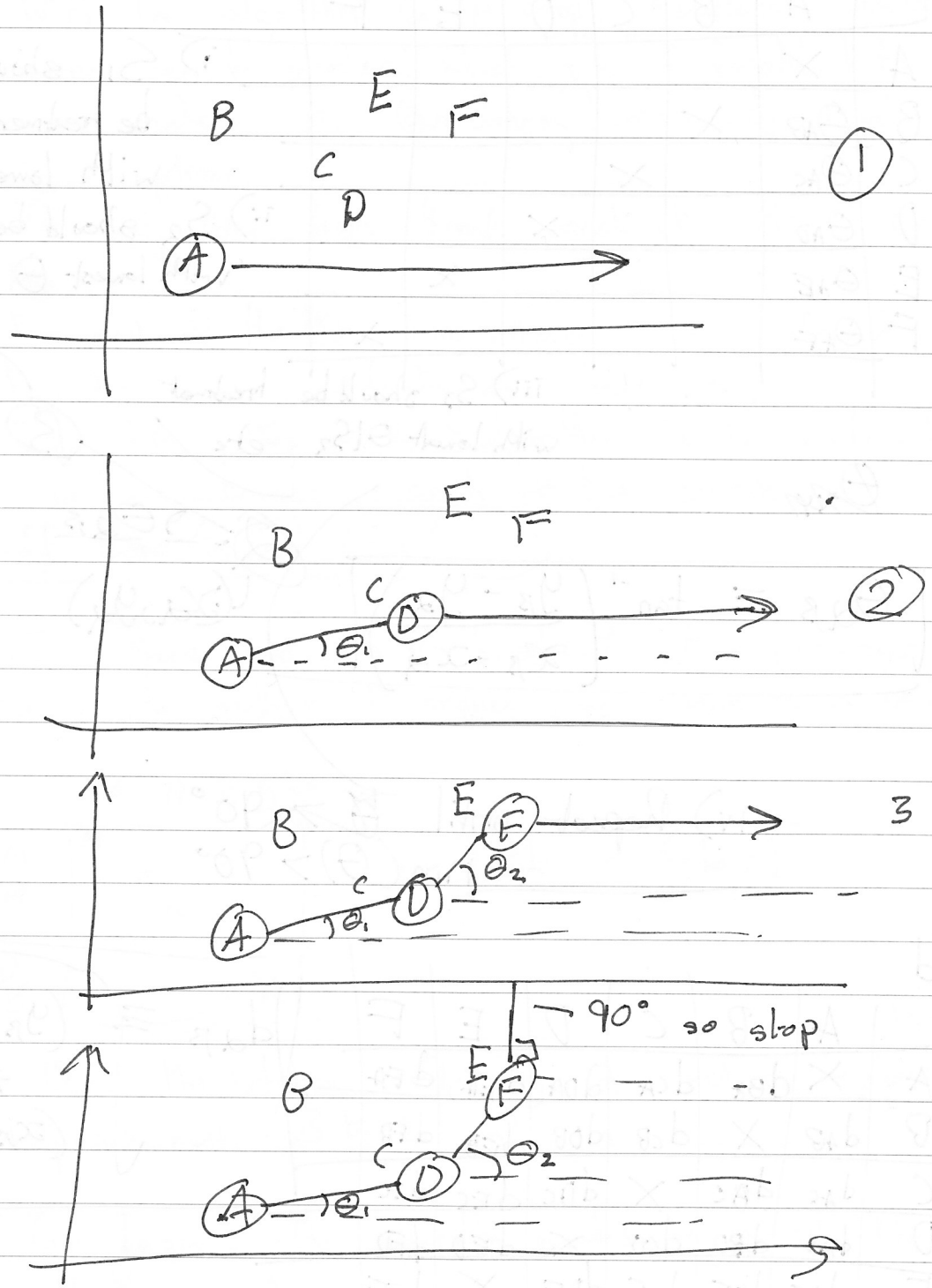
(3) ~~If~~ When the (treatment) string touches another

4) Continue to move the string in an anticlockwise direction until it either (reach) touches another point or is in the vertical position.

4a) If the vertical position is reached, stop

4b) If (the) another pin is reached, then tie the string to this pin, and go back to step 2.

5) The pins connected by the line form the efficiency frontier, and the angles of the lines from the horizontal position determine the ICBR of each treatment.



