NCGC National Clinical Guideline Centre

Final guidance

Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease

Clinical Guideline 148

Methods, evidence and recommendations

August 2012

FINAL VERSION

Commissioned by the National Institute for Health and Clinical Excellence

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Update information

October 2023: We updated the recommendation on suspected cancer pathway referral for possible bladder cancer in line with NHS England's standard on faster diagnosis of cancer. People should have a diagnosis or ruling out of cancer within 28 days of referral.

Minor changes since publication

December 2024: We added links to relevant technology appraisal guidance in the section on pharmacological treatments. This is to provide easy access to relevant guidance at the right point in the guideline only and is not a change in practice.

November 2021: We added a link to NICE's shared decision making guideline in recommendation 1.2.4. We incorporated footnote text into the recommendations to meet accessibility requirements.

See https://www.nice.org.uk/guidance/cg148 for all current recommendations and the evidence behind them.

Published by the National Clinical Guideline Centre at
The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT

First published August 2012

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Acknowledgments

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1 Acronyms and abbreviations

FCC	Family Centred Care
CIC	Clean intermittent catheterisation
SCI	Spinal Cord Injury
UTI	Urinary Tract Infection
LUT	Lower urinary tract
NLUTD	Neurogenic lower urinary tract dysfunction
VUR	vesicoureteral reflux
EDSS	Expanded Disability Status Scale
EMG	Electomyography
NMES	Neuromusclar electrical stimulation
PFTA	pelvic floor training and advice
PFMT	Pelvic floor muscle training

2 Introduction

The lower urinary tract (LUT) consists of the urinary bladder and the urethra. Its function is to store and expel urine in a coordinated and controlled manner. The storage phase of the micturition cycle is characterised by the muscle of the bladder wall (the detrusor) remaining relaxed while the urethral sphincters are contracted strongly enough to prevent urinary incontinence. Conversely, during bladder emptying, the detrusor contracts and the urethral sphincters relax.

The central and peripheral nervous systems regulate this activity. Sensory nerves carry information from the bladder, urethra and pelvic floor to the spinal cord with the key sensory input passing into the sacral segments (the conus medullaris). Messages are relayed to the brainstem and are then distributed widely to other areas of the brain. These brain centres are involved in processing information about the bladder and urethra and entering urinary tract sensation into consciousness. Higher brain centres control activity in the brainstem centres that coordinate the reflexes that regulate urine storage and voiding. The brainstem centres send impulses down the spinal cord to the micturition centres in the sacral spinal cord from where nerves pass to the muscle of the bladder wall and urethral sphincters.

Therefore, it is apparent that while voluntary control over LUT function is reliant on higher level functioning in the brain, the function of the lower urinary tract is also dependent on there being intact neural pathways, which not only travel the length of the spinal cord but also run in peripheral nerves to and from the bladder and urethra. Because control over urine storage and voiding is complex, and is dependent on neurological elements that are widely distributed in anatomical terms, the function of the lower urinary tract can be affected by a wide range of neurological diseases.

Urinary symptoms can arise due to neurological disease in the brain, the suprasacral spinal cord, the sacral spinal cord (the conus medullaris) or the peripheral nervous system. Damage within each of these areas of the neuroaxis tends to produce characteristic patterns of bladder and sphincter dysfunction (see table 1). Table 1: Lower urinary tract dysfunctions that can be seen with damage at different levels within the nervous system.

Table 1: Lower urinary tract dysfunctions that can be seen with damage at different levels within the nervous system.

	Bladder function	Sphincter function
Brain conditions	Overactive (neurogenic detrusor overactivity) – more common. Underactive – less common.	Usually normal. Coordinated with bladder function.
Suprasacral spinal cord conditions	Overactive (neurogenic detrusor overactivity).	Uncoordinated with bladder function in some cases (detrusor sphincter dyssynergia).
Sacral spinal cord or peripheral nerve conditions	Underactive. Impaired bladder compliance in some cases.	Underactive.

Note: The table provides an overview of typical patterns of neurogenic lower urinary tract dysfunction. Individual patients will exhibit a pattern of dysfunction which is dependent on the site and severity of the neurological damage. The effect of neurological damage on urinary tract sensation is variable; sensation may be absent (e.g. in complete spinal cord injury), impaired or preserved.

The nature of the insult to the nervous system is also relevant. In the paediatric population the neurological damage is often the result of congenital and perinatal defects such as cerebral palsy, spina bifida (myelomeningocoele) or sacral agenesis. It is also possible to distinguish between conditions that produce a fixed or stable insult to the nervous system (for example stroke, spinal cord injury and cauda equina compression) and those that produce progressive damage through processes that might be inflammatory or degenerative. Examples of progressive conditions include the dementias, Parkinson's disease, multiple sclerosis and peripheral neuropathy (see table 2).

