NHS England

Evidence Review:

Tolvaptan for hyponatraemia secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in patients requiring cancer chemotherapy

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Prepared by **Turnkey Clinical Evidence Review Team on behalf of NHS England Specialised Commissioning**

Contents

1. Introduction

Hyponatraemia (serum sodium <135 mmol/L) is common, affecting up to 30% of hospitalised patients. In 35% of these patients, hyponatraemia is attributed to the Syndrome of Inappropriate Antidiuresis (SIADH). SIADH is characterised by the continued production of the hormone vasopressin (AVP) at plasma osmolalities below the normal osmotic threshold for AVP release, leading to increased renal water resorption through activation of AVP-dependent water channels in the distal nephron. Profound biochemical hyponatraemia resulting in significant symptoms and signs is a medical emergency, treated with hypertonic fluid under close supervision. However, the majority of clinical situations involve less profound hyponatraemia, together with symptoms and signs that are less marked. Treatment of the precipitating cause of SIADH, together with fluid restriction, is the common first-line approach in this situation. Demeclocycline has been used in patients with refractory SIADH. However, its utility is limited by adverse effects (gastrointestinal upset, photosensitivity and renal toxicity), unpredictable response, delayed onset of action and limited availability.

Hyponatraemia is common in cancer patients, especially those with lung cancers, some of which secrete AVP leading to worsening hyponatraemia. Small cell lung cancer is notorious for causing SIADH although other cancers also lead to this syndrome. This policy concerns patients with mild to moderate hyponatraemia secondary to SIADH, where the hyponatraemia is preventing chemotherapy from proceeding. Chemotherapy requires adequate pre-hydration which often causes a dilutional hyponatraemia. This hyponatraemia can lead to seizures and so a normal serum sodium level is required prior to commencing chemotherapy. It is in these patients that fluid restriction would be ineffective and contraindicated. It is also in this subgroup of patients that randomised controlled trials would, for ethical reasons, not be possible and thus the ability to gather sufficient evidence is limited and clinical consensus must be used to give context to the evidence demonstrated. Whilst the evidence outlined in this policy demonstrates the efficacy of tolvaptan in increasing sodium concentration, the evidence does not however provide a framework to highlight the clinical significance of this rise in sodium concentration. Tolvaptan is proposed in patients with malignant disease, where chemotherapy is being delayed due to hyponatraemia.

Tolvaptan (Samsca) is an orally acting, selective vasopressin V2 receptor antagonist that blocks the binding of vasopressin to V2 receptors in the collecting duct of the kidney, reducing water reabsorption. The resulting aquareis addresses the dilutional hyponatraemia that is the central feature of SIADH. The maximum rate of change of sodium concentration occurs in the first 24 hours of treatment. The usual treatment regime with tolvaptan would last a maximum of four to ten days and it is not anticipated to be used for medium or long-term treatment of hyponatraemia. This policy concerns the use of tolvaptan for mild or moderate hyponatraemia, not severe or profound hyponatraemia, in alignment with the licence.

2. Summary of results

Summary

The evidence of effectiveness of tolvaptan (for short-term treatment of mild to moderate hyponatraemia) is mainly based on two well-designed prospective studies and a small number of case series from the UK. The first is an extension study of patients from the original Study of Ascending Levels of Tolvaptan in Hyponatraemia (SALT1 and SALT2) studies. Verbalis et al (2011) (Level 1++ evidence), report on a sub-group analysis of patients from the original SALT1 and SALT2 trial with 'Syndrome of Inappropriate ADH secretion' (SIADH), which can arise from various causes including malignancy, central nervous system pathology, certain medications and other factors. The other is a double blind randomised controlled trial (RCT) conducted in 37 Chinese patients with hyponatraemia secondary to SIADH (placebo=18, tolvaptan=19) by Chen et al 2014 (Level 1+ evidence). In addition, a US cost-effectiveness study by Dasta et al (2012) (Level 1 evidence) sought to evaluate the potential hospital cost savings associated with tolvaptan usage among patients with the SIADH based on the SALT1 and SALT2 trials by constructing a cost-offset model to evaluate the impact of tolvaptan on hospital resource usage, mainly the length of stay (LOS). Although LOS was lower for patients treated with tolvaptan compared to placebo, this was not statistically significant (see part 3 below for details).

Both prospective studies indicated that tolvaptan has a prompt biochemical effect improving serum sodium concentration (so addressing hyponatraemia), and that this reduces the need for fluid restriction, allowing patients

to have a more normal fluid intake. Whilst this would theoretically reduce the need for hospital admission or prolongation of an existing stay, Dasta et al (2012) did not confirm this at a level of statistical significance.

Detailed Evidence

Part 1: Clinical Effectiveness

Verbalis et al (2011) analysed of a subgroup of 110 patients with a primary diagnosis of SIADH from the original SALT studies, assigned to either tolvaptan 15-30mg daily (52) or oral placebo (58). In each treatment group, 42 patients completed the full 30-day treatment period. Another smaller subgroup of SIADH patients (based on urine sodium concentration) was also identified and reviewed (24 patients in the tolvaptan group and 25 patients in the placebo group).

The primary outcomes were the change in the average daily area under curve (AUC) for the serum sodium concentration from baseline to both day four and to day 30. In the SIADH subgroup, patients on tolvaptan had highly significant (P<0.0001) improvements in serum sodium concentrations relative to the placebo group at day 4 (5.28±3.35mmol/L vs 0.47±2.81mmol/L respectively) and day 30 (8.07±4.55mmol/L vs 1.89±4.13 mmol/L). The smaller subgroup of SIADH patients showed similar results at day four (4.61±1.97mmol/L vs 0.96±2.78mmol/L; P<0.0001) and day 30 (6.28 ±3.17mmol/L vs 2.03±4.37mmol/L; P<0.0001). Withdrawal of tolvaptan therapy resulted in the re-establishment of baseline hyponatremia (serum sodium concentration) within seven days.

