# NCCHTA

# 19 January 2009

## 1. Title of the project:

Sugammadex for reversal of muscle relaxation in general anaesthesia.

## 2. Name of TAR team and project 'lead'

Centre for Reviews and Dissemination/Centre for Health Economics
University of York

Dr Nerys Woolacott
Senior Research Fellow
CRD
University of York
YO10 5DD

Tel: +44 (0)1904 321074
Fax: +44 (0)1904 321041

## 3. Plain English Summary

Neuromuscular blocking agents (NMBAs) are routinely used as muscle relaxants in anaesthesia. NMBAs enable relaxation of the vocal cords for the passage of a tracheal tube, and adequate relaxation of the muscles of the abdomen and diaphragm for surgical access. There are two types of NMBA: depolarising (e.g succinylcholine/suxamethonium) which are rapid in onset and have a short duration of effect, but are associated with a number of adverse effects; and non-depolarising (e.g. rocuronium, vecuronium, atracurium) which have a longer time to onset and a longer duration of action.

Following surgery, the effect of the muscle relaxant is usually reversed by administering an anticholinesterase such as neostigmine. The drugs used to reverse the neuromuscular blockade have their own side-effects, which additional drugs are required to counteract. Sugammadex, a novel reversal agent, is able, unlike older reversal agents, to reverse 'deep' neuromuscular blockade, can be used for immediate reversal, and has a sufficient duration of action to prevent reoccurrence of paralysis. However, it is only effective with two aminosteroidal NMBAs: rocuronium and, to a lesser degree, vecuronium.

The aim of this project is to systematically review existing studies to determine how effective sugammadex is for the reversal of muscle relaxation during general anaesthesia. The project will also investigate, through the use of an economic model, whether sugammadex would be cost effective in UK practice.

## 4. Decision problem

- **Objective**

The objective of this technology assessment is to determine how clinically effective and cost effective sugammadex is for the reversal of muscle relaxation during general anaesthesia in UK practice. Sugammadex only reverses the effects of the aminosteroidal drugs, rocuronium and vecuronium.

- **Background**

The use of NMBAs is an established part of anaesthetic practice. Neuromuscular blockade (NMB) provides adequate muscle relaxation for tracheal intubation and surgical access. Prior to the use of NMB, muscle relaxation could only be achieved by deepening anaesthesia excessively, with consequent increased risk of delaying awakening and adverse respiratory and cardiac complications.[1] It is estimated that approximately 3.6 million general anaesthetic procedures with mechanical ventilation (requiring muscle relaxation) are carried out each year in the UK. Of these, approximately 0.8 million currently use rocuronium or vecuronium for muscle relaxation and an estimated 66% of these will require reversal (currently 528,000 procedures)[2] , though this figure may well be higher.

NMBAs contain a similar quaternary ammonium group to acetylcholine, the neurotransmitter that initiates muscle contraction, and like acetylcholine they act at the post-junctional nicotinic receptor of the neuromuscular junction. NMBAs may be depolarising, such as succinylcholine (suxamethonium), or non-depolarising, such as rocuronium or vecuronium.[1]

Depolarising agents depolarise the muscle fibre membrane by opening ion channels in the same way as acetylcholine, but unlike acetylcholine they are not hydrolysed by acetylcholinesterase and remain longer at the neuromuscular junction. Thus depolarisation lasts longer, which results in a brief period of repetitive excitation that may bring about transient muscle fasciculations (twitches) before the muscle relaxation.[3] Succinylcholine is the only depolarising NMBA in clinical use, and is the one most frequently used in emergency situations for tracheal intubation due to its rapid onset of action: neuromuscular blockade with Succinylcholine is achieved in 40 to 60 seconds.[4] However, there are many (albeit uncommon) conditions in which succinylcholine is contraindicated, including major burns (beyond 48 hrs) and major nerve or spinal cord injuries, due to the risk of hyperkalaemia (excessive levels of potassium), possibly leading to fatal cardiac arrhythmias.[4] Rarely, certain patients have an inability to breakdown succinylcholine in the plasma due to a genetic abnormality in their plasma cholinesterase and its duration of action is then prolonged.[1]

