Health Economics Analysis plan

Sugammadex for prevention of post-operative pulmonary complications: A pragmatic randomised trial

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2 Administrative information

This document describes the intended analysis and reporting of economic data within the SINFONIA trial. This Health Economics Analysis Plan (HEAP) is designed to ensure that there is no conflict with the SINFONIA Trial Protocol and associated Statistical Analysis Plan (SAP), and it should be read in conjunction with them. The Trial Protocol provides in detail: trial design and methods, amendments, documentation, oversight, roles and responsibilities, and the statistical analysis of clinical and patient outcome measures.

3 Trial introduction and background

3.1 Trial background and rationale

Each year, more than 3 million patients are administered a general anaesthetic agent as part of their surgical procedure in the NHS [1]. Complications after surgery and anaesthesia are common, particularly, post-operative pulmonary complications (PPCs), which have a significant negative effect on patient recovery, survival and length of hospital stay [2-5]. PPCs are associated with increased resource use and are estimated to cost the NHS over £280 million per year in treatment costs. Preventing PPCs will lead not only to improved patient outcomes, but also, substantial cost and efficiency benefits to the NHS.

While many risk factors for PPCs relate to the surgical procedure or the patient and are not easily modifiable, the use (and reversal of) Neuro-Muscular Blocking Agents (NMBAs) as part of general anaesthesia is an important modifiable risk factor [6]. Currently in the NHS, anaesthetists choose between neostigmine and sugammadex to reverse the effects of NMBAs after surgery. Compared to neostigmine, sugammadex reverses NMBAs more rapidly and reliably, but evidence for its clinical effectiveness remains limited [7], and life-threatening anaphylactic reactions to sugammadex, although rare in the UK, remain a concern [8]. The SINFONIA trial specifically examines the risks and benefits associated with the use of sugammadex.

3.2 Objectives of the trial

3.2.1 Primary objective

The primary objective is to determine whether sugammadex is superior to neostigmine after elective or emergency major abdominal or non-cardiac thoracic surgery in terms of days alive and at home at 30 days (DAH30). The primary outcome measure is the DAH30, a continuous score between 0 and 30 reflecting the total number of days a patient spends alive and at home in the 30 days following surgery.

3.2.2 Secondary objectives

The secondary objectives are to determine whether sugammadex is superior to neostigmine in terms of prevention of post-operative pulmonary complications, mortality, and other patient-centred outcomes; to determine the cost effectiveness of the use of sugammadex compared to neostigmine; and to estimate the rate of allergic sensitisation after a single exposure to sugammadex. The secondary outcome measures are:

1. Post-operative Pulmonary Complications within seven days after surgery
2. Mortality at 30 and 180 days after surgery
3. Quality of recovery on the first post-operative day (QoR-15)
4. Health-related quality of life at 7, 30 and 180 days (EQ-5D-5L)
5. Allergic reaction within 24 hours after administration of sugammadex and neostigmine
6. Health resource use during the 180 days after surgery
7. Rate of allergic sensitisation to sugammadex

3.3 Trial population

3.3.1 Inclusion criteria

Participants are eligible to be included in the trial if they meet the following criteria:

1. Patients presenting for elective or emergency major abdominal or non-cardiac thoracic surgery
2. Age ≥ 50 years
3. Planned use of rocuronium or vecuronium for neuromuscular blockade
4. Planned reversal of neuromuscular blockade at the end of surgery

3.3.2 Exclusion criteria

1. Known allergy to sugammadex, neostigmine or glycopyrrolate
2. Lack of written informed consent for trial participation
3. Planned invasive mechanical ventilation before or after surgery
4. Previous participation in SINFONIA trial
5. Clinician refusal (with reason)

3.4 Interventions

Participants will be randomised to receive either sugammadex or neostigmine.

3.5 Trial design

SINFONIA is a multi-centre pragmatic randomised trial comparing the clinical and cost-effectiveness of sugammadex and neostigmine. The trial will take place in approximately 40 NHS hospitals with a planned sample size of 2500. Recruited participants will be randomised on a 1:1 basis to receive either

sugammadex or neostigmine, and follow-up will be for 180 days. The trial has a planned duration of 54 months and will close when 2,500 participants have been randomised, the last participant has completed final follow-up, and all trial activities are complete.