This study also reported that patients treated with tolvaptan were managed in an outpatient setting without fluid restriction, avoiding the need for hospital admission to fluid restrict patients and monitor urine output. Relative to the placebo group, the tolvaptan group had both larger mean fluid intake (2016±1234ml vs 1563±966 ml; P=0.049) and larger mean urine output (3057±1701ml vs 1758±928 ml; P<0.001).

The study by Chen et al (2014) is a double-blind RCT with good study methodology including randomisation, patient selection criteria, and statistical analysis. The results show the tolvaptan group (15-60mg daily) had better outcomes for the primary end point. Average daily changes in serum sodium levels from baseline to day four were 1.9±2.9mmol/L (1.9±2.9mEq/L) in the placebo group and 8.1±3.6mmol/L (8.1±3.6mEq/L) in the tolvaptan group, and to day seven were 2.5±3.9mmol/L (2.5±3.9mEq/L) for the placebo group and 8.6±3.9mmol/L (8.6±3.9mEq/L) for the tolvaptan group. The differences between the two groups were significant (ANCOVA, P<0.0001) both at days four and seven. Outcomes for secondary endpoints were also positive.

In the context of the research question, the biggest limitation is that neither of the studies analysed outcome results by level of severity of hyponatraemia (e.g. mild, moderate) and the studies excluded patients who were treated with demeclocycline. Therefore generalisation of results to the specific cohort described in the research questions is limited.

Evidence from case series comes from both UK and international studies. A UK study by Tzoulis et al (2015) (Level 3 evidence), is based on real-life experience from patients admitted to a general hospital in the UK. Veghasiya et al (2012) is a European case series comparing the effect of tolvaptan in small number of patients with SIADH and heart failure (both Level 3 evidence).

The study by Tzoulis et al (2015) is a retrospective case study of outcomes for 64 patients with hyponatraemia due to SIADH who were treated with tolvaptan 15-30 mg, either as first line therapy or following other treatments including fluid restriction and/or demeclocycline. The mean serum sodium increase 24 hours after tolvaptan initiation was 9.0±3.9mmol/L. At the end of tolvaptan therapy, serum sodium increase was 13.0±5.9mmol/L with 96.7% of patients having serum sodium increases ≥5mmol/L in 48 hours.

A study by Vaghasiya et al (2012) studied the effect of a single 15mg dose of Tolvaptan in 13 patients with hyponatraemia, of whom 8 patients had SIADH. The mean serum sodium rise was 6.4mmol/L in 24 hours. Three patients, all with SIADH, showed an 8mmol/L rise in serum sodium within 12 hours.

Part 2: Clinical effectiveness versus fluid restriction and/or demeclocycline

There are no head-to-head comparisons of tolvaptan against fluid restriction or demeclocycline in the management of hyponatraemia secondary to SIADH. There is some evidence (Level 3) that tolvaptan is effective in improving serum sodium levels in patients with persistent hyponatraemia following treatment with fluid

restriction. Due to small numbers of patients in relevant case series, it is not possible to conclude on the evidence in circumstances where demeclocycline was used.

Tzoulis et al (2015) included patients who had persistent hyponatraemia or failed to correct after initial treatment with fluid restriction (majority) and demeclocycline in small number. In this study, 86% of the patients (52/61) were treated with fluid restriction and/or demeclocycline as a first or second line treatment. Tolvaptan was used as first-line agent in 9/61 cases after failure of other therapeutic modalities including fluid restriction or demeclocycline. This study showed nearly 96.7% of patients having serum sodium increase ≥5mmol/L in 48 hours.

Another limitation in evidence generation for the research question is the lack of standardised protocol for identifying SIADH and treatment of SIADH across hospitals in the UK and other places in the world. This was evident from a study of the hyponatraemia registry by Greenberg et al (2015), which showed that only 47% of the 1,597 patients with SIADH as identified by treating physicians had all three cardinal diagnostic tests performed, and 11% underwent none. The full diagnostic criteria include normal thyroid and adrenal function, but only 21% of identified SIADH patients underwent cortisol and thyroid hormone determinations, along with the required electrolyte and osmolality measurements.

Part 3: Cost effectiveness

There are no studies evaluating the cost effectiveness of tolvaptan in the subset of patients as defined in the research question. However, evidence for cost effectiveness for use of tolvaptan in patients with hyponatraemia due to SIADH comes from a study by Dasta et al (2012). The primary objective of this study was to evaluate the potential hospital cost savings associated with tolvaptan usage among patients with SIADH (based on the SALT1 and SALT2 trials) by constructing a cost-offset model to evaluate the impact of tolvaptan on hospital resource usage, mainly the length of stay (LOS) among patients with the SIADH.

The analysis was conducted from the perspective of hospitals in the United States and the total number of patients admitted with SIADH was obtained from Nationwide Inpatient Sample (NIS). The hospital costs and LOS associated with SIADH was collected from The Healthcare Cost and Utilization Project (HCUP) database for adult (age >18 years) patients with a primary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for the SIADH of 253.6.

The estimates for effectiveness were based on SALT1 and SALT2 results in which the SIADH subpopulation had a significant estimated improvement in serum sodium concentration of 5.28 ± 3.35mEq/L by the fourth day such that 60% of patients with the SIADH receiving tolvaptan had normalised serum sodium levels, in comparison with 11.5% of patients receiving placebo. However, the mean hospital LOS in tolvaptan was lower by 1.21 days (not statistically significant). LOS in tolvaptan (n = 52) was 4.98 ± 6.61 days compared to 6.19 ± 7.89 days in patients who received a placebo (n = 58). The relative difference in LOS due to tolvaptan usage in the SALT1 and SALT2 trials was 19.5%.

The main limitations of the study from the perspective of the research questions were that the cost analysis is based on hospitals in the USA (limiting the ability to draw direct comparison with other health care systems), and that whilst the research question focuses mainly on mild and moderate SIADH, nearly 50% of SIADH patients in the two studies which are used in economic modelling had moderate to severe hyponatraemia defined as Na <130mmol/L. Therefore generalising these results to the population stated in the research questions is limited.