Non-depolarising agents compete with acetylcholine at the binding site, limiting or preventing depolarisation.[1] There are a number of non-depolarising agents in use in clinical practice in the UK which are of two types of chemical structure: pancuronium, rocuronium and vecuronium (aminosteroidal agents); and atracurium, cisatracurium and mivacurium (benzylisoquinoliniums). Pancuronium was the first aminosteroidal NMB introduced into clinical practice in the 1960s, but due to its

vagolytic and sympathomimetic effects and long duration of action it is now only used occasionally and mainly in cardiac surgery.[1] Mivacurium, (which is also broken down by plasma cholinesterase), atracurium and cisatracurium have the advantage of degrading in the plasma. Atracurium and cisatracurium are used in patients with poor renal function.[1]

Once surgery is complete, the patient must regain muscle strength and protective laryngeal reflexes before removal of the endotracheal tube, i.e. they must have recovered from the neuromuscular blockade. Spontaneous recovery from succinylcholine induced neuromuscular blockade occurs rapidly enough to be clinically acceptable (6 to 10 minutes),[4] but with non-depolarising agents reversal agents are often administered to hasten recovery. Under certain specialised surgical procedures, reversal of neuromuscular blockade may also be required during surgery, when the surgeon may need to test muscle function to ensure no nerve damage has taken place.

In current clinical practice, the reversal agents in use are anticholinesterase drugs (acetylcholinesterase inhibitors), most commonly neostigmine. Muscarinic receptor antagonists (eg. glycopyrrolate) are always administered with acetylcholinesterase inhibitors to prevent the muscarinic side effects. There are some limitations to the use of these reversal agents; acetylcholinesterase inhibitors are ineffective in reversing deep blockade nor can they be used to effect immediate reversal of block as a period of recovery is required before they can be administered. Furthermore, the duration of action of some anticholinesterases such as edrophonium may be shorter than the length of action of the NMBA, leading to reappearance of block, or residual paralysis.

There are two main scenarios where neuromuscular blockade is used:
(a) 'Routine' intubation for major surgery. Patients will have fasted in preparation for elective surgery and the stomach will be empty, hence there is less risk of aspiration of stomach contents into the lungs on induction of anaesthesia. NMB can be shallow or deep depending on the type of surgery needed and, whilst recovery can be spontaneous, blockade is usually reversed with an appropriate pharmacological agent. In UK clinical practice the anticholinesterase/antimuscarinic combination used most commonly is neostigmine in combination with glycopyrrolate.

(b) Rapid sequence induction for emergency surgery or when the stomach is thought to be full. Tracheal intubation, and therefore the onset of neuromuscular block, must be rapid to minimise the risk of aspiration of gastric contents. The standard drug used for this is succinylcholine (suxamethonium), which has the most rapid onset of action. Larger than standard doses of rocuronium can also be used to achieve almost as rapid an onset of blockade, without the side-effects of succinylcholine.

There is the possibility in both scenarios that a 'cannot intubate/cannot ventilate' emergency can occur, requiring immediate reversal of blockade if the patient is to survive without hypoxic brain damage. Where non-depolarising NMBAs have been used, there is at present an unavoidable delay before reversal agents such as neostigmine can be administered if they are to be effective. This is of particular concern in rapid sequence induction if rocuronium has been used because in higher doses rocuronium has a long duration of action of at least 90 minutes.

Sugammadex is a newly developed agent for the reversal of both 'shallow' and 'deep' neuromuscular blockade induced by rocuronium or vecuronium. The depth of block is defined by monitoring the neuromuscular response to stimulation using electromyography, mechanomyography or acceleromyography. Standard methods of stimulation include post-tetanic count (PTC) and train-of-four (TOF) stimulation. For reversal of 'deep' (or 'profound') neuromuscular block, a 4 mg/kg dose of sugammadex is administered at a PTC of 1–2. For reversal of 'shallow' block, as defined in the proposed indications for sugammadex, a dose of 2 mg/kg is administered on reappearance of the second spike ($T_2$) in response to TOF stimulation. 'Shallow' neuromuscular block as defined here corresponds to 'moderate' block in the terminology of Fuchs-Buder et al.[5] and to the level of block at which it is first possible to obtain an efficient effect with neostigmine.