Frontier = A, D, F

⑥ The pinboard and string approach forms the basis of the computer algorithm discussed below.

Θ	(S1) A	(S2) B	(S3) C	(S4) D	E	F
A	X					
B	Θ_{AB}	X				
C	Θ_{AC}		X			
D	Θ_{AD}			X		
E	Θ_{AE}				X	
F	Θ_{AF}					X

i) S_1 should be treatment with lowest y

ii) S_2 should be treatment with lowest $\Theta | S_1$

iii) S_3 should be treatment with lowest $\Theta | S_2$ etc

$$\theta_{\alpha\beta} \equiv \tan^{-1}\left(\frac{y_\beta - y_\alpha}{x_\beta - x_\alpha}\right)$$

iv) Repeat until $\theta > 90°$

$\min(\theta) > 90°$

d

	A	B	C	D	E	F
A	X	d_{BA}	d_{CA}	d_{DA}	d_{EA}	d_{FA}
B	d_{AB}	X	d_{CB}	d_{DB}	d_{EB}	d_{FB}
C	d_{AC}	d_{BC}	X	d_{DC}	d_{EC}	d_{FC}
D	d_{AD}	d_{BD}	d_{CD}	X	d_{ED}	d_{FD}
E	d_{AE}	d_{BE}	d_{CE}	d_{DE}	X	d_{FE}
F	d_{AF}	d_{BF}	d_{CF}	d_{DF}	d_{EF}	X

$$d_{\alpha\beta} \equiv \sqrt{(y_\beta - y_\alpha)^2 + (x_\beta - x_\alpha)^2}$$

2.3.2 The Algorithm

1) The points and lines approach can be automated as a computer algorithm, allowing it to be produced for each of the PSA runs.
2) With the algorithm, (so) (a coop) additional summary measures can be produced which may be of benefit to the decision makers in quantifying uncertainty about decision options.
3) The algorithm loops through each of the M runs of the PSA.
4) For each of the PSA runs, there is a different configuration of coordinates (as shown in)
5) The first step of the algorithm is to calculate the angles between each of the points.
6) If there (is (a) fire (by

6) If there are five treatments, this produces a 5 × 5 (an) matrix of angles, as shown in X below

	A	B	C	D	E
A	✱	r			
B			λ		
C				x	
D					
E					X

Table X (below)

7) Using the notation ΘαΔβ, α refers to (point α) the start point, and β to the end point.

8) To begin, the algorithm needs to identify the point with the lowest cost.
9) In our example this is X. The column marked X shows the angles from that point to other points.

10) If all of the points are over 90°, then the algorithm stops as there are no more points on the efficiency frontier.
11) If not, the algorithm identifies the treatment with the smallest angle.
12) In this case, this is treatment Y, which becomes the next treatment in the sequence.
13) The process then repeats using column Y, until no further treatments are identified.

14) The distance between points can also be identified using (d) pythagorus. This produces a distance matrix alongside the angle matrix

$d_{\alpha\beta} \equiv$

15) The ICER is calculable directly from the angle matrix using the following formula

$$ICER \equiv \begin{cases} \frac{\Delta C}{\Delta E} \tan\theta & \text{iff } 0 \leq \theta \leq \frac{\pi}{2} \\ \text{Dominated} & \text{iff } \frac{\pi}{2} \leq \theta \leq \pi \\ \text{Disinvestment} & \text{iff } \pi \leq \theta \frac{3\pi}{2} \\ \text{Dominating} & \text{iff } \frac{3\pi}{2} \leq \theta \leq 2\pi \end{cases}$$

NEW SUBSECTION : Uses ①

16) (Confidence) (credible intervals around the ICERs can be calculated (as) For comparisons not involving disinvestment by defining Dominated as $+\infty$ and dominating as $-\infty$, then sorting values from lowest to highest.

17) Where (a given pr) some (values repeat) extremes

include the southwest quarter, disinvestment, the proportion of times disinvestment is indicated & can also be presented.