Part 4: Safety

There are no studies evaluating the safety of tolvaptan specifically in the cohort of patients defined in the research question. However, evidence of safety using tolvaptan in hyponatraemia in patients with SIADH is available mainly from the study by Verbalis et al (2011), and very limited data in the case series by Tzoulis et al (2011).

Exceeding protocol-recommended correction limits for serum sodium concentration following tolvaptan treatment is a known complication. In Verbalis et al (2011), of the 51 patients treated with tolvaptan, three (5.9%) exceeded protocol recommended correction limits of an increase in serum sodium >12mmol/L in the first 24 hours of correction and >18mmol/L in the first 48 hours of correction: one with a correction of 13mmol/L and two with a correction of 14mmol/L over the first 24 hours of therapy. All three of the patients with overly rapid correction had marked hyponatraemia (baseline serum [Na+] <130mmol/L).

Slightly higher rates were seen in study by Tzoulis et al (2015) where 18% (10/61) had more than recommended correction at 24 hours and 21% at 48 hours.

Thirst and dry mouth were the most common tolvaptan-related adverse events in the SALT trials. In the study by Verbalis et al (2011), these adverse events were relatively similar between the two treatment groups and occurred in 9 (18%) and 8 (16%) patients respectively on tolvaptan and 5 (9%) and 6 (10%) patients respectively on placebo in this SIADH subgroup analysis. However the potentially drug-related adverse events of dizziness, vomiting, hypotension, and nasopharyngitis occurred at slightly higher rates in the placebo group.

In the study by Verbalis et al (2011), in the tolvaptan and placebo groups, 10 (19%) and 16 (28%) patients respectively discontinued from the trial before completing the 30-day treatment period. Of these, five patients (10%) on tolvaptan and seven patients (12%) on placebo withdrew specifically for adverse experiences.

Verbalis et al (2011) reported four deaths (one in the tolvaptan group and three in the placebo group). None of the deaths were considered to be treatment related. Tzoulis et al (2015) reported five deaths but it is not clear how many of them were linked to Tolvaptan.

In the main, short-term treatment with tolvaptan is usually well-tolerated.

3. Research questions

(1a) Is tolvaptan (Samsca) clinically effective at improving serum sodium concentration in patients with mild to moderate SIADH associated hyponatraemia (with no impairment of neurological state), in whom a poor response or lack of response to fluid restriction and/or demeclocycline is (i) preventing urgent evidence based interventions from going ahead, or (ii) causing a prolonged hospital admission due to severity of symptoms attributable to hyponatraemia?

(1b) Is tolvaptan more effective than fluid restriction and demeclocycline in achieving normalisation of serum sodium concentration and prevention of the effects of hypernatraemia?

(2) Is tolvaptan a cost effective treatment in patients with mild to moderate SIADH associated hyponatraemia (with no impairment in neurological state), in whom a poor response or lack of response to fluid restriction and/or demeclocycline is (i) preventing urgent evidence based interventions from going ahead, or (ii) causing a prolonged hospital admission due to severity of symptoms attributable to hyponatraemia?

(3) Is tolvaptan a safe treatment in patients with mild to moderate SIADH associated hyponatraemia (with no impairment in neurological state), in whom a poor response or lack of response to fluid restriction and/or demeclocycline is (i) preventing urgent evidence based interventions from going ahead, or (ii) causing a prolonged hospital admission due to severity of symptoms attributable to hyponatraemia?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1++	RCT	Tolvaptan=52, placebo=52	Tolvaptan 15-30 mg	Clinical effectiveness of the intervention	Change in the average daily area under the curve (AUC) for the serum [Na+] from baseline to day 4 and from baseline to day 30, the absolute serum [Na+] at each visit, and the percentage of patients with serum [Na+] that had normalised (>135 mmol/l) at each visit.	This is an extended analysis of SALT1 and SALT2 RCT trial where patients with SIADH were analysed separately for effectiveness and safety. A total of 448 patients received study medication in the original two SALT trials, 110 of whom had a primary diagnosis of SIADH derived by the investigator using standard clinical criteria. Of these 52 SIADH patients who were randomly assigned to oral tolvaptan other 58 SIADH subjects randomly assigned to oral placebo. In each treatment group, 42 patients completed the full 30-day treatment period. The results show that in patients with SIADH, improvement in serum [Na+] was significantly greater (P<0.0001) with tolvaptan than placebo over the first 4 days of therapy as well as the entire 30-day study, with minimal side effects of increased thirst, dry mouth, and urination. Only 5.9% of tolvaptan-treated patients had overly rapid correction of hyponatraemia as defined by current guidelines. After discontinuation of tolvaptan, serum [Na+] declined to values similar to placebo. A significant positive treatment effect favouring tolvaptan on the physical component, and a near significant trend on the mental component, was found using the SF-12 Health Survey. Tolvaptan was associated with a significantly reduced incidence of fluid restriction.	Fluid intake and output on day one, institution of fluid restriction or use of i.v. saline as rescue therapy, and the change from baseline in scores on the Physical Component Summary (PCS) and Mental Component. Summary (MCS) of the Medical Outcomes Study 12 item Short-Form (SF-12). General Health Survey.	A significant positive treatment effect favouring tolvaptan on the physical component, and a near significant trend on the mental component, was found using the SF-12 Health Survey. Tolvaptan was associated with a significantly reduced incidence of fluid restriction.	Verbalis, Joseph G.; Adler, Suzanne; Schrier, Robert W.; Berl, Tomas; Zhao, Qiong; Czerwiec, Frank S.; SALT Investigators. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur. J. Endocrinol. 2011;164(5):725-732.	Adverse events were defined as any new medical problem or exacerbation of an existing medical problem according to the Medical Dictionary for Regulatory Activities (MedDRA, registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)).	As in primary outcome	Study population: hyponatraemia due to SIADH Overall comments: This is an extended analysis of SALT1 and SALT2 RCT trial where patients with SIADH were analysed separately for effectiveness and safety. A total of 448 patients received study medication in the original two SALT trials, 110 of whom had a primary diagnosis of SIADH derived by the investigator using standard clinical criteria. Of these 52 SIADH patients who were randomly assigned to oral tolvaptan other 58 SIADH subjects randomly assigned to oral placebo. In each treatment group, 42 patients completed the full 30-day treatment period. The results show that in patients with SIADH, improvement in serum [Na+] was significantly greater (P<0.0001) with tolvaptan than placebo over the first 4 days of therapy as well as the entire 30-day study, with minimal side effects of increased thirst, dry mouth, and urination. Only 5.9% of tolvaptan-treated patients had overly rapid correction of hyponatraemia as defined by current guidelines. After discontinuation of tolvaptan, serum [Na+] declined to values similar to placebo. A significant positive treatment effect favouring tolvaptan on the physical component, and a near significant trend on the mental component, was found using the SF-12 Health Survey. Tolvaptan was associated with a significantly reduced incidence of fluid restriction. This is well conducted trial with sound methodology including patient selection and ascertainment of outcomes. Some of the limitations is that the subgroup analysis may not be sufficiently powered to detect the difference as the sample size in original studies SALT 1 and SALT2 was based on studying tolvaptan for euvolemic and hypervolaemic conditions causing hyponatraemia. Secondly in the context of the research questions, nearly 50% of the SIADH had ‘marked’ hyponatraemia of Na=<130mmol/l so it is difficult to answer the research question relating cohort i.e. SAIDH with mild to moderate hyponatraemia who have failed on first line of treatment.