Sugammadex forms very tight one-to-one complexes with rocuronium or vecuronium, encapsulating these drugs and hence reducing the concentration of NMBA at the neuromuscular junction and rapidly terminating the block.[6] Unlike acetylcholinesterase inhibitors, sugammadex can reverse deep blockade and can be given for immediate reversal of block without the need to wait for partial recovery.[7] Sugammadex has no effect on acetylcholinesterase, eliminating the need for concomitant anticholinergic drugs.[6] For patients requiring rapid sequence induction of anaesthesia for endotracheal intubation, the immediate reversal possible with sugammadex could enable large doses of rocuronium to be used in the knowledge that should a 'cannot intubate/cannot ventilate' situation occur the blockade will be reversible.[7] The rocuronium + sugammadex combination may provide an onset of effect and rapid reversal at least equal to succinylcholine, but with a better safety profile, resulting in benefits in terms of avoidance of adverse events, and a lower morbidity and mortality. Overall, potential clinical benefits for the use of sugammadex include increased patient safety, improved surgical conditions and reduced incidence of residual paralysis on recovery.[6]

- **Scope of technology assessment**

This technology assessment will investigate the use of sugammadex in the two main scenarios described which use neuromuscular blockade:

- For routine intubation, the intervention of interest is rocuronium + sugammadex or vecuronium + sugammadex. The doses of sugammadex are 2 mg/kg for 'shallow' (or 'moderate'[5]) blockade and 4 mg/kg for antagonism of 'deep' blockade. These will be compared with rocuronium or vecuronium + neostigmine/glycopyrrolate and atracurium, cisatracurium or mivacurium + neostigmine/glycopyrrolate. The option of administering these NMBAs with no reversal agent or placebo will also be evaluated.
- In rapid sequence induction the intervention of interest is rocuronium + 16 mg/kg sugammadex and this will be compared with succinylcholine (suxamethonium).

Although the systematic review of clinical trials will encompass all patient populations studied in randomised controlled trials (RCTs), given the many factors such as surgical procedure, fitness for surgery, renal function, age etc. that can impact on outcome following neuromuscular blockade and its reversal, the technology assessment will focus on the use of sugammadex in a generally representative surgical population.

Outcome measures will include the speed of reversal measured by train-of-four (TOF) stimulation with neuromuscular monitoring, plus clinical signs of recovery.[8, 9] With rapid sequence induction, the speed of onset of neuromuscular blockade will also be compared. The adverse event profile of NMBA + sugammadex will be compared with that of NMBA + neostigmine/glycopyrrolate, or succinylcholine. Attempts will be made to value and compare the increased margin of control and safety that is anticipated with sugammadex combinations. Outcomes measuring patient experience with recovery will also be sought.

## 5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in CRD Report 4 2008,[10] and the QUORUM statement.[11]

- **Search Strategy**

The search strategy will comprise the following main elements:

For clinical effects, the following databases will be searched: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Citation Index, BIOSIS, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA). Where the number of records is potentially large, a methodological search filter devised to identify RCTs will be included in the strategy.

In addition, information on studies in progress, unpublished research or research reported in the grey literature will be identified by searching ISI Proceedings Science & Technology, Inside Conferences, ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, Clinical Trial Results and World Health Organization International Clinical Trials Registry Platform (ICTRP). All resources will be searched from their inception to the most recent date available. There will be no restriction by study design, country of origin, language or publication date.

Internet searches will be carried out using the specialist search gateways intute (www.intute.ac.uk) and MedlinePlus (http://www.nlm.nih.gov/medlineplus/) to identify relevant resources. Potentially relevant websites identified during the initial internet gateway searches will then be searched and browsed. Examples of organisation websites to be searched include the Royal College of Anaesthetists, Association of Anaesthetists of Great Britain and Ireland, Anaesthesia Research Trust, American Society of Anesthesiologists, European Society of Anaesthesiology (ESA), World Federation of Societies of Anaesthesiologists, and the National Library for Health (NLH) Surgery, Theatres & Anaesthesia Specialist Library.

The following conference proceedings will be searched: Annual Meeting of the European Society of Anaesthesiology (2004-2008), American Society of Anesthesiologists Annual Meeting (2001-2008), Association of Anaesthetists of Great

Britain and Ireland Annual Congress (2004-2007), and the World Federation of Societies of Anaesthesiologists Congress (2008).

Search alerts (details of newly published articles retrieved using a saved search sent by e-mail) will be set up in a number of journals: Anaesthesia, British Journal of Anaesthesia, European Journal of Anaesthesiology, Anesthesiology, and Anesthesia and Analgesia. Search alerts will also be set up to run weekly in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE.

Information on adverse effects will be identified from established sources of information on adverse drug reactions, for example, FDA website, EMEA EPArs, and SPCs, Meyler's side effects of drugs, and Martindale: the complete drug reference.

Details of published and unpublished studies of sugammadex (including full clinical trial reports if appropriate) will be requested from the manufacturer.

The bibliographies of all relevant reviews and guidelines and all included studies will be checked for further potentially relevant studies.