Treat Vector	Prop disinvest	Mean ICER	Median ICER (No disinvest)	2.5%, 97.5%
$S_1 \rightarrow S_2$	~	~	~	(~ , ~)
$S_2 \rightarrow S_3$	~	~	~	(~ , ~)
$S_3 \rightarrow S_4$	~	~	~	(~ , ~)
$S_4 \rightarrow S_5$	~	~	~	(~ , ~)

17) Where (par) (an) there is a wide credible interval around an ICER, this is an indication that it may be worth choosing to be indifferent between two or more options and revisiting the analysis, or alternatively considering (how) whether one is willing to pay the upper estimates or accept the possibility of disinvestment

USES 2 : Path Robustness

18) Another metric that could be produced (based on) (using) this approach is the robustness of the efficiency as a whole, and of components within that sequence.

19) As an example, if the B best path identified using mean estimates is E A C, then the proportion of PSA runs where this was also identified could be calculated.

20) The robustness of the components could also be calculated and reported, as shown in X below

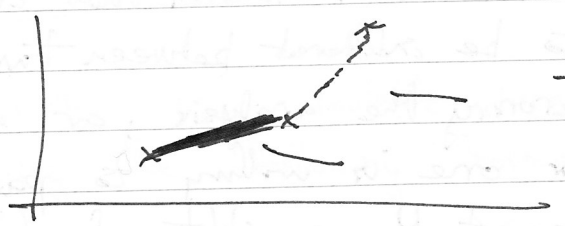
(PTO)

Sequence / component		% agreement
whole sequence	EAG	~~
starting point	E	~~
line 1	EA	~~
line 2	AG	~~

table X

21) This information can be used to identify (the) how robust the sequence is, and (the) what parts of the sequence are most and least robust.

22) Path robustness Infographic.



Thickness indicates robustness of path sequence.

2.4 Net benefit

1) X has recently argued that the comparative & cost effectiveness of treatments be ranked using a net benefit framework.
2) This approach requires that the willingness to pay threshold λ be known (or assumed) in advance.
3) (If) The approach has advantages in terms of (converting) presenting in) showing (which treat) how treatments) the rankings of treatments ((incl) in terms of cost-effectiveness, instead of just showing which is 'most cost-effective'.
4) The approach involves (identifying) drawing a series of parallel lines on the scatterplot, which intersect with the treatments (and) points.
The (via) position (of) that these lines then intersect with the x-axis then indicates the net ~~monetary~~ health benefit (check) of each treatment option; and the position that these treatments intersect the y-axis indicates the ranking of each treatment's net ~~health~~ ~~monetary~~ benefit (check)

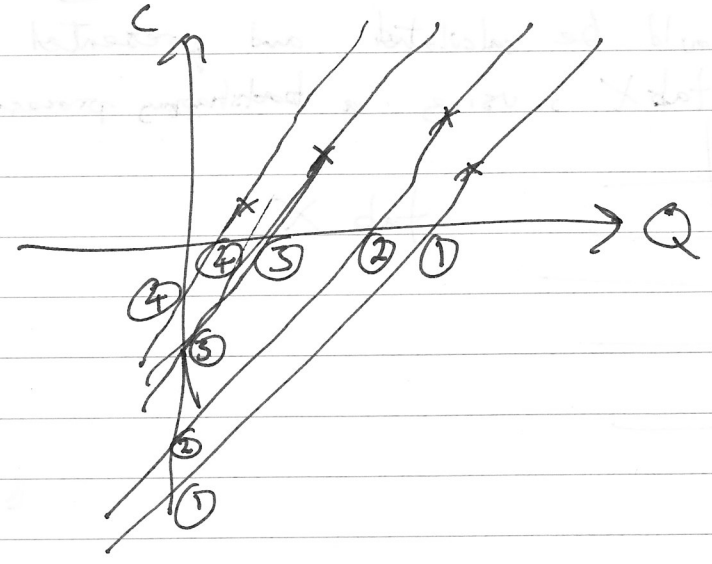


Fig X

5) (alculating the net monetary benefit and net health benefit (ie) given λ is trivially simple. ~~If q_2 and~~

$$NMB \equiv C_2 - \lambda q_2$$

$$\boxed{NMB \equiv C_2 - \lambda q_2}$$

$$\boxed{NHB \equiv \frac{\lambda q_2 - C_2}{\lambda}}$$

6) It follows from this approach that histograms and density probs of the PSAs at each treatment option could be produced, showing overlap between rankings, as in Fig X below