1+	RCT	Placebo=18, tolvaptan=19	Tolvaptan (15-60mg daily)	Clinical effectiveness of the intervention	Average daily sodium changes from baseline to day 4 and day 7	For the primary endpoints, average daily changes in serum sodium levels from baseline to day 4 were 1.9 2.9mmol/L (1.9 - 2.9mEq/L) in the placebo group and 8.1 3.6mmol/L (8.1 3.6mEq/L) in the tolvaptan group, and were 2.5 3.9mmol/L (2.5 3.9mEq/L) to day 7 for the placebo group and 8.6 3.9mmol/L (8.6 3.9mEq/L) for the tolvaptan group. The differences between the two groups were significant (ANCOVA, P<0.0001) both at days 4 and 7.	(1) Proportion of patients with normalised serum sodium levels at day 4 and day 7; (2) time to first normalisation of serum sodium levels; (3) change in serum sodium from baseline to days 4 and 7; (4) proportion of patients requiring further fluid restriction during study drug medication period; (5) 24-hour urine output and (6) proportion of patients with treatment failure who needed saline infusion or oral salt capsule to correct hyponatraemia during treatment.	(1) At days 4 and 7, daily urine output and proportions of patients with normalized serum sodium were significantly superior in the tolvaptan group. (2) Daily serum sodium levels showed that serum sodium levels increased in the tolvaptan group as early as 8 hours after the first dose and approached the normal range rapidly, but this trend was not observed in the placebo group. (3)The cumulative urine output at day 1 was greater for the tolvaptan group than that of the placebo group (P<0.001). (4) Two patients had treatment failure in the placebo group; there was no treatment failure in the tolvaptan group. (4) The numbers of patients requiring fluid restriction were 14 and 5 in the placebo and tolvaptan groups, respectively.	Chen, Shi; Zhao, Jia-Jun; Tong, Nan-Wei; Guo, Xiao-Hui; Qiu, Ming-Cai; Yang, Gang-Yi; Liu, Zhi-Min; Ma, Jian-Hua; Zhang, Zhen-Wen; Gu, Feng. Randomized, double blinded, placebo-controlled trial to evaluate the efficacy and safety of tolvaptan in Chinese patients with hyponatraemia caused by SIADH. J Clin Pharmacol 2014;54(12):1362-1367.	The incidence rates of adverse events (AEs) in the placebo and tolvaptan groups were 17 (70.8%) and 18 (85.7%), respectively. Six (25.0%) and 12 (57.1%) of them were considered as potentially related to the study drug by the investigators. The most common AEs occurring during the study in the tolvaptan group were dry mouth (42.9% in the tolvaptan group compared with 20.8% in the placebo group) and thirst. One serious AE occurred in tolvaptan group (death) and none in the placebo group.	As in primary and secondary outcomes	Study population: Hyponatraemia due to SIADH Overall comments: This is a double blinded RCT with good study methodology including randomisation, patient selection criteria, and statistical analysis. The results show the tolvaptan group had better outcomes for both primary and secondary end points but had higher rate of adverse events including one death which was not attributed to tolvaptan. However the study subjects were grouped as mild or marked hyponatraemia based on baseline sodium but there is no analysis of outcome results presented by these subgroups. The results the of the study are generalisable but due to lack of subgroup analysis cannot conclude effectiveness of tolvaptan by different level of severity of hyponatraemia. Also in terms of research questions, as the study subjects with demeclocycline were excluded from the study and water restriction was not initial treatment, the results can not answer the research question one.