4 Economic approach/overview

In accordance with this HEAP, a prospective economic evaluation will be conducted from an NHS and personal social services (PSS) perspective, as specified by the NICE reference case recommendations [9]. The aim of the economic evaluation is to determine the cost-effectiveness of sugammadex compared with neostigmine in patients aged 50 years or older undergoing elective or emergency major abdominal or non-cardiac thoracic surgery. Using individual patient-level data from the SINFONIA trial, a within-trial economic evaluation will be conducted, adopting a cost-utility analysis approach. Patient-level treatment effects will be summarised as overall costs and quality-adjusted life years (QALYs). As follow-up is limited to 6 months, costs and benefits will not be discounted. Analyses will be conducted according to intention-to-treat (ITT) principles, providing summaries and estimates of effects based on allocated (as per randomisation) treatment groups [10]. The ITT approach includes all randomised participants, regardless of adherence, thereby preserving the benefits of randomisation and ensuring that the results reflect the likely effectiveness and costs of interventions in real-world clinical practice.

5 Economic data collection and management

5.1 Resource use and cost

The following patient level resources will be recorded and valued.

5.1.1 Identification of resources

1. Resource use from an NHS and PSS perspective, including
    - intervention received in either arm
    - intensive care stay
    - hospital stay
    - access to further secondary care services after discharge (e.g., readmission, outpatients)
    - the subsequent need to use community care services (e.g., in primary care)

5.1.2 Measurement of resource-use data

Resource use during the index admission will be recorded on case report forms (CRFs), with subsequent healthcare resource use after discharge also documented on CRFs at follow-up visits on days 30 and 180 post-intervention.

5.1.3 Valuation of resource-use data

All resources will be valued in monetary terms by multiplying quantities used by their respective UK NHS unit costs, adjusted to the most recent year. NHS and PSS costs will be sourced from the National Schedule of NHS Costs [11], PSSRU cost compendium [12], and BNF [13].

5.2 Outcomes

5.2.1 Identification of outcomes

The primary economic outcome measure will be QALYs [14], which combine mortality and morbidity into a single measure (ranging from 0 for death to 1 for perfect health, with possible negative values). QALYs will be derived from the EQ-5D-5L, a NICE-recommended, preference-based instrument assessing five dimensions of health, each with five levels.

5.2.2 Measurement of outcomes

Health-related quality of life will be assessed using the EQ-5D-5L at baseline and day 7 during the index admission, and at days 30 and six months post-surgery via telephone follow-up by site research staff.

5.2.3 Valuation of outcomes

EQ-5D-5L responses will be converted into health utility scores using the UK value set recommended by NICE at the time of analysis [15,16]. Patient level QALY estimates will be calculated as the area-under-the the utility curve of the EQ-5D utility scores from baseline to 6 months post-randomisation, using the trapezoidal rule. Baseline EQ-5D-5L will be included to minimise bias in the QALY calculation, and to adjust subsequent analyses [17,18].

6 Economic data analysis

Analyses will be undertaken using both STATA and the R programming software, and reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [19].

6.1 Descriptive analysis

A descriptive summary of the completeness of data, resource use, cost and EQ-5D for the two groups will be presented in tables (as shown in Tables 1 and 2 in the Appendix). This will describe the contribution of each kind of resource to overall costs and help identify where cost differences arise.

6.2 Base case analysis

The base case analysis will report within-trial incremental costs and QALYs, adjusted for trial stratification covariates. If more than 5% of cost or QALY data are missing, the mechanisms of missingness will be explored and multiple imputation will be used to address missing data in the base-case analysis [20-23].

6.2.1 Imputation of missing data

Imputation of missing data will be conducted according to good practice guidance [21], using fully conditional multiple imputation by chained equations implemented through the MICE package in Stata 18 (StataCorp, USA). Imputation will be performed separately by treatment group, with the number of imputed datasets determined by the extent of missing data and confirmed using the fraction of missing information in the base case model. Predictive mean matching using the five nearest neighbours (knn = 5) will be used to enhance plausibility and robustness of imputed values. All imputed variables and relevant baseline variables that plausibly predict missingness will be included as predictors. Analysis of each dataset will be conducted using bivariate regression and results pooled using Rubin's combination rule to allow inferential statistics. Diagnostic plots will be implemented to compare the distribution of imputed and observed values.