Titles and abstracts will be examined for relevance by two reviewers independently; all potentially relevant papers will be ordered. All full papers will be screened by at least two reviewers independently; relevance to the review and the decision to include studies or not will be made according to the inclusion criteria detailed below. Disagreements will be resolved by consensus.

- **Inclusion criteria**

Studies will be eligible for inclusion in the review if they meet the following inclusion criteria:

***Population***

Trials of human patients of any age and health status, undergoing in-hospital surgery involving general anaesthesia and requiring neuromuscular blockade.

***Interventions***

Sugammadex administered as different doses for reversal of NMB: (a) 2 mg/kg or 4mg/kg sugammadex for reversal of 'shallow' (or 'moderate'[5]) NMB or 'deep' NMB, respectively, induced by rocuronium or vecuronium and (b) 16 mg/kg for immediate reversal of NMB induced by rocuronium.

***Comparators***

Routine intubation (elective surgery, empty stomach):

For routine intubation, trials comparing any of the following NMBAs + reversal agent combinations will be included:

- rocuronium or vecuronium + sugammadex
- rocuronium, vecuronium, atracurium, cisatracurium or mivacurium + neostigmine/glycopyrrolate

- rocuronium, vecuronium, atracurium, cisatracurium or mivacurium + no reversal (i.e. spontaneous recovery) or placebo.

Comparisons not involving sugammadex may be included to develop a network of evidence related to the reversal of neuromuscular blockade in elective surgery.

Rapid sequence induction:
For rapid intubation and immediate reversal of neuromuscular blockade, trials of rocuronium + sugammadex compared with spontaneous recovery from succinylcholine induced neuromuscular blockade will be included.

***Outcomes***
Studies reporting the following outcomes will be included in the review: speed of reversal of neuromuscular block as measured by train-of-four (TOF) monitoring (e.g. recovery of the $T_4/T_1$ ratio, i.e. ratio of the height of the fourth twitch to that of the first, to 0.9) and clinical signs of recovery (e.g. able to perform the five second head lift test[8, 9]); occurrence of residual paralysis; adverse event profile of intervention and comparators. Studies reporting outcomes relating to the patient's experience of recovery and any outcomes relating to improved control of anaesthesia or resource use will also be included.

The primary outcome to be used in the review will be decided once the primary studies have been identified and the most useful outcome measures reported in the primary literature established.

***Study Design***
For the assessment of the treatment effect of sugammadex only parallel-group randomised controlled trials (RCTs) will be included. However, studies of other designs may be used as sources of data if they contribute significantly to the assessment of the clinical effectiveness of sugammadex.

- **Safety/adverse events**

Data on the safety and adverse event profiles of NMBAs, neostigmine and glycopyrrolate will be sought from high-quality summary information sources. Additional safety data for sugammadex will be sought from the manufacturer, including pooled analyses of safety data.

- **Exclusion criteria**

Animal models, preclinical and biological studies, reviews, editorials, and opinions will be excluded.

- **Data extraction strategy**

Data will be extracted independently by one reviewer using a standardised data extraction form and checked by one other reviewer. Discrepancies will be resolved through discussion and checked by a third reviewer where necessary.

- **Quality assessment strategy**

The quality of RCTs will be assessed using the checklist advised in CRD Report 4 2008,[12] adapted as necessary to incorporate topic-specific quality issues. The quality

of the individual studies will be assessed by one reviewer and independently checked for agreement by a second reviewer. Any disagreements will be resolved through consensus and checked by a third reviewer where necessary.

- **Methods of analysis/synthesis**

Data from the individual studies will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses. Meta-analysis will be carried out using fixed or random effects models, using appropriate software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the $\chi^2$ test for homogeneity and the $I^2$ statistic.

It is anticipated that the network of evidence relating to neuromuscular blockade and its reversal in fasted patients undergoing scheduled surgery (routine intubation) will be analysed using a mixed treatment comparison model [13] including all RCTs comparing two or more of the interventions (NMBA + reversal agent or spontaneous recovery/placebo) of interest. Studies that compare different doses or administration strategies of the same NMBA or reversal agent will not be included, with the exception of studies comparing different doses of sugammadex. The modelling will be carried out using the Bayesian analysis software WinBUGS.

- **Methods for estimating quality of life and resource use (costs)**

Direct evidence from studies assessing reversal of NMB in general anaesthesia will be sought. Quality of life and resource use outcome data will be extracted from all trials included in the clinical review, where available. To inform the discussion and the economic analysis, evidence of the relationship between reversal of neuromuscular block and quality of life/resource use will be sought. This will include a limited (given the time constraints of the review) systematic review of the literature relating those endpoints recorded in the trials to quality of life and resource use.