Table 2: Examples of neurological conditions that can affect lower urinary tract function

	Congenital and perinatal lesions	Acquired, stable conditions	Acquired, progressive or degenerative conditions
Brain conditions	Cerebral palsy	Stroke Head injury	Multiple sclerosis Parkinson's disease Dementias
Suprasacral spinal cord conditions	Spinal dysraphism (e.g.myelomeningocoele)	Spinal cord injury	Multiple sclerosis Cervical spondylosis with myelopathy
Sacral spinal cord or peripheral nerve conditions	Spinal dysraphism (e.g. myelomeningocoele) Sacral agenesis Ano-rectal anomalies	Cauda equina syndrome Spinal cord injury Peripheral nerve injury from radical pelvic surgery	Peripheral neuropathy.

Given that such a wide range of neurological conditions can impact on the function of the LUT, it is not surprising that the subsequent urinary dysfunction is variable. Some patients with neurogenic lower urinary tract dysfunction (NLUTD) experience symptoms which relate to impaired urine storage, such as increased frequency of micturition (by day and/or night), urinary urgency and urinary incontinence. Bladder emptying will be a problem for other individuals; voiding symptoms include hesitancy, a slow urinary stream, the need to strain and urinary retention. Storage and voiding problems may also arise in combination.

Urinary tract symptoms have a significant impact on quality of life. For example they can cause embarrassment, lead to social isolation and impair activities of daily living. One of the most distressing symptoms that arises from NLUTD is urinary incontinence. The severity and nature of neurological incontinence is dependent on many factors, including the site, the extent and the evolution of the neurological lesion. Incontinence can arise as a result of overactivity of the bladder,

dysfunction of the urethral sphincters or a combination of the two. Although incontinence is much more prevalent in the neurological, as opposed to general, population, the prevalence of incontinence in the neuropathic population is not well established and data on this question is difficult to obtain.

There are also secondary effects that can arise as a result of dysfunction of the LUT. There is a markedly increased risk of urinary tract infection in patients with NLUTD. The morbidity associated with recurrent urinary tract infections can be severe. NLUTD can have further important impacts beyond the difficulty presented by overt symptoms. For example, kidney function can be lost as a result of abnormally high pressures within the bladder, from the effects of urinary tract infection and as a result of urinary tract stone disease. It has long been established that conditions such as spinal cord injury and spina bifida are associated with a high risk of renal complications. However, there are considerable difficulties when trying to estimate the risk of renal deterioration in the individual patient, despite the improved appreciation of pathophysiology which has accompanied the introduction of urodynamic investigations into clinical practice. Historically, conditions such as spinal cord injury were associated with very low life expectancy, which was partly due to the high incidence of renal failure, but urinary tract sepsis also contributed to the premature death.

It is also frequently the case that medical interventions do not restore normal urinary function. Quality of life is affected by the medical management regime which is used to treat the NLUTD; many patients will have to cope with the side effects of medication, the social and psychological consequences of using intermittent self-catheterisation, the impact of indwelling catheterisation or the continuing use of pads or appliances.

The impact of urinary symptoms and the management regime that is put in place will fall on both the patient and their carers. There is therefore a risk that carers' quality of life can also be adversely affected by NLUTD; there may be issues in relation to the physical demands of looking after the urinary tract needs of a disabled person, as well as psychological, relationship and social pressures.

There are often a number of possible treatment strategies available to an individual patient. A comprehensive review of the benefits and risks of different management strategies, in both the short and long term, is required in order to inform patients and carers when they are faced with making decisions regarding treatment options. Meeting the requirements for informed consent presents particular challenges when treating patients with NLUTD. The issues involved can be complex and some patients will have a cognitive impairment which will impact on their ability to understand, retain and process information. There is a need for clinical teams to have access to decision tools that help patients who are faced with a choice between different treatment options.

It is apparent that the selection of a management strategy for an individual patient should involve the patient, carers and the clinical team and will involve consideration of a wide range of issues. The agreed treatment regime will have to meet the dual requirements of patient and carer acceptability and be associated with satisfactory clinical outcomes. Because of the proximity of the neurological centres controlling bowel and sexual functions to those involved in LUT function, many patients with neurological disease will have a combination of urinary, bowel and sexual dysfunction. The clinical team should not treat LUT problems in isolation but should address associated problems in other systems using a holistic approach.