6.2.2 Analysis of cost-effectiveness and characterising sampling uncertainty

Bivariate regression analysis in the form of seemingly unrelated regressions (with bootstrapping) will be used for the joint analysis of costs and QALYs in the base-case analysis. This method provides estimates in natural units, respecting the correlation of costs and outcomes within the data, and allows adjustment for a set of covariates, which can be explored, and which improve precision [24]. Baseline health-related quality-of-life scores will be included within models to adjust for potential baseline imbalances. Trial randomisation stratification variables will also be included in the base case model. Non-parametric bootstrapping will be used to characterise sampling error: presenting the replicates on the cost-effectiveness plane. If there are distributional or computational concerns, the univariate net-benefit approach will be considered. The incremental cost-effectiveness ratio (ICER), calculated as the ratio of mean differences in costs and QALYs between treatment groups, will be reported with a 95% confidence interval. Findings will be assessed against the NICE-recommended threshold of £25,000–£35,000 per QALY [9].

6.2.3 Characterising uncertainty for decision makers

Uncertainty will be characterised using cost-effectiveness acceptability curves (CEACs). CEACs show the probability of an intervention being cost-effective at different willingness-to-pay thresholds and explicitly highlight the uncertainty within the decision problem. To avoid the issues related to uncertainty around cost-effectiveness ratios, net-monetary benefit will be estimated and graphed with its 95% confidence interval at different willingness-to-pay thresholds. The NMB describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at (up to) the same threshold.

Findings from cost-effectiveness analyses remain uncertain because of the imperfect information they use. If a wrong adoption decision (e.g., to make a treatment available) is made this will bring with it costs in terms of health benefit forgone: the NMB framework allows this opportunity loss to be determined and guide whether further research should be conducted to eliminate uncertainty. This uncertainty will be characterised via the expected value of perfect information (EVPI). The EVPI is the upper limit of the value to a healthcare system of further research to eliminate uncertainty [26]. Figures 1-4 in the Appendix illustrates how the base case economic analysis will be presented.

6.3 Sensitivity analyses

In addition to the base case analysis, the following sensitivity analyses will be considered:

1. Complete case bivariate analysis (if imputation is used for the base case model)
2. Subgroup analyses (of the trial stratification variables)

7 Decision analytic modelling

To validate within trial analysis without the need for further modelling one of three conditions should be true.

1. The group mean costs and QALYs converge during the trial
2. The ICER is robustly dominated (i.e. net costs increase, net QALYs decrease)
3. The ICER is robustly dominant (i.e. net costs decrease, net QALYs increase)

Should none of these conditions be observed, more extensive economic modelling using decision-analytic methods may be considered to extend the target population, time horizon and decision context drawing upon best available information from the literature and stakeholder consultations to supplement the trial data. A key unknown is the long-term potential harm for patients receiving sugammadex when undergoing subsequent surgery under anaesthesia. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. If longer term decision modelling is undertaken, then costs and outcomes will be discounted at 3.5% after the first year of randomisation in line with NICE reference case [9].