**6. Report methods for synthesising evidence of cost-effectiveness**

The sources detailed in Section 5 NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluations Database (HEED) will be used to identify economic evaluation studies of sugammadex in comparison with other forms of reversal. In addition, economic evaluations of other forms of NMB reversal will be identified to provide insights into modelling approaches. A broad range of economic studies will be considered including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond *et al.*[14] This information will be tabulated and summarised within the text of the report. In particular, information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality of life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and

approaches to quantifying decision uncertainty (e.g. deterministic / probabilistic sensitivity analysis).

The review will examine any existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review. The presence of any data gaps (e.g. resource use data) that may need to be filled during the development of the model will be identified and additional searches may be required.

Although not part of a formal NICE technology appraisal, it is hoped that it will be possible to gain access to Schering-Plough's economic model (to be submitted to the Scottish Medicines Consortium). This will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

**Development of a new decision-analytic model**

Subject to the availability of existing models and evidence, a new decision-analytic model may be developed to estimate the cost-effectiveness of sugammadex versus the range of comparators described above. The perspective will be that of the National Health Services and Personal Social Services. Productivity costs, such as time to return to normal activities, are not included within this perspective but may be included as a secondary analysis. Both cost and QALY will be discounted at an annual rate of 3.5% if the time horizon of the model is greater than one year.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies, in a way which is clinically acceptable
- To populate this model using the most appropriate data identified systematically from published literature and routine data sources.
- To relate intermediate outcomes (e.g. TOF, adverse events) to final health outcomes, expressed in terms of quality-adjusted life years (QALYs). This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the mean cost-effectiveness of sugammadex against other comparators, based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.
- Consistent with available evidence to report cost-effectiveness of alternative treatments for specific sub-groups of patient. This may include cost-effectiveness by patients underlying risk of particular clinical events.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an

uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this *parameter uncertainty,* is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, *decision uncertainty.* This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

- To inform future research priorities in the NHS, the model will be used to undertake analyses of the expected value of perfect information. These take the decision uncertainty associated with analysis and quantify the cost of this uncertainty in terms of health gain forgone and resources wasted by making the wrong decision. This cost of uncertainty represents the value of perfect information, and this can be estimated for the model overall and for individual parameters.

## 7. Expertise in this TAR team

Duncan Chambers, Research Fellow (dc510@york.ac.uk). Three years' experience as a systematic reviewer for NICE and HTA Programme projects.

Morag Heirs, Research Fellow (mkc500@york.ac.uk). Two years experience in systematic reviews and related methodology. She has produced a systematic review for the Cochrane Collaboration.

Fiona Paton, Research Fellow (fcwp500@york.ac.uk). Nine month's experience in systematic reviews. She has worked on a systematic review for NICE.

Nerys Woolacott, Senior Research Fellow/Reviews Manager (nw11@york.ac.uk). Five years' experience in health technology assessment, systematic reviews and review methodology. She has produced systematic reviews for HTA, NICE, Department of Health and others.

Steven Duffy, Information Officer (sbd4@york.ac.uk). 10 years experience as an information specialist. He has produced the information components of reviews funded by HTA, NICE, Policy Research Programme, Department of Health, Service Delivery Organisation and others.

Mike Paulden, Research Fellow in Health Economics (mdp502@york.ac.uk). 9 months experience in economic evaluation including a HTA for NICE.

Mark Sculpher, Professor of Health Economics (mjs23@york.ac.uk). 20 years experience in economic evaluation and health technology assessment. This includes studies for NICE and a range of research funders.

Professor Jennifer M Hunter, (jennie@liverpool.ac.uk), Division of Clinical Science (Anaesthesia), University of Liverpool.

Jonathan Wilson, Consultant Anaesthetist York NHS Trust (Jonathan.RJT.Wilson@york.nhs.uk).

- **Role of clinical experts**

Two clinical experts (Prof. J. Hunter and Dr J. Wilson) will be collaborating on the project and will provide expert input on the existing research in this field.

- **TAR Centre**

The Technology Assessment Review team at the University of York is drawn from two specialist centres: the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE).

CRD undertakes reviews of research about the effects of interventions used in health and social care (www.york.ac.uk/inst/crd). The centre maintains various databases, provides an enquiry service and disseminates results of research to NHS decision makers.