A diverse range of interventions are used in the management of NLUTD and there is considerable variation in clinical practice. Furthermore, access to supplies of aids and to specialist advice and services lacks uniformity. The need to improve integration and expertise in continence services within the NHS has been recognised for many years and these requirements clearly extend into the field of neurogenic incontinence. People can be managed in a variety of different settings ranging from the community to specialist surgical services so that the integration between community, primary care and secondary/tertiary hospital services is of great importance. The transition from paediatric to adult services requires particularly careful management.

The economic cost of managing NLUTD is considerable. There are major costs associated with containment products, the use of drug treatments and surgical interventions. There is also a further huge financial impact as a result of patient requirements for carer, nursing and medical support. The ability of an individual to work can be affected by their NLUTD which has an obvious financial impact for the individual and for society in general. Further significant expenditure is associated with the follow up of patients, some of whom are placed on long-term urinary tract surveillance.

3 Development of the guideline

3.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- the quick reference guide (QRG) presents recommendations in a suitable format for health professionals
- information for the public ('understanding NICE guidance' or UNG) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

3.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

To produce a clinical guideline on the management of incontinence in neurological disease in all ages.

3.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Mr. Simon Harrison in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every five weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted Meta analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

3.4 What this guideline covers

The guideline covers adults and children (from birth) with lower urinary tract dysfunction resulting from neurological disease or injury.

The clinical areas covered included:

- Assessment of lower urinary tract function and criteria for referral to specialist assessment.
- Physical interventions to aid urinary storage including behaviour and bladder training, pelvic floor muscle exercises and neuromuscular stimulation.
- Pharmacological therapies to aid urinary storage and surgical procedures to treat incontinence and improve bladder storage capacity.
- Physical aids and drug therapy to improve bladder emptying.
- Urinary diversion procedures
- Appliances and equipment to contain urinary incontinence

For further details please refer to the scope in Appendix A [and review questions in section 4.1].

3.5 What this guideline does not cover

The guideline did not consider general management of the underlying disorder, management of associated faecal incontinence, sexual dysfunction or psychological problems, or management of comorbidities.

3.6 Relationships between the guideline and other NICE guidance

Delete sections if not applicable to your guideline.

NICE Clinical Guidelines to be updated by this guidance:

Multiple sclerosis. NICE clinical guideline 8 (2003). Available from www.nice.org.uk/guidance/CG8

Related NICE Interventional Procedures:

Laparoscopic augmentation cystoplasty (including clam cystoplasty). NICE interventional procedure guidance 326 (2009). Available from www.nice.org.uk/guidance/IPG326

Single-incision sub-urethral short tape insertion for stress urinary incontinence in women. NICE interventional procedure guidance 262 (2008). Available from www.nice.org.uk/guidance/IPG262

Suburethral synthetic sling insertion for stress urinary incontinence in men. NICE interventional procedure guidance 256 (2008). Available from www.nice.org.uk/guidance/IPG256

Insertion of extra urethral (non-circumferential) retropubic adjustable compression devices for stress urinary incontinence in men. NICE interventional procedure guidance 224 (2007). Available from www.nice.org.uk/guidance/IPG224

Insertion of biological slings for stress urinary incontinence. NICE interventional procedure guidance 174 (2006). Available from www.nice.org.uk/guidance/IPG154

Intramural urethral bulking procedures for stress urinary incontinence. NICE interventional procedures guidance 138 (2005). Available from www.nice.org.uk/guidance/IPG138

Insertion of extra urethral (non-circumferential) retropubic adjustable compression devices for stress urinary incontinence in women. NICE interventional procedure guidance 133 (2005). Available from www.nice.org.uk/guidance/IPG133

Transobturator foramen procedures for stress urinary incontinence. NICE interventional procedure guidance 107 (2005). Available from www.nice.org/guidance/IPG107

Sacral nerve stimulation for urge incontinence and urgency-frequency. NICE interventional procedure guidance 82 (2004). Available from www.nice.org.uk/guidance/IPG82

Percutaneous posterior tibial nerve stimulation for overactive bladder syndrome. NICE interventional procedure guidance. Publication expected Autumn 2010.