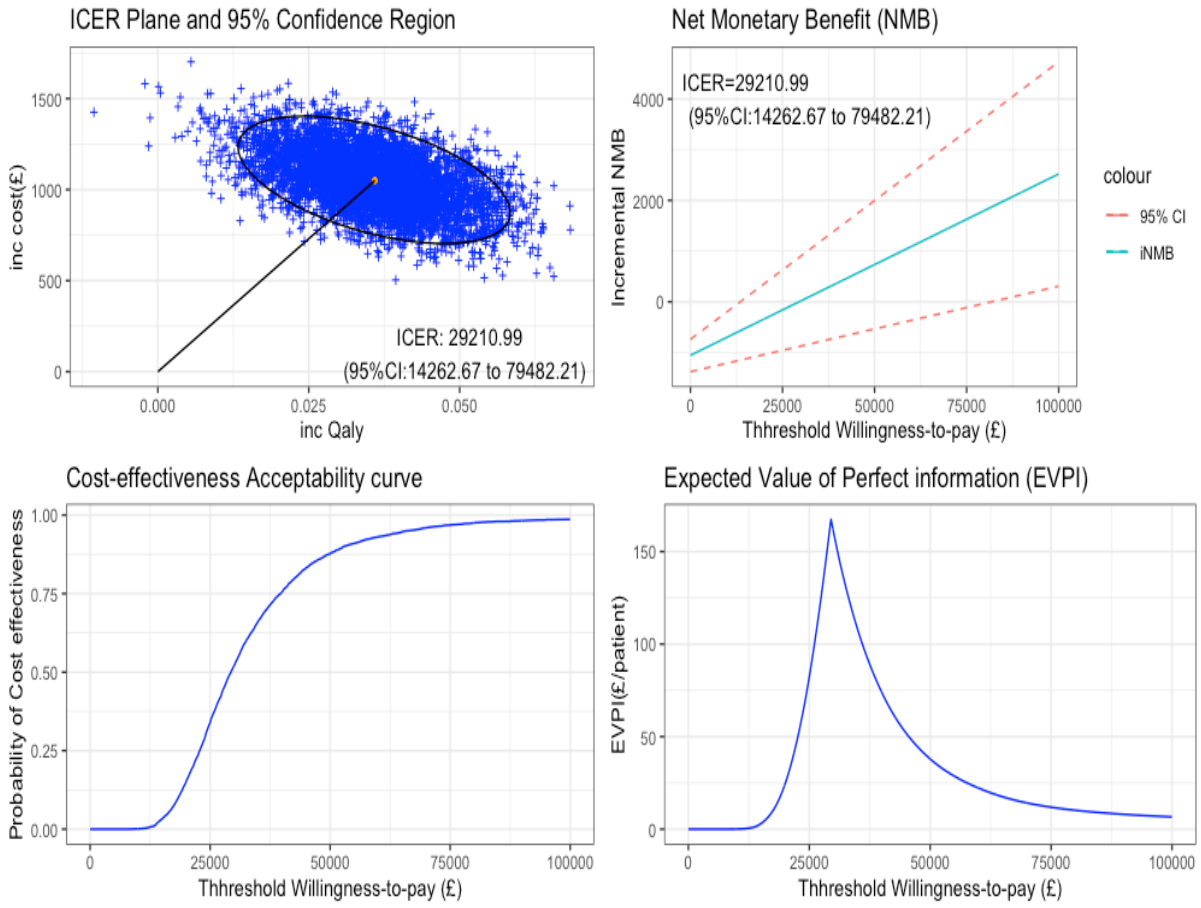
Appendix

Table 1. Completeness of data by follow-up visit			
	Control[1]	Intervention[2]	Total
	n (%, N)	n (%, N)	n (%, N)
Health status[3]			
EQ-5D Baseline			
EQ-5D 7 days			
EQ-5D 30 days			
EQ-5D 6 months			
EQ-5D All visits			
Resource use[4]			
Inpatient			
Outpatient			
Residential			
Community			
Work absence			
1 Neostigmine			
2 Sugammadex			
3 EQ-5D-5L index score			
4 Range shown, lowest to highest completion at measurement points			

Table 2. Health Status, resource use and cost (complete cases)			
	Control	Intervention	Difference
	mean (SD)	mean (SD)	mean (SD)
Health Status[1]			
EQ-5D Baseline			
EQ-5D 7 daya			
EQ-5D 30 days			
EQ-5D 6 months			
QALYs			
Resource use (all visits)			
Inpatient days			
Anaesthesia			
Initial ICU/HDU stay			
Other auxiliary treatments			
Other hospital stay as part of index admission			
Outpatient visits			
A&E visits			
Other hospital visit			
Residential nursing care			
Community ward			
Rehabilitation ward			
Nursing home			
Other residential nursing care			
Community			
GP surgery visits			
GP home visits			
GP telephone contacts			
Practice nurse contacts			
District nurse contacts			
Physiotherapy contacts			
NHS Direct contacts			
Calls for ambulance/paramedic			
Occupational therapy contacts			
Social worker			
Counsellor			
Home help/care worker			
Day centre			
Lunch or social club (NHS/Social Care)			
Food, medicine or laundry services			

Patient/Family support groups			
Other community contacts			
Cost[2]			
A: Cost (NHS and Social care)			
B: Cost (Societal)			
1 EQ-5D-5L index score			
2 Time from work is not included in the analytic perspective, which includes health service and personal social services costs			

Figures 1-4 Presentation of base case economic analysis (illustrative example)



REFERENCES

1. Abbott, T.E.F., Fowler, A.J., Dobbs, T.D., Harrison, E.M., Gillies, M.A. and Pearse, R.M., 2017. Frequency of surgical treatment and related hospital procedures in the UK: a national ecological study using hospital episode statistics. **British Journal of Anaesthesia**, 119(2), pp.249-257.
2. Miskovic, A. and Lumb, A.B., 2017. Postoperative pulmonary complications**. British Journal of Anaesthesia**, 118(3), pp.317-334.
3. Fernandez-Bustamante, A., Frendl, G., Sprung, J., Kor, D.J., Subramaniam, B., Ruiz, R.M., Lee, J.W., Henderson, W.G., Moss, A., Mehdiratta, N. and Colwell, M.M., 2017. Postoperative pulmonary complications, early mortality, and hospital stay following noncardiothoracic surgery: a multicenter study by the perioperative research network investigators. **The Journal of the American Medical Association surgery**, 152(2), pp.157-166.
4. Canet, J., Gallart, L., Gomar, C., Paluzie, G., Valles, J., Castillo, J., Sabate, S., Mazo, V., Briones, Z., Sanchis, J. and ARISCAT group, 2010. Prediction of postoperative pulmonary complications in a population-based surgical cohort. **The Journal of the American Society of Anesthesiologists**, 113(6), pp.1338-1350.
5. Mazo, V., Sabate, S., Canet, J., Gallart, L., De Abreu, M.G., Belda, J., Langeron, O., Hoeft, A. and Pelosi, P., 2014. Prospective external validation of a predictive score for postoperative pulmonary complications. **Anesthesiology**, 121(2), pp.219-231.
6. Kirmeier, E., Eriksson, L.I., Lewald, H., Fagerlund, M.J., Hoeft, A., Hollmann, M., Meistelman, C., Hunter, J.M., Ulm, K., Blobner, M. and Gurumeta, A.A., 2019. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. **The Lancet Respiratory Medicine**, 7(2), pp.129-140.
7. Hristovska, A.M., Duch, P., Allingstrup, M. and Afshari, A., 2017. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. **Cochrane Database of Systematic Reviews**, (8).
8. Harper, N.J.N., Cook, T.M., Garcez, T., Farmer, L., Floss, K., Marinho, S., Torevell, H., Warner, A., Ferguson, K., Hitchman, J. and Egner, W., 2018. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). **British Journal of Anaesthesia**, 121(1), pp.159-171.
9. NICE. Guide to the methods of technology appraisal 2013.
10. Sedgwick P. What is intention to treat analysis? BMJ 2013; 346 doi: https://doi.org/10.1136/bmj.f3662
11. NHS. (2021). National Schedule of NHS costs 2019-2020. https://www.england.nhs.uk/national-cost-collection/#ncc1819.

12. Jones, K.C. and Burns, A., 2021. Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury. DOI:10.22024/UniKent/01.02.92342
13. BNF.(2022). Available at https://bnf.nice.org.uk/
14. Herdman, M., Gudex, C., Lloyd, A., Janssen, M.F., Kind, P., Parkin, D., Bonsel, G. and Badia, X., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research, 20(10), pp.1727-1736.
15. NICE. Position statement on use of the EQ-5D-5L value set for England (updated October 2019) https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l
16. Van Hout, B., Janssen, M.F., Feng, Y.S., Kohlmann, T., Busschbach, J., Golicki, D., Lloyd, A., Scalone, L., Kind, P. and Pickard, A.S., 2012. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in health*, *15*(5), pp.708-715.
17. Dritsaki, Melina, Felix Achana, James Mason, and Stavros Petrou. "Methodological issues surrounding the use of baseline health-related quality of life data to inform trial-based economic evaluations of interventions within emergency and critical care settings: a systematic literature review." *Pharmacoeconomics* 35, no. 5 (2017): 501-515.
18. Manca, A., Hawkins, N. and Sculpher, M.J., 2005. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health economics*, *14*(5), pp.487-496.
19. Husereau, D., Drummond, M., Augustovski, F., de Bekker-Grob, E., Briggs, A.H., Carswell, C., Caulley, L., Chaiyakunapruk, N., Greenberg, D., Loder, E. and Mauskopf, J., 2022. Consolidated health economic evaluation reporting standards (CHEERS) 2022 explanation and elaboration: a report of the ISPOR CHEERS II Good Practices Task Force. Value in Health, 25(1), pp.10-31.
20. Glick, H.A., Doshi, J.A., Sonnad, S.S. and Polsky, D., 2014. Economic evaluation in clinical trials. OUP Oxford.
21. Sterne, J.A., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A.M. and Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj*, *338*.
22. Faria, R., Gomes, M., Epstein, D. and White, I.R., 2014. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics*, *32*(12), pp.1157-1170.
23. White, I.R., Royston, P. and Wood, A.M., 2011. Multiple imputation using chained equations: issues and guidance for practice. *Statistics in medicine*, *30*(4), pp.377-399.

24. Willan, A.R., Briggs, A.H. and Hoch, J.S., 2004. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. Health economics, 13(5), pp.461-475.
25. Claxton, K., Sculpher, M. and Drummond, M., 2002. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). The Lancet, 360(9334), pp.711-715.