2+	Cohort	111 patients of which 59 (53.2%) had SIADH	Tolvaptan (15mg initially and increased to 30mg or 60mg if patient continued to have hyponatraemia)	Safety of the intervention	Safety with long term tolvaptan	Not available by SIADH subgroup. (1) 64/111 patients withdrew from the study during the 214-week treatment period, 19 withdrew for a treatment-emergent adverse event (AE) of any cause. The AEs in six of these 19 patients subsequently resulted in death (cardiac failure [two patients], oesophageal varices, hepatic cirrhosis, cerebral haemorrhage, and gastrointestinal haemorrhage). The AEs in the remaining 13 patients led to discontinuation but not death (ventricular tachycardia, vertigo, gastrointestinal haemorrhage, vomiting, gait disturbance, irritability, serum creatinine increase, serum sodium increase, anorexia, bladder cancer, dysphasia, myocardial infarction, psychotic disorder, renal failure, and pruritus). An additional 13 patients died as an outcome of an AE without being withdrawn from the study as a result of the event (cardiac failure [three patients], renal failure [two patients], hepatorenal syndrome, cardiorespiratory arrest, cardiac arrest, pneumonia, cerebral haemorrhage, respiratory failure, sepsis, and urosepsis). Thus, a total of 19 patients died during the 212 patient-years of exposure: nine deaths per 100 patient-years of exposure. (2) 105 of 111 patients experienced an AE. AEs that occurred in >10% of patients (drug-related or unrelated) included peripheral oedema (25 patients), hyponatraemia (23 patients), anemia (20 patients), diarrhoea (19 patients), urinary tract infection (18 patients), nausea (17 patients), fatigue (15 patients), hypokalaemia (14 patients), headache (14 patients), ascites (13 patients), hypotension (13 patients), pneumonia (13 patients), cardiac failure (12 patients), thirst (12 patients), and dizziness (12 patients). (3) The most common AEs assessed by the investigator as being potentially related to tolvaptan use were pollakiuria (11 patients); thirst (10 patients); fatigue (six patients); and dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral oedema, and acute renal failure (four patients each).	Efficacy - Sodium level compared to baseline	Serum sodium measured according to severity of hyponatraemia and underlying cause. (1) The correction rate had similar kinetics for all groups, except a steeper initial response for the marked hyponatraemia subgroup. (2) Comparisons versus baseline were statistically significant ($P < 0.05$) for patients with mild hyponatraemia at all time points apart from week 214 and the follow-up visit; for patients with marked hyponatraemia at all visits apart from weeks 202 and 214. (3) Comparisons versus baseline were statistically significant ($P < 0.05$) for patients with congestive heart failure (CHF) at all time points but weeks 190, 202, and 214 and the follow-up visit; for patients with cirrhosis at 8 hours, day 31, weeks 10, 18, and 50, and the follow-up visit; and for patients with SIADH/other at all visits but week 214 and the follow-up visit.	Berl, Tomas; Quittnat-Pelletier, Friederike; Verbalis, Joseph G.; Schrier, Robert W.; Bichet, Daniel G.; Ouyang, John; Czerwiec, Frank S.; SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatraemia. J. Am. Soc. Nephrol. 2010;21(4):705-712.	As in primary outcome	As in secondary outcome	Study population: Patients who had hyponatraemia and completed the 30-day treatment phase and 7-day follow-up period in SALT1 and SALT2. Overall comments: SALTWATER is a 4-year sequential, open-label extension of the randomised, placebo-controlled, double-blind Study of Ascending Levels of Tolvaptan in Hyponatraemia (SALT1 and SALT2) and included 111 patients. The objective of SALTWATER was to assess whether tolvaptan maintained its safety and efficacy over a prolonged period in a substantial number of patients who had hyponatraemia and were treated with a flexible-dosage regimen. Of the 111 prospectively followed 52.3% had SIADH and others had hyponatraemia due to heart failure and cirrhosis. The results for the primary end point are not available by subgroups but presented for the whole group. Key points are: more than 90% (105/111) developed adverse events of which 52 (46.8) were drug related and 30 (27%) discontinued due to death (11) and adverse event (19). There is no subgroup analysis by SIADH and other causes of hyponatraemia or severity of hyponatraemia. Regarding efficacy, a secondary endpoint , in the SIADH group, the sodium level compared to baseline was significantly higher at different follow-up times except week 214 and subsequent follow-up. However, there is no information on how this improved sodium level correlated with improvement in patient related symptoms. Overall the results of the study are limited due to lack of comparator group and open label study leading to bias. It appears that there are very high number who develop side effects and high withdrawal from the study. From perspective of the research questions, the results are not available for the defined cohort except secondary end point, therefore it is not possible to extrapolate the results of primary endpoint to the cohort defined in the research questions and this study has therefore not been included in the evidence review.

3	Case series	61 patients	Tolvaptan 15mg as an initaiting dose	Clinical effectiveness of the intervention	Serum sodium correction at 24 and 48 hours after initiation of tolvaptan and at the end of treatment episode. For the purpose of evaluating the effectiveness of tolvaptan, response to treatment was defined as serum sodium increase by ≥5 mmol/l from baseline or serum sodium at the end of treatment episode >130 mmol/.	45 of 61 (73.7%) patients were under the care of medical specialities and 16 of 61 (26.3%) patients were under the care of surgical specialities. The aetiology of SIADH was malignancy (24.6%), unknown (24.6%), central nervous system (CNS) pathology/neurosurgery (16.4%), pulmonary illness (14.7%), drug-related (9.8%), postoperative (6.6%) and miscellaneous (3.3%). Hyponatraemia was newly diagnosed in 41 of 61 (67.2%) patients. The remaining 20 of 61 (32.8%) patients had hyponatraemia in the recent past as evidenced by at least one serum sodium value <135 mmol/l in the preceding 6 months. Tolvaptan was used as first-line agent in 9 of 61 cases (14.8%), as second-line in 37/61 patients (60.6%), or third-line treatment in 15/61 patients (24.6%) after failure of other therapeutic modalities including fluid restriction or demeclocycline. The mean serum sodium increase 24 hours after tolvaptan initiation was 9 ± 3.9 mmol/l. Excessive correction of hyponatraemia was observed in 23% of patients with all these patients having baseline serum sodium <125 mmol/l, but no cases of osmotic demyelination syndrome were recorded. The rate of overly rapid correction in patients under the care of medical specialities was 20.0% (9/45) vs 31.2% (5/16) in surgical patients. The difference was not statistically significant (P = 0.490). At the end of tolvaptan therapy, serum sodium increase was 13±5 5.9 mmol/l with 96.7% of patients having serum sodium increase ≥5 mmol/l in 48 hours. There was a negative significant correlation (P = 0.012) between baseline serum sodium and 24 hour change; for every 1 mmol/l reduction in baseline value, serum sodium increased by an additional 0.23 mmol/l (95% CI 0.05–0.41).	Serum sodium concentration 3 days and 5 days after tolvaptan withdrawal.	(1) Serum sodium decrease of ≥5 mmol/within first 5 days after discontinuation of tolvaptan was observed in 21 of 49 (42.8%) patients with half of these (11/21) patients being administered another course of tolvaptan as inpatients. (2) The inpatient mortality rate in this cohort was 8 2%. The mean length of hospital stay was 22.6 ± 17.2 days with serum sodium of 132 ±5.0 mmol/l at hospital discharge. A significant proportion of patients (17/56 or 30 3%) were discharged with serum sodium <130 mmol/l. In total, 20 of 56 (35 7%) patients were discharged on therapy for SIADH, including 11 patients on fluid restriction; 6 on tolvaptan (all of whom had SIADH due to malignancy); 3 on demeclocycline.	Tzoulis, Ploutarchos; Waung, Julian A.; Bagkeris, Emmanouil; Carr, Helen; Khoo, Bernard; Cohen, Mark; Bouloux, Pierre Marc. Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion. Clin. Endocrinol. (Oxf) 2015;0(0):0.	As in secondary outcome	As in primary outcome measures	Study population: All adult hospitalised patients with SIADH who met all essential diagnostic criteria for SIADH, including euvolaemia, hyponatraemia and low serum osmolality with inappropriately raised urine osmolality and sodium, normal adrenocortical reserve and exclusion of hypothyroidism. Overall comments: This is a retrospective case study of 64 patients with hyponatraemia due to SIADH and were treated with tolvaptan. The study included a good patient selection criteria with statistical methodology. The study showed that at the end of 48 hours, 96.7% had an increase of 9+/- 3.9 mmol in serum sodium. Excessive correction was noted in 23% cases. Mortality rate was 8.2% with 22.6 days of hospital stay. Nearly 30% were discharged with hyponatraemia (Na <130 mmol/l). This study describes the situation in a day-to-day practice but has a number of limitation for wider generalisability including; a lack of comparator group, retrospective case selection and data extraction, lack of specific protocol for initiation and withdrawal of treatment as recognised by the authors. We also do not know the outcomes in many with SIADH who may not have treatment with tolvaptan and reasons for the same which bias the results.