Related NICE Clinical Guidelines:

Constipation in children and young people. NICE clinical guideline 99 (2010). Available from www.nice.org.uk/guidance/CG99

Male lower urinary tract symptoms. NICE clinical guideline 97 (2010). Available from www.nice.org.uk/guidance/CG97

Chronic kidney disease. NICE clinical guideline 73 (2008). Available from www.nice.org.uk/CG73

Urinary tract infection in children. NICE clinical guideline 54 (2007). Available from www.nice.org.uk/guidance/CG54

Faecal incontinence. NICE clinical guideline 49 (2007). Available from www.nice.org.uk/guidance/CG49

Dementia. NICE clinical guideline 42 (2006). Available from www.nice.org.uk/guidance/CG42

Parkinson's disease. NICE clinical guideline 35 (2006). Available from www.nice.org.uk/guidance/CG35

Urinary incontinence. NICE clinical guideline 40 (2006). Available from www.nice.org.uk/guidance/CG40

Nocturnal enuresis in children (bedwetting). NICE clinical guideline 111 (2010). Available from www.nice.org.uk/guidance/CG111

Patient experience in adult NHS services. NICE clinical guideline 138 (2012). Available from: http://guidance.nice.org.uk/CG138

Infection: prevention and control of healthcare-associated infections in primary and community care. NICE clinical guideline 139 (2012). Available from: http://guidance.nice.org.uk/CG139

NICE Related Guidance currently in development:

Spasticity in children. NICE clinical guideline. Publication expected July 2012.

Urinary Incontinence in Women. NICE clinical guideline. Publication expected July 2013.

Chronic kidney disease (update). Publication date to be confirmed.

4 Methods

This chapter sets out in detail the methods used to generate the recommendations that are presented in the subsequent chapter. This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009 [1].

4.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). The question 'What criteria of signs/symptoms should be used to refer patients for specialist assessment?' was based GDG expert opinion and no literature search was performed. The questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). The outcomes are presented according to importance (of improving patient outcomes or minimising harm). Further information on the outcome measures examined follows this section.

Chapter	Review questions	Outcomes
1	Does the use of clinical assessment, urine culture, a residual urine estimate or a bladder diary/frequency volume chart change the management of patients with neurological disease?	• Change in outcomes
1	Does the use of urodynamics (filling cystometry, leak point pressure measurements, pressure-flow studies of voiding, video urodynamics) direct treatment or stratify risk of renal complications (such as hydronephrosis)	• Direct treatment • Stratify risk
2	Do behavioural management programmes (timed voiding, voiding on request, prompted voiding, bladder retraining, habit retraining, urotherapy) compared with a) each other b) usual care, improve outcomes?	• Frequency of voiding by day and night • No. of incontinence episodes per week • Patient and carer perception of symptoms • Quality of life • Treatment adherence • Adverse events
2	What is the safety and efficacy of antimuscarinics compared with a) placebo or treatment as usual b) other antimuscarinics for the treatment of incontinence due to neurological disease/ overactive bladder due to neurological disease?	• Quality of life. • Frequency of voiding by day and night. • Number of incontinence episodes per week. • Maximum cystometric capacity • Bladder compliance • Residual urine Patients and carers' perception of symptoms. • Kidney function (hydronephrosis) • Adverse events, including urinary tract infections, renal complications and unscheduled hospital admissions. • Treatment adherence

Chapter	Review questions	Outcomes
2	What is the safety and efficacy of detrusor injections of botulinum toxin type A or B compared with a) usual care b) antimuscarinics c) augmentation cystoplasty in neurological disease?	• Quality of life • Frequency of voiding by day and night. • Number of incontinence episodes • Urgency • Increased bladder capacity • Residual urine • Kidney function • Adverse events, including urinary tract infections, unscheduled hospital admissions, generalised muscle weakness • Treatment continuance
2	What is the safety and efficacy of augmentation cystoplasty compared with a) botulinum toxin b) usual care in neurological disease c) urinary diversion?	• Incontinence level • The need for intermittent catheterisation • Quality of life / patient or carer perception of symptoms • Adverse events, including UTIs, renal complications, bladder stones, metabolic complications, cancer and unscheduled hospital admissions. • Bladder capacity and detrusor pressures
3	Does pelvic floor muscle training with or without electrical stimulation or biofeedback compared with treatment as usual, improve outcomes?	• Frequency of voiding by day and night • No. of incontinence episodes per week • Quality of life • Maximum cystometric capacity • Residual urine • Treatment adherence
3	What is the safety and efficacy of urethral tape and sling surgery compared with a) bladder neck closure b) usual care in neurological disease?	• Number of incontinence episodes per week. • Severity of incontinence. • Symptoms relating to bladder emptying, for example poor urinary stream, need for intermittent catheterisation. • Quality of life. • Patients and carers' perception of symptoms. • Adverse events, including urinary tract infections, renal complications, bladder stones and unscheduled hospital admissions. • Damage caused by catheterisation
3	What is the safety and efficacy of artificial urinary sphincters compared with usual care in neurological disease?	• Incontinence level – frequency and severity • Symptoms relating to bladder emptying • Quality of life / patient or carer perception of symptoms • Adverse events, including UTIs, renal complications, bladder stones, infection of prosthesis, device failure and unscheduled hospital admissions.
4	What is the safety and efficacy of alpha blockers compared with a) other adrenergic antagonists b) placebo/usual care for the treatment of	• Quality of life • Frequency of voiding by day and night

Chapter	Review questions	Outcomes
	incontinence due to neurological disease?	• Urgency • Symptoms relating to bladder emptying, for example poor urinary stream • Q-max (maximum flow rate) • Residual urine volume • Adverse events, including postural hypotension and other unscheduled hospital admissions. • Treatment adherence
5	Do prophylactic antibiotics compared with a) no treatment b) other antibiotics reduce the risk of symptomatic urinary tract infections?	• Symptomatic urinary tract infections (UTIs) • Adverse events
6	What are the long term risks associated with the long term use of intermittent catheterisation, indwelling catheters and penile sheaths?	• Quality of life • Long term risks as specified in question • Include kidney, bladder and renal stones (urolithiasis, renal lithiasis and nephrolithiasis) • Cystolithiasis • Pyelonephritis
6	What is the safety and efficacy of the catheter valve compared with urinary drainage bags in neurological disease?	• No. of incontinence episodes per week • Patient and carer perception of symptoms • Quality of life • Kidney function (hydronephrosis) • Treatment adherence • Adverse events (UTI, catheter blockage) • Successful trial without a catheter
6	What is the efficacy of the ileal conduit diversion compared with usual care in neurological disease?	• Quality of life • Patient or carers' perception of symptoms • Adverse events, including urinary tract infections, renal complications, pyocystis, complications with the stoma (e.g. parastomal hernia) and unscheduled hospital admissions.
7	Does monitoring or do surveillance protocols improve patient outcomes?	• Quality of life • Kidney function • Renal impairment (hydronephrosis, urinary tract stones, urinary tract infection, malignancy (bladder cancer) • Unplanned hospital admissions
8	What interventions or configuration of services improve outcomes when a patient is transferred from child to adult services?	• Patient Experience • Quality of Life • Morbidity (renal impairment, incontinence, urinary tract infections) • Continuity of Care • Readmission to hospital
8	For patients and their carers with lower urinary tract dysfunction associated with neurological disorders, what are the experiences of access to and interaction with services that address these issues?	• Quality of life • Patients satisfaction

Chapter	Review questions	Outcomes
8	Does the provision of information and support regarding the different management systems improve patient outcomes?	• Frequency of voiding by day and night • No. of incontinence episodes per week • Symptoms related to bladder emptying e.g. poor urinary stream • Patient and carer perception of symptoms • Quality of life • Kidney function (hydronephrosis) • Maximum cystometric capacity • Bladder compliance • Residual urine • Treatment adherence • Adverse events

4.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify relevant evidence within published literature. These searches were conducted in accordance with The Guidelines Manual [2009][1]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in the English language. All searches were conducted in the following core databases: MEDLINE, Embase, Cinahl and The Cochrane Library. An additional subject specific database (PsycINFO) was used for the patient information question. All searches were updated on 10th January 2012. No papers after this date were considered.

The accuracy of search strategies was assured by cross-checking with: the bibliographies of relevant key papers, search strategies in other systematic reviews, and GDG-recommended studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix C.

During the scoping stage, a topic-specific search was conducted for guidelines/reports in the generic websites listed below, and in those of relevant specialist organisations. Searches for grey or unpublished literature were not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net/)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (www.nice.org.uk/)
- Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/)
- NHS Evidence (www.evidence.nhs.uk/)
- TRIP Database (www.tripdatabase.com/)

4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify relevant health economic evidence within published literature. A broad search relating to the guideline population was conducted in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED)

and Health Technology Assessment (HTA) database, with no date restrictions applied. Using a specific economic filter, the search was also run in MEDLINE and Embase from 2009 - to ensure recent publications that had not yet been indexed by the aforementioned databases were identified. Where possible, searches were restricted to articles published in the English language.

The search strategies for health economics are included in Appendix C. All searches were updated on 10th January 2012. No papers published after this date were considered.

4.3 Evidence of effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix D.
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual [1].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix F.
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
    - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
    - Observational studies: data presented in modified GRADE profiles
    - Qualitative studies: each study summarised in a table where possible, otherwise presented in a narrative.

The modified GRADE profile contains all the same elements as the profile generated by the software GRADEpro (for example including study limitations and imprecision) but enables data to be presented in one cell for ease of readability.

4.3.1 Inclusion/exclusion

See the review protocols in Appendix D for full details. The following inclusion/exclusion criteria are of note. A minimum sample size of 20 participants was the minimum requirement for studies to be included on the question on antimuscarinincs. For the question on behaviour therapy the population included elderly patients without neurological disease or injury. For the question on access to and experience of services the population included patients with neurological disease or injury who did not necessarily have incontinence. For this question, the websites of stakeholder organisations were searched for relevant audit or survey data.

4.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: incontinence, measures of renal function (frequency of occurrence), adverse events and treatment continuance. The continuous outcomes incontinence (frequency of incontinence episodes) and urodynamics investigations were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used.

When no events were recorded in the control arm, the Peto odds ratio was calculated. The risk difference was used to derive the absolute effects.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity.

For continuous outcomes, the means and standard deviations were required for meta-analysis. In some cases data relative risks (categorical outcomes) and mean difference (continuous outcomes) could not be calculated (for example medians or p values only were presented). Here, we presented the data available but do not assess imprecision. Evidence statements are not produced for these outcomes.

For categorical outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

4.3.3 Types of analysis

Estimates of effect from individual studies were based on Intention To Treat (ITT) analysis with the exception of the outcome of experience of adverse events where Available Case Analysis (ACA) was used (or ITT if this was not possible). ITT analysis is where all participants that were randomised are considered in the final analysis based on the intervention and control groups to which they were originally assigned. We assumed that participants in the trials lost to follow-up did not experience an outcome of interest (categorical outcomes) and they would not considerably change the average scores of their assigned groups (for continuous outcomes).

It is important to note that ITT analyses tend to bias the results towards no difference. ITT analysis is a conservative approach to analyse the data, and therefore the effect may be smaller than in reality.

4.3.4 Types of studies

For the intervention reviews, randomised controlled trials (RCTs) were the considered the most robust type of study design that could produced an unbiased estimate of effect. However for some questions, RCTs were not available and the GDG considered evidence from observational studies to be relevant. This is detailed in the review protocols in Appendix D.

4.3.5 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings characteristics and findings was presented as one table in this guideline. This table includes pooled outcome data, where appropriate, an absolute measure of the intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in Table 1 and each graded using the quality levels listed in Table 4: The main criteria considered in the rating of these elements are discussed below (see section 4.3.5 Grading of Evidence). Footnotes were used to

describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 3: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 4:Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 5:Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.6 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias were rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections.

4.3.7 Study limitations

The main limitations for randomised controlled trials are listed in Table 6.

Table 6: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Carry-over effects in cross-over trials • Recruitment bias in cluster randomised trials

4.3.8 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

4.3.9 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

4.3.10 Imprecision

The sample size, event rates, the resulting width of confidence intervals and the minimal important difference in the outcome between the two groups were the main criteria considered.

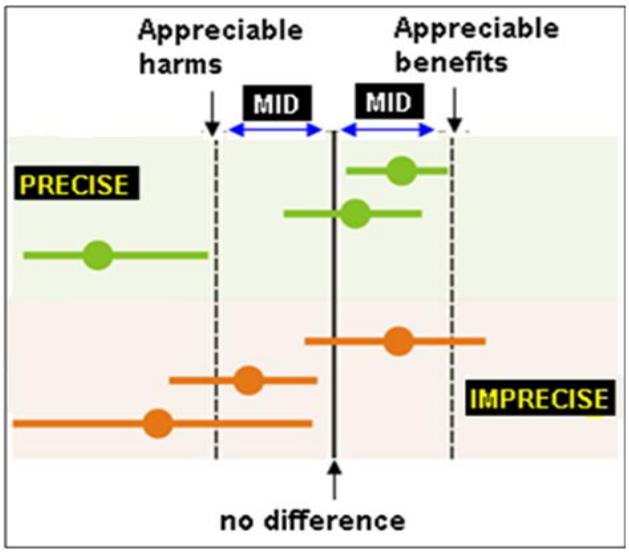
The thresholds of important benefits or harms, or the MID (minimal important difference) for an outcome are important considerations for determining whether there is a "clinically important" difference between intervention and control groups and in assessing imprecision. For continuous outcomes, the MID is defined as "the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, ether beneficial or harmful, and that would lead the patient or clinician to consider a change in the management [2 3 4 5]. An effect estimate larger than the MID is considered to be "clinically important". For dichotomous outcomes, the MID is considered in terms of changes of absolute risk.