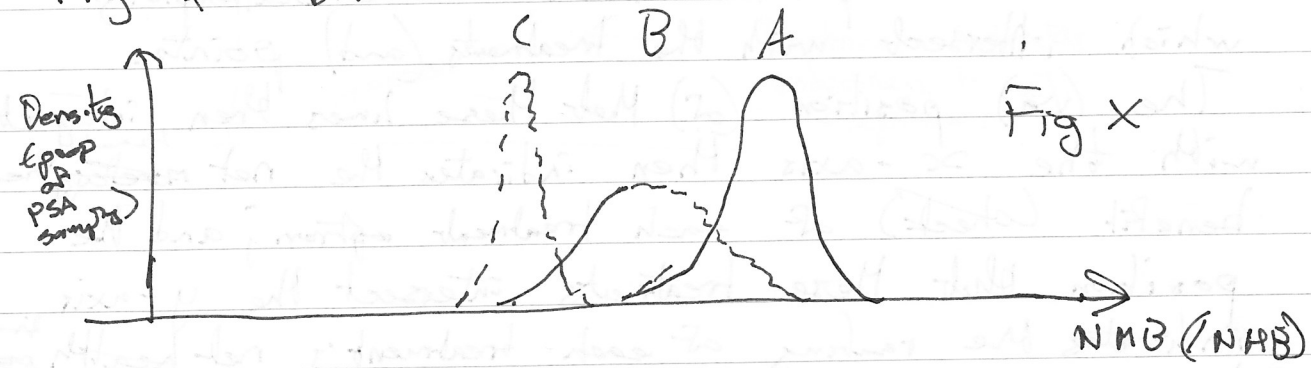


Fig X

7) Additionally, the proportion of crossovers between any two ranked treatments could be calculated and presented in tabular form, as in tab X, using a bootstrapping process.

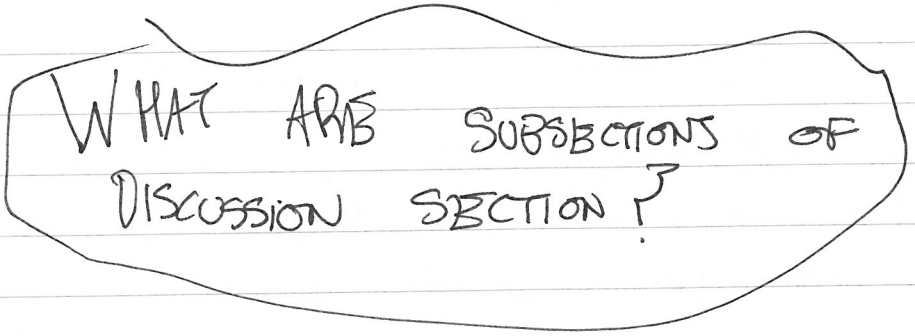
Prop > than ..	B	C	A	E
Rank 1 B	X	0.51	0.14	0.99
2 C		X		
3 A			X	
4 E				X

tab X

8) So long as there is some level of (agl) consensus as to λ, the presentation of this uncertainty (in the net benefit framework is simple and easy to understand and could be considered in addition to or instead of the more complex methods described previously.

3.0 Discussion

1) The approaches described here differ in terms of their (use) ease of application and the information they provide.
2) All approaches (are potentially useful in) are potentially (useful) informative (a)



Para 1: Summary of what found
Para 2: Short comings
Para 3: How relates to other findings
Para 4: Implications for research
Para 5: Implications for clinical practice

3.1 Discussion - Summary of what found

This paper found that a number of approaches exist or could be developed for (un) using PSA for informing the decision about whether two or more treatments should be considered equivalent

3.2 Discussion - Shortcomings

- Not looked at actual case studies
- Algorithms not developed
- Whether to be indifferent depend on more than just this; also clinical factors
- Algorithms / approaches not in easy to use form
- Approach potentially 'rewards' underpowered trials.

3.3 How relates to other findings

- Unsure
- IS THIS THE FIRST?

3.4 Implications for research

- Review of existing models & (5) HTAs, when decisions are close.
- Developments of methods & promotion of them
- Developments - consultation - about guideline (rules) about when to be in different

3.5 Implications for clinical practice

- Potential for greater (availability) patient and clinician choice
- Some potential for slightly less 'efficient' NHS as a result of accepting slightly less CE treatments through.

Presentation idea