3	Other	1.597 patients with SIADH	No treatment, fluid restriction, normal saline, tolvaptan, withdrawal of SIADH causing medications	Clinical effectiveness of the intervention	Achieving correction benchmarks for sodium concentration including Na+≥130 mEq/L, Na+ >5mEq/L, Na+>135 mEq/l.	Only 47% of patients with SIADH as identified by treating physicians had all three cardinal tests performed, and 11% underwent none. The full diagnostic criteria include normal thyroid and adrenal function, but only 21% of identified SIADH patients underwent cortisol and thyroid hormone determinations, along with the required electrolyte and osmolality measurements. With regard to treatment, 11% of SIADH patients did not receive specific therapy, while 30% had one treatment episode and 59% has two treatment episodes. The most common modes of treatment for SIADH were fluid restriction (26%), Normal saline (23%), combination of fluid restriction and normal saline (7%). 7% of the SIADH patients received tolvaptan. In terms of achieving correction bench marks for sodium, 57% of SIADH patients achieved Na>130mEq/L, 69% achieved a raise of Na ≥5 mEq/L and 25% achieved Na >135 mEq/L at the end of initial therapy episode. Outcomes of tolvaptan treatment in SIADH patients are not reported separately but are available for for the whole cohort including 1,490 patients with hypovolemic hypernatremia (CHF and cirrhosis) and 1,597 patients with euvolemic hyponatraemia. The results show that after adjustment for baseline sodium using logistic regression, tolvaptan was consistently better compared with fluid restriction in achieving all of the pre-specified sodium correction benchmarks, but using tolvaptan was also associated with rapid increase in sodium concentration and therefore risk of osmotic demyelination syndrome.	None	None	Greenberg, Arthur; Verbalis, Joseph G.; Amin, Alpesh N.; Burst, Volker R.; Chiodo, Joseph A.; Chiong, Jun R.; Dasta, Joseph F.; Friend, Keith E.; Hauptman, Paul J.; Peri, Alessandro; Sigal, Samuel H.. Current treatment practice and outcomes. Report of the hyponatraemia registry. Kidney Int. 2015;88(1):167-177.	one reported	As in primary outcome	Strudy population: Hyponatraemia due to SIADH Overall comments: This is a retrospective study of patients treated for hyponatraemia of various causes that were included in a large sized registry based in the USA and Europe. The study includes very limited information with regard to SIADH and use of tolvaptan in SIADH. The study shows that there is very poor methodology for diagnosis of SIADH. Only 47% of patients with SIADH as identified by treating physicians had all three cardinal tests performed, and 11% underwent none. The full diagnostic criteria include normal thyroid and adrenal function, but only 21% of identified SIADH patients underwent cortisol and thyroid hormone determinations, along with the required electrolyte and osmolality measurements. With regard to treatment 11% of SIADH patients did not receive specific therapy while 30% had one treatment episode and 59% has two treatment episodes. The most common modes of treatment for SIADH were fluid restriction (26%), Normal saline (23%), combination of fluid restriction and normal saline (7%). 7% of the SIADH pateints received tolvaptan however outcomes of tolvaptan treatment in SIADH patients are not reported separately but are available for the whole cohort including 1,490 patients with hypovolemic hypernatremia (CHF and cirrhosis) and 1,597 patients euvolemic hyponatraemia. The results show that after adjustment for baseline sodium using logistic regression, tolvaptan was consistently better compared with fluid restriction in achieving all of the pre-specified sodium correction benchmarks, but using tolvaptan was also associated with rapid increase sodium concentration and therefore risk of osmotic demyelination syndrome. So in summary although tolvaptan appears to achieve better outcomes other modes of treatment including fluid restriction and normal saline, as there is no subgroup analysis of tolvaptan in SIADH patients, this study offers very limited information to answer research questions.

3	Other	182 HIV pateints with persistent hyponatraemia. Of which 9 with persistent hyponatraemia were treated with tolvaptan (6 euvolumic hyponatraemia and 3 with hypervolemic hyponatraemia).	Tolvaptan in 9 patients with persistent hyponatraemia (6 euvolaemic and 3 hypervolaemic).	Clinical effectiveness of the intervention	Increased in [Na]	Of the 6 euvolaemic patients treated with tolvaptan 15 mg, all achieved raised serum sodium concentrations. However there is no information on the normal level achieved nor the time when the raised level was achieved.	None	None	Wen, Ying; Zhou, Ying; Wang, Wen; Wang, Yu; Lu, Xu; Sun, CuiMing; Liu, Pei. Characteristics of persistent hyponatraemia and tolvaptan treatment in nine hospitalized patients with advanced HIV disease. HIV Clin Trials 2014;15(3):126-132.	None reported	As in primary outcome	Study population: HIV patients with hyponatraemia Overall comments: This is a prospective study of outcomes of treatment of hyponatraemia in 69 HIV patients. All causes of hyponatraemia were included. 9 patients (6 euvolaemic and 3 hypevolaemic) were treated with tolvaptan for persistent hyponatraemia. The paper report that all achived rise in sodium concentration but there is poor reporting on the level, time period and sodium concentration at the end of treatment phase. The geralisability of results is limited due to non-random patient selection, and poor reporting on small number of patients who were treated with tolvaptan.
3	Case series	13 patients of which 8 patients had SIADH	Tolvaptan 15mg	Clinical effectiveness of the intervention	Post tolvaptan serum sodium level, urine osmality, and arginine vasopressin (AVP)	All patients had an increase in serum]Na] from 122.5 ± 4.2 to 128.9 ± 4.1 mEq/L (P < 0.05). The mean increase in serum [Na] of 6.4 mEq/L (range 2-10 mEq/L) 24 hours post-tolvaptan was not different in the two groups of patients, but SIADH patients had higher pre and post-tolvaptan serum sodium levels than CHF patients. Urine osmolalities (UOsm) decreased in all patients, and the patients with SIADH had significantly higher baseline UOsm and a larger decrease in UOsm 12 hours post-tolvaptan administration when compared with the CHF patients. AVP levels did not change post-tolvaptan administration. However, the magnitude of increase in serum sodium levels was inversely related to pre-tolvaptan AVP levels in the SIADH subgroup (r = -0.7, P = 0.01). Three SIADH patients received small amounts of dextrose solution (D5W) to attenuate changes in serum sodium. No significant changes in mean arterial pressure, serum potassium, serum glucose, and blood urea nitrogen or serum creatinine were observed.	None	0	Vaghasiya, Rick P.; DeVita, Maria V.; Michelis, Michael F.. Serum and urine responses to the aquaretic agent tolvaptan in hospitalized hyponatremic patients. Int Urol Nephrol 2012;44(3):865-871.	None mentioned in abstract	As in primary outcome	Study population: Hyponatraemia due to SIADH Overall comments: This is small sized case series of 13 patients with hyponatraemia of whom 8 had diagnosis of SIADH. The results showed that that all patient had an increase in the serum sodium concentration from baseline of 6meq/l 24 hours post tolvaptan. Similarly patients with SIADH showed decreases in urine osmolality due to natriuretic effects of tolvaptan and no difference in AVP levels. The generalisation of study results are limited due to the small number, retrospective case selection and lack of comparator group for SIADH patients with placebo or other alternate treatment for SIADH induced hyponatraemia.

0	Other	N/a	Tolvaptan 15-30mg	Cost effectiveness	Potential cost savings associated with the use of tolvaptan in patients with the SIADH based on the SALT1 and SALT2 trials based on a economic cost-offset model.	N/a	None	None	Dasta, Joseph F.; Chiong, Jun R.; Christian, Rudell; Lin, Jay. Evaluation of costs associated with tolvaptan-mediated hospital length of stay reduction among US patients with the syndrome of inappropriate antidiuretic hormone secretion, based on SALT-1 and SALT-2 trials. Hosp Pract (1995) 2012;40(1):41821.	N/a	N/a	Study population: Hyponatraemia due to SIADH Overall comments: This is a cost effectiveness study based on a cost offset model. The primary objective of this study was to evaluate the potential hospital cost savings associated with tolvaptan usage among patients with the SIADH based on the SALT1 and SALT2 trials by constructing a cost-offset model to evaluate the impact of tolvaptan on hospital resource usage, mainly the length of stay (LOS) among patients with the SIADH. The analysis was conducted from the perspective of hospitals in the United States (currency converted for this review) and the total number of patients admitted with SIADH was obtained from Nationwide Inpatient Sample (NIS). The hospital Costs and LOS associated with SIADH was collected from The Healthcare Cost and Utilization Project (HCUP) database for adult (age >18 years) patients with a primary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for the SIADH of 253.6. The estimates for effectiveness were based on SALT1 and SALT 2 results in which the SIADH sub-population had a significant estimated improvement in serum sodium concentration of 5.28 ± 3.35 mEq/L by the fourth day such that 60% of patients with the SIADH receiving tolvaptan had normalized serum sodium levels, in comparison with 11.5% of patients receiving placebo. The mean hospital LOS in tolvaptan was lower by 1.21 (not statistically significant). LOS in tolvaptan (n = 52) was 4.98 ± 6.61 days compared to 6.19 ± 7.89 days in patients who received a placebo (n = 58). The relative difference in LOS due to tolvaptan usage in the SALT1 and SAL-2 trials was 19.5%. Sensitivity analyses were performed as components of the economic model to evaluate the range of the potential cost reduction associated with tolvaptan due to variation in the estimated model parameters. To determine the upper and lower bounds of the cost-offset estimate, each of the following variables was individually evaluated and allowed to vary by ± 20%: hospitalisation cost per day, LOS for SIADH related hospitalizations, duration of tolvaptan usage, daily cost of tolvaptan, and the relative tolvaptan-associated LOS reduction. Results: A total of 21,718 adult patients hospitalised with a primary diagnosis of the SIADH were identified from the HCUP 2009 NIS database and had a mean LOS of 5.7 days and mean total hospital costs of £5,801. Based on

													the estimated 19.5% relative reduction in LOS demonstrated by the sub analysis of the SALT1 and SALT2 trial patients, the tolvaptan-mediated reduction in total hospital costs among HCUP patients with SIADH was £1,133.97 per admission. After taking into account the £669.32 as the costs of tolvaptan for four days (£167.33 per day), the cost offset was £464.51 per hospitalisation and £10,039,824 for HCUP SIADH population. In sensitivity analysis, among the variables tested, hospitalisation cost per day, LOS for SIADH-related hospitalisations, and the tolvaptan-associated LOS reduction had a higher impact on the total cost offset estimate (£224–£691). Variations of duration of tolvaptan use and daily cost of tolvaptan had a smaller impact on the estimate of total cost offset (£330 to £598). The Monte Carlo simulation showed the mean total cost offset was £463.84 ± £2.26 and the 95% CI for the total cost-offset reduction to be £48.65 to £940.36. The main limitation of the study in relation to our research questions are: (1) Cost analysis from the perspective of hospitals in the USA. (2) The number of SIADH patients is based on estimation from a insurance based database and we know from studies the practise of diagnosis of SIADH in inconsistent and therefore the number estimated could be an underestimate or an overestimate. It is not cleat from the paper if this particular variable was part of the sensitivity analysis. (3) Our research focus is mainly on mild and moderate SIADH, however nearly 50% SIADH patients in SALT1 and SALT2, the two studies which are used in economic model, had nearly 50% of patients with marked hyponatremia defined as Na+<130 mmol/l. So generalising these results to our research population is limited.

3	Case series	14 patients with 15 episodes of hospital admission.	Tolvaptan 15-30mg	Clinical effectiveness of the intervention	Change in serum sodium from baseline to cessation of tolvaptan therapy.	Fourteen patients were treated with tolvaptan. There were eight women and six men (mean age 72 ±16 (mean ± standard deviation), range 36 to 90 years) with a mean BMI of 24.9 ± 8.67, 13.9 to 46.4 kg/m2. On admission to hospital, hyponatraemia was present in all 15 episodes, whilst severe hyponatraemia (serum sodium < 125 mmol/L) was present in 12/15 episodes (80%). The initial therapy for 12 episodes was fluid restriction to one litre (mean duration 5.9 ± 3.1, 2-12 days) prior to commencement of tolvaptan. Demeclocycline was used in two episodes in conjunction with fluid restriction, and once without any fluid restriction, prior to tolvaptan therapy. One patient had been treated with 100 mL of 3% hypertonic saline infusion once, three days prior to tolvaptan therapy. Tolvaptan was initiated when conventional methods were considered to be ineffective and fluid restriction was discontinued when tolvaptan therapy was commenced. The median duration of tolvaptan therapy in the 15 episodes was 3 days (1 to 21 days): 15mg of tolvaptan was used in 14 episodes with no dose changes, while 30mg of tolvaptan was used in one episode in a patient who had previously been treated with 15mg of tolvaptan and was readmitted with hyponatraemia. There was a significant rise in serum sodium level before (mean sodium 120.1 ± 4.6, 108-126 mmol/L) and after (mean sodium 131.9 ± 3.6, 125-139 mmol/L, P<0.0001) tolvaptan therapy. The maximum rate of change of sodium was observed in the first 24 hours of therapy (mean 6.7 ± 2.8, 1-11 mmol/L). One patient developed acute severe hyponatraemia (serum sodium <120 mmol/L) following vigorous large volume fluid resuscitation for acute renal impairment. In no patient did the rate of change in serum sodium rise exceed 12 mmol/L in 24 hours and/or 18 mmol/L in 48 hours at any point whilst on tolvaptan, a rate of change above which osmotic demyelination syndrome is a risk. The mean length of stay for the 14 episodes (excluding one episode where the patient died as an inpatient on the 27th day of admission) was 25.4 ± 12.3 (12-48 days).	None	None	Rajendran, Rajesh; Grossman, Ashley B.; Kar, Partha. Vasopressin receptor antagonist in the treatment of the syndrome of inappropriate antidiuretic hormone in general hospital practice. Endocr. J. 2012;59(10):903-909.	One death and paper does not report an anlaysis of adverse reactions.	As in primary outcome	Study population: Hyponatraemia due to SIADH. Overall comments: This is retrospective case series of 14 patients (15 episodes) treated with tolvaptan for SIADH related hyponatraemia. All patients were identified and treated as per hospital protocol and all patients met the diagnostic criteria for SIADH except one. Data were extracted retrospectively from computer records but it is unclear if the investigator were blind to the study objective. The majority of patients had severe hyponatraemia (80%) and were treated with fluid restriction and two patients with demeclocycline. Tolvaptan was initiated when conventional methods were considered to be ineffective. Following treatment with tolvaptan there was a significant rise in serum sodium level before (mean sodium 120.1 ± 4.6, 108-126 mmol/L) and after (mean sodium 131.9 ± 3.6, 125-139 mmol/L, P<0.0001) tolvaptan therapy. The maximum rate of change of sodium was observed in the first 24 hours of therapy (mean 6.7 ± 2.8, 1-11 mmol/L). Although the patient selection was based on an agreed criteria the study has some limitaions including; retrospective nature of case selection, lack of comparator group to estimate size of benefit, lack of information on blinding of the investigator to the study objective and no correlation of improvement in symptoms and sign and improved sodium concentration. Most importantly from the contect of research question, as the majority of patients in this study had severe hyponatraemia (80%), the application of the results to the research questions are limited.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
Updated search terms - Population	Hyponatraemia Hyponatremia SIADH ADH Syndrome, Inappropriate Syndrome, Inappropriate ADH Syndrome of Inappropriate ADH (SIADH) Secretion Schwartz-Bartter Syndrome Schwartz Bartter Syndrome Inappropriate Vasopressin Secretion Syndrome
Updated search terms - Intervention	Tolvaptan Samsca Vasopressin receptor antagonist V2 receptor antagonist Vasopressin receptor antagonists V2 receptor antagonists
Updated search terms - Comparator	Fluid restriction Demeclocycline
Updated search terms - Outcome	N/a

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	N/a
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist)
	Specific exclusion criteria
	N/a