The difference between two interventions, as observed in the studies, was compared against the MID when considering whether the findings were of "clinical importance"; this is useful to guide decisions. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to strongly recommend one intervention over the other based on that outcome.

We searched the literature for published studies which gave a minimal important difference point estimate for the outcomes specified in the protocol and agreement was obtained from the GDG for their use in assessing imprecision throughout the reviews in the guideline. Only one such MID was identified and this was for the Incontinence-Quality of Life (I-QoL) questionnaire with an MID of 13 points [6]. For those outcomes where no specific MID was set by the GDG, the default GRADE pro MIDs were used. For categorical data, we checked whether the confidence interval of the effect crossed one or two ends of the range of 0.75-1.25. For quantitative outcomes two approaches were used. When only one trial was included as the evidence base for an outcome, the mean difference was converted to the standardized mean difference (SMD) and checked to see if the confidence interval crossed 0.5. However, the mean difference (95% confidence interval) was still presented in the Grade profile. If two or more included trials reported a quantitative outcome then the default approach of multiplying 0.5 by standard deviation (taken as the median of the standard deviations across the meta-analyzed studies) was employed. When the default MIDs were used, the GDG would assess the estimate of effect with respects to the MID, and then the imprecision may be reconsidered.

The confidence interval for the pooled or best estimate of effect was considered in relation to the MID, as illustrated in Figure 1. Essentially, if the confidence interval crossed the MID threshold, there was uncertainty in the effect estimate in supporting our recommendation (because the CI was consistent with two decisions) and the effect estimate was rated as imprecise.

Figure 1: Illustration of precise and imprecision outcomes based on the confidence interval of outcomes in a forest plot



Source: Figure adapted from GRADEPro software.

MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results.

4.3.11 Evidence statements

Evidence statements summarising the results of the trials by outcome were produced for all study types. For RCTs the statements were based on the statistical significance of the results. Statements were not produced when no estimation of the intervention effect could be calculated. A substantial proportion of the evidence for this guideline was from observational studies (in particular before and after studies). To aid the reader of the guideline, the decision was taken to summarise these studies with evidence statements describing the overall direction of the results. If the studies were too heterogeneous, statements summarising the main conclusion of each study were produced.

4.4 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

4.4.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.

- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual [1].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G.
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

4.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have had an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix H [1] and the health economics research protocol in Appendix D.

*W*hen no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

4.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual, Appendix H [1]. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity[7].

Table 7: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-

Item	Description
	effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost-effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost-effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost-effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost-effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost-effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual, Appendix G [1]

Where economic studies compare multiple strategies, results are presented in the economic evidence profiles for the pair-wise comparison specified in the review question, irrespective of whether or not that comparison was 'appropriate' within the analysis being reviewed. A comparison is 'appropriate' where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Footnotes indicate if a comparison was 'inappropriate' in the analysis.

4.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendix I for details of the health economic analysis/analyses undertaken for the guideline.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money [1].

In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix F
- Summary of clinical and economic evidence and quality (as presented in chapters 6 - 13)
- Forest plots and summary ROC curves (Appendix H)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix I

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG, or methods of formal consensus were applied. The GDG may also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (See Section 5.3). The main considerations specific to each recommendation are outlined in the Evidence to Recommendation Section preceding the recommendation section.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

4.5.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE's Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

4.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

5 Guideline summary

5.1 Key priorities for implementation

From the full set of recommendations, the GDG selected ten (10) key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual [1]. The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

The following recommendations have been identified as priorities for implementation:

Assessment of lower urinary tract dysfunction in patients with neurological conditions

1. When assessing lower urinary tract dysfunction in a person with neurological disease, take a clinical history, including information about:
   - urinary tract symptoms
   - neurological symptoms and diagnosis (if known)
   - clinical course of the neurological disease
   - bowel symptoms
   - sexual function
   - comorbidities
   - use of prescription and other medication and therapies.
2. If the dipstick test result and person's symptoms suggest an infection, arrange a urine bacterial culture and antibiotic sensitivity test before starting antibiotic treatment. Treatment need not be delayed but may be adapted when results are available.
3. Be aware that bacterial colonisation will be present in people using a catheter and so urine dipstick testing and bacterial culture may be unreliable for diagnosing active infection.
4. Refer people for urgent investigation if they have any of the following 'red flag' signs and symptoms:
   - haematuria
   - recurrent urinary tract infections (for example, three or more infections in the last 6 months)
   - loin pain
   - recurrent catheter blockages (for example, catheters blocking within 6 weeks of being changed)
   - hydronephrosis or kidney stones on imaging
   - biochemical evidence of renal deterioration.

Information and support

5. Offer people with neurogenic urinary tract dysfunction, their family members and carers specific information and training. Ensure that people who are starting to use, or are using, a bladder management system that involves the use of catheters, appliances or pads:
   - receive training, support and review from healthcare professionals who are trained to provide support in the relevant bladder management systems and are knowledgeable about the range of products available
   - have access to a range of products that meet their needs
   - have their products reviewed, at a maximum of 2 yearly intervals.

Treatment to improve bladder storage

6. Offer bladder wall injection with botulinum toxin type A[a] to adults:
   - with spinal cord disease (for example, spinal cord injury or multiple sclerosis) **and**
   - with symptoms of an overactive bladder **and**
   - in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.
7. Ensure that patients who have been offered continuing treatment with repeated botulinum toxin type A injections have prompt access to repeat injections when symptoms return.

Treatment to prevent urinary tract infection

8. Do not routinely use antibiotic prophylaxis for urinary tract infections in people with neurogenic lower urinary tract dysfunction.

Monitoring and surveillance protocols

9. Offer lifelong ultrasound surveillance of the kidneys to people who are judged to be at high risk of renal complications (for example, consider surveillance ultrasound scanning at annual or 2 yearly intervals). Those at high risk include people with spinal cord injury or spina bifida and those with adverse features on urodynamic investigations such as impaired bladder compliance, detrusor-sphincter dyssynergia or vesico-ureteric reflux.

Access to and interaction with services

10. When managing the transition of a person from paediatric services to adult services for ongoing care of neurogenic lower urinary tract dysfunction:
    - formulate a clear structured care pathway at an early stage and involve the person and/or their parents and carers
    - involve the young person's parents and carers when preparing transfer documentation with the young person's consent
    - provide a full summary of the person's clinical history, investigation results and details of treatments for the person and receiving clinician
    - integrate information from the multidisciplinary health team into the transfer documentation
    - identify and plan the urological services that will need to be continued after the transition of care
    - formally transfer care to a named individual(s).

5.2 Full list of recommendations

The following recommendations apply to adults, children and young people unless otherwise stated.

CLINICAL ASSESSMENT

1. When assessing lower urinary tract dysfunction in a person with neurological disease, take a clinical history, including information about:
   - urinary tract symptoms
   - neurological symptoms and diagnosis (if known)
   - clinical course of the neurological disease

[a] At the time of publication (August 2012), botulinum toxin type A did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.

- bowel symptoms
- sexual function
- comorbidities
- use of prescription and other medication and therapies.

2. Assess the impact of the underlying neurological disease on factors that will affect how lower urinary tract dysfunction can be managed, such as:
   - mobility
   - hand function
   - cognitive function
   - social support
   - lifestyle.
3. Undertake a general physical examination that includes:
   - measuring blood pressure
   - an abdominal examination
   - an external genitalia examination
   - a vaginal or rectal examination if clinically indicated (for example, to look for evidence of pelvic floor prolapse, faecal loading or alterations in anal tone).
4. Carry out a focused neurological examination, which may need to include assessment of:
   - cognitive function
   - ambulation and mobility
   - hand function
   - lumbar and sacral spinal segment function.
5. Undertake a urine dipstick test using an appropriately collected sample to test for the presence of blood, glucose, protein, leukocytes and nitrites. Appropriate urine samples include clean-catch midstream samples, samples taken from a freshly inserted intermittent sterile catheter and samples taken from a catheter port. Do not take samples from leg bags.
6. If the dipstick test result and person's symptoms suggest an infection, arrange a urine bacterial culture and antibiotic sensitivity test before starting antibiotic treatment. Treatment need not be delayed but may be adapted when results are available.
7. Be aware that bacterial colonisation will be present in people using a catheter and so urine dipstick testing and bacterial culture may be unreliable for diagnosing active infection.
8. Ask people and/or their family members and carers to complete a 'fluid input/urine output chart' to record fluid intake, frequency of urination and volume of urine passed for a minimum of 3 days.
9. Consider measuring the urinary flow rate in people who are able to void voluntarily.
10. Measure the post-void residual urine volume by ultrasound, preferably using a portable scanner, and consider taking further measurements on different occasions to establish how bladder emptying varies at different times and in different circumstances.
11. Consider making a referral for a renal ultrasound scan in people who are at high risk of renal complications such as those with spina bifida or spinal cord injury.

12. Refer people for urgent investigation if they have any of the following 'red flag' signs and symptoms:
