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FOCCUS trial: Pre-operative fluid loading for high risk patients undergoing major elective surgery: A cost-effectiveness analysis

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The FOCCUS trial - background

- Patients undergoing major surgery are at significant risk of death or major morbidity
- Pre-operative optimisation is a complex intervention involving pre-operative fluid loading in an Intensive Care Unit (ICU), optimisation of oxygen delivery using inotropes as well as post-operative ICU admission
- Poor penetration into clinical practice
- low levels of implementation in most countries.

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Trial design

- Multi-centred pragmatic randomised controlled trial
  - 3 centres in Scotland randomised patients
  - One of only a few surgical trials to incorporate economic evaluation at the time of start-up.

- Original 2*2 factorial design
  - (1) HDU vs. ICU
    - Difficulties with randomisation
    - Comparison abandoned – small number randomised
  - (2) Fluid vs. No fluid

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Intervention

- ward-based pre-operative fluid loading
- pre-operative fluid therapy (25ml/kg) in the ward using Hartmann's solution
- Administered over 6 hours prior to surgery
- Patients receiving bowel preparation received an additional 10ml/kg Hartmann's solution (12 hours before surgery) irrespective of trial group allocation - best clinical practice

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Objective

- Clinical
  - To determine if pre-operative fluid loading in the 6 hours before surgery significantly reduced hospital length of stay

- Health economic
  - Cost-effectiveness of the fluid loading intervention measured as cost (£Sterling) per quality adjusted life year (QALY) gained.

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Cost-effectiveness methods (Costs)

- Intervention costs:
  - Time of HCPs to deliver intervention and monitor patient, fluid costs
- Costs of health care resource use:
  - Secondary
    - Time in theatre, time in recovery (ICU / HDU), time on ward, subsequent hospital admissions, outpatient clinics
  - Primary
    - GP visits, Nurse consultations, contacts with other health care professionals
  - Prescribed medications
- Out of pocket costs to patient
  - Private health care, insurance costs, out of pocket expenses

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Cost-effectiveness methods (Effects)

- EQ-5D, population tariffs for the UK, (*Dolan , 1996)*
  - Collected at 48 hours, 1 month, 3 months and 6 months follow up
- Utility scores weighted for the length of time in each reported health state
- assume linear extrapolation between time points
- QALYs generated using area under the curve methodology
- No extrapolation of benefit beyond 6 months follow up

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Cost-effectiveness methods (Analysis)

- Mean cost and QALY differences between both arms of the trial
  - Adjusted for covariates of age, sex, centre where procedure administered, level of severity of heart disease, base line EQ-5D score
- Results reported as Incremental costs per QALY gained (ICER)

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Sensitivity Analysis

- Deterministic:
  - Imputation method for missing data (e.g. MI using ICE)
  - Base line EQ-5D score (e.g. EQ-5D unconscious state (-0.402))
  - Distribution of costs (e.g. gamma distribution)
  - Outlying cost and QALY data (e.g. 5% high and low cost outliers)
  - High intervention cost scenario (worst case scenario)
  - Low intervention cost scenario (best case scenario)
- Stochastic: (e.g. bootstrapped 1000 iterations, CEACs)

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Cost-effectiveness methods (missing data)

- Substantial problem in many trials collecting patient reported outcomes
  - However for FOCCUS, missing data evenly distributed across groups
  - Assume data were missing completely at random (MCAR)
  - Sensitivity analysis used multiple imputation based on iterative chained equations (m=5 data points imputed)
- Other imputations:
  - If patient has died (EQ-5D = 0)
  - Practical assumptions based on patient reported resource use.

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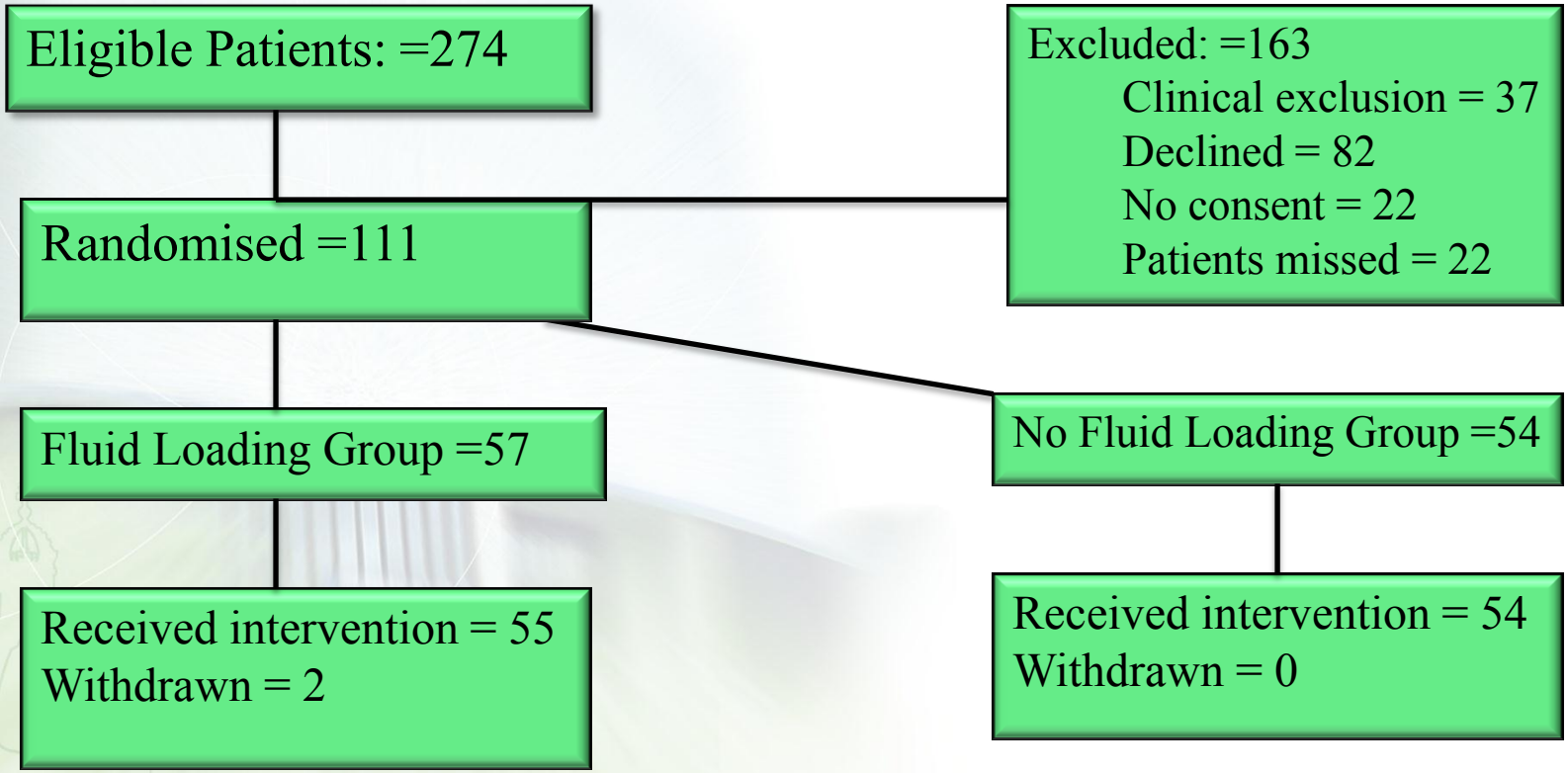
Randomisation



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Missing Data

- Full EQ-5D data existed for 64/109 participants (59%) with no participants missing all of their data.

- 72/109 (66%) of patient questionnaires returned

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Mean Costs

	Mean (SD) cost per patient (£)		Mean cost diff. (95% CI) [p Value]
	Fluid group (N=55)	No fluid loading (N=54)	
Intervention	51(0)	0(0)	51 (51 – 51)
Total inpatient length of stay	7,273 (9,478)	9,585 (10,688)	-2,988 (-7,300 to 1,324) p = 0.174
Total subsequent admissions	2,270 (6,787)	1,600 (3,221)	643 (-1,176 to 2,462) P = 0.488
Total outpatient visits	313 (400)	252 (258)	64 (-61 to 190) P = 0.317
Total primary care visits	303 (824)	162 (312)	133 (-96 to 363) P = 0.254
Medications	163 (240)	140 (197)	50 (-30 to 130) P = 0.218
Overall Total Cost of health care resources	10,373 (12,860)	11,739 (11,438)	-2,047 (-6,947 to 2,854) P = 0.254

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Mean QALY outcomes

	Fluid		No Fluid	
EQ-5D	N	Mean (SD)	N	Mean (SD)
EQ5D Base line	55	0.71 (0.34)	53	0.75 (0.30)
EQ5D 48 hours	50	0.16 (0.33)	49	0.28 (0.38)
EQ5D 1 month	48	0.65 (0.32)	45	0.59 (0.29)
EQ5D 3 months	45	0.74 (0.26)	46	0.67 (0.32)
EQ5D 6 months	40	0.76 (0.27)	38	0.73 (0.29)
Mean Total QALY	34	0.3527 (64.37 Days)	30	0.3175 (57.94 Days)
Mean QALY Difference [Bootstrapped 95%CI]*		0.0431 QALY [-0.0171 to 0.1033]; p=0.161);		

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Cost-effectiveness results – Base case

Base case ICER calculations

	Mean cost (£)	Inc. Cost (£)*	Mean QALY	Inc. QALY*	ICER (£/QALY)	Threshold analysis*: probability of cost-effective at alternative values of willingness to pay for a QALY (%) £10k	£20k	£30k	£50k
No Fluid loading	11,739		0.3175			15.6	13.5	10.6	8.0
Fluid loading	10,373	-2,047	0.3527	0.0431	Dominant	84.4	86.5	89.4	92.0

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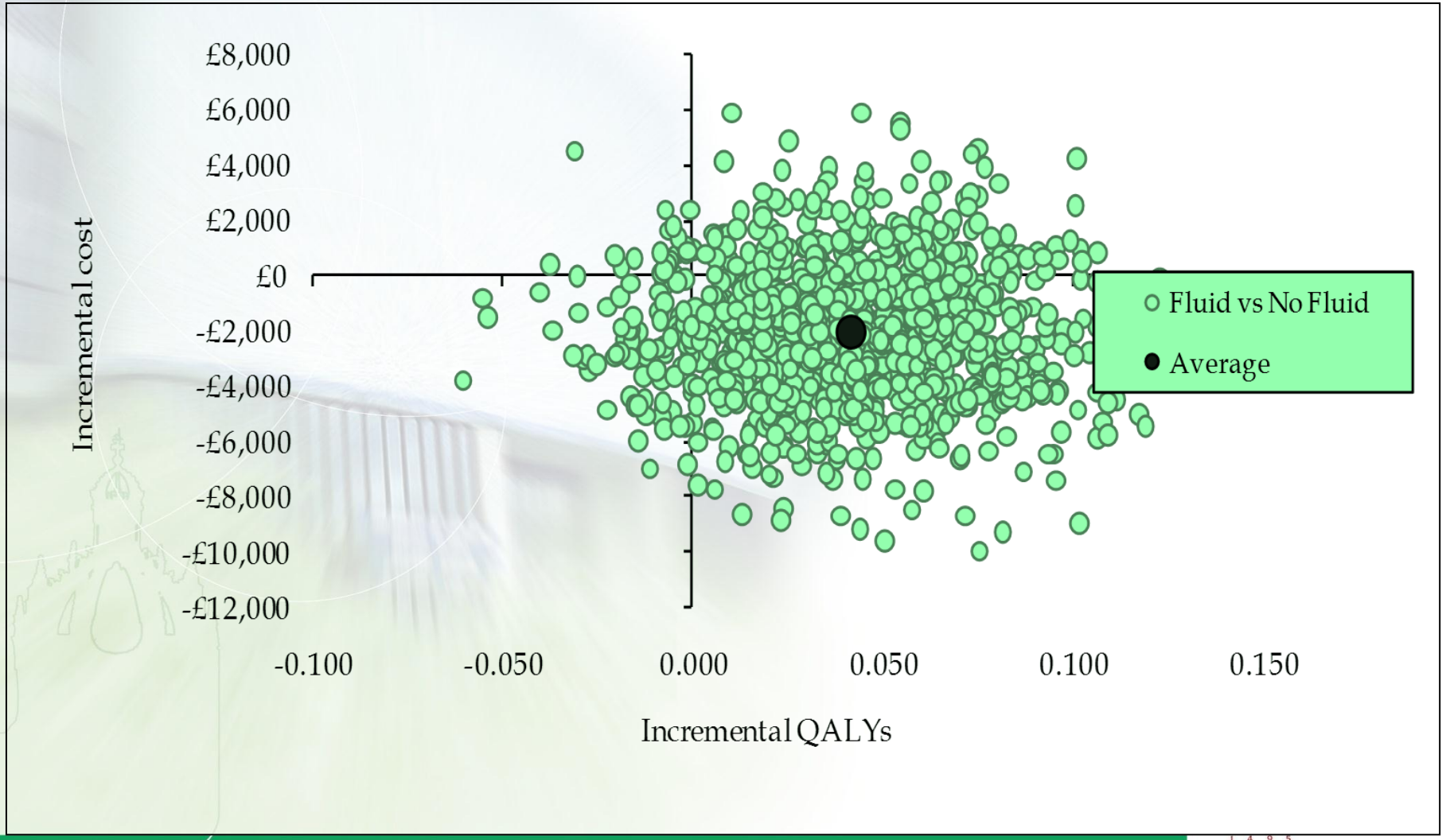
Scatter plot of bootstrapped estimates



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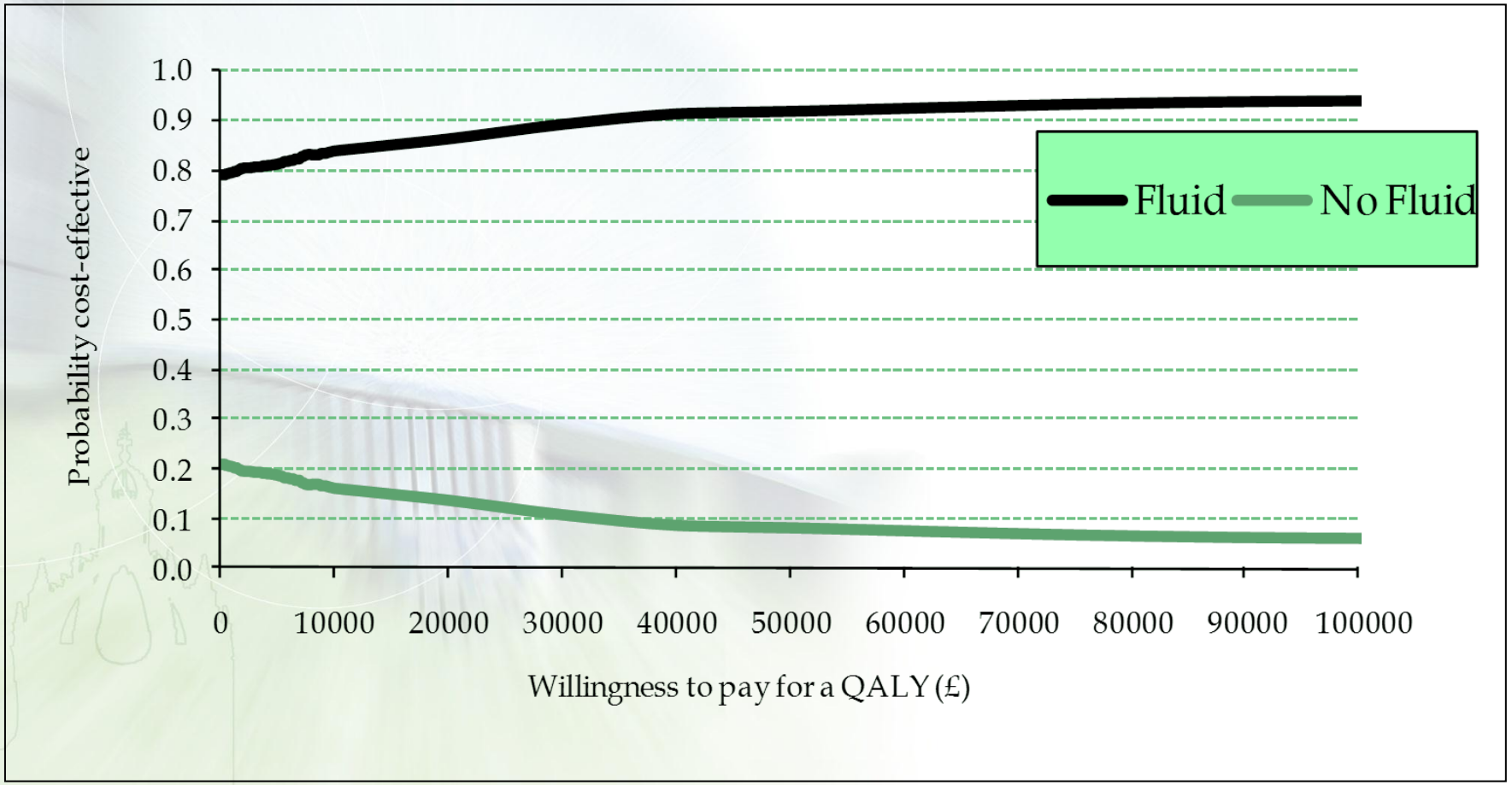
Cost-effectiveness acceptability curve



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Conclusion

- Observations and comments on results:
  - Fluid loading is on average less costly and more effective (QALYs) than no fluid loading
  - Additional intervention costs are offset by cost savings from reduced hospital length of stay
  - Fluid loading is highly likely to be cost-effective compared with an alternative of no fluid loading as part of routine clinical care

- Should our results be reproducible in a larger scale trial, then pre-operative fluid loading should be adopted as standard surgical practice through out the UK and further afield.

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Further work

- We have some data relating to ICU / HDU comparison randomisation.
- No such data is available anywhere else and would be useful to publish in order to inform future economic modelling and evaluation methods.

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Thank you

Please let me know of any comments of queries you may have.

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