CHE undertakes research and training in all areas of health economics (www.york.ac.uk/inst/che). The bulk of the input into the TARs comes from the programme for economic evaluation and health technology assessment which specialises in decision analysis and Bayesian methods in economic evaluations.

Recent TARs undertaken by CRD/CHE at York relate to catheter ablation for atrial fibrillation, stapled haemorrhoidopexy and endovascular stents for abdominal aortic aneurysms.

- **Team members' contributions**

Duncan Chambers - Reviewer will contribute to the review protocol, study selection, data extraction, validity assessment and report writing in the clinical effectiveness review.

Morag Heirs – Reviewer will contribute to the review protocol, study selection, data extraction, validity assessment and report writing in the clinical effectiveness review.

Fiona Paton – Reviewer will contribute to the review protocol, study selection, data extraction, validity assessment and report writing in the clinical effectiveness review.

Nerys Woolacott – Review manager will provide input at all stages, comment on various drafts of the protocol and report; overall responsibility for project co-ordination.

Steven Duffy - Information specialist responsible for devising the search strategy, carrying out the literature searches and maintaining the literature database.

Mike Paulden – Health economist will contribute to the cost-effectiveness review and development of the cost-effectiveness model.

Prof. Mark Sculpher – Senior health economist responsible for managing the cost-effectiveness review and development of the cost-effectiveness model.

Prof. Jennie Hunter - School of Clinical Sciences, University of Liverpool. Will provide clinical input at all stages, comment on various drafts of the report and contribute to the discussion section of the report.

Dr Jonathan Wilson – Consultant Anaesthetist, York NHS Trust. Will provide clinical input at all stages, comment on various drafts of the report and contribute to the discussion section of the report.

## 8. Competing interests of authors

In the past Prof Hunter has had funding for a clinical trials of sugammadex from Organon/Schering Plough. She has no current funding related to sugammadex.

## 9. Timetable/milestones

| Milestones | Timetable |
|---|---|
| Protocol development | Up to 29th July 2008 |
| Protocol submitted to HTA | 31st August 2008 |
| Literature search | July 2008 (with current awareness searches throughout project) |
| Relevance and inclusion assessment | August 2008 |
| Data extraction and quality assessment | September to October 2008 |
| Analysis / modelling | October 2008 |
| Report production | October to November 2008 |
| Report submission to HTA | 19th December 2008 |

## 10. References

1. Aitkenhead AR, Smith G, Rowbotham DJ, editors. *Textbook of anaesthesia*. 5th ed. Edinburgh: Churchill Livingstone, Elsevier, 2007.
2. National Horizon Scanning Centre. *Sugammadex (Org 25969) for reversal of muscle relaxation in general anaesthesia: horizon scanning technology briefing*. Birmingham: National Horizon Scanning Centre (NHSC); 2006.
3. Fink H, Blobner M, Martyn JA. Neuromuscular blocking agents and reversal drugs. In: Evers A, Maze M, editors. *Anesthetic pharmacology: physiologic principles and clinical practice.* Philadelphia, PA: Churchill Livingstone; 2004. p. 573-97.
4. Combs JM, Combs GN. A literature review of the newest muscle relaxant: ORG 9426 *CRNA* 1994;5:104 -12.
5. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. *Acta Anaesthesiol Scand* 2007;51:789-808.
6. Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg* 2007;104:575-81.
7. Nicholson WT, Sprung J, Jankowski CJ. Sugammadex: a novel agent for the reversal of neuromuscular blockade. *Pharmacotherapy* 2007;27:1181-8.
8. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block. II. *Br J Anaesth* 1971;43:478-85.

9. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block. I. *Br J Anaesth* 1971;43:473-7.
10. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care. CRD Report 4 [forthcoming]*. 3rd ed. York: University of York; 2008.
11. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;354:1896-900.
12. Hemmerling TM, Geldner G. Sugammadex: good drugs do not replace good clinical practice. *Anesth Analg* 2007;105:1506.
13. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331:897-900.
14. Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.

## 11. Appendices

Draft search strategy

The following draft search strategy to identify studies about sugammadex was devised for MEDLINE in the OvidSP interface.

1. sugammadex.ti,ab,rn,nm.
2. (org 25969 or org25969).ti,ab,rn,nm.
3. bridion.ti,ab,rn,nm.
4. 343306-79-6.rn.
5. (selective adj3 relaxant$).ti,ab.
6. SRBA.ti,ab.
7. or/1-6
8. Animals/
9. Humans/
10. 8 not (8 and 9)
11. 7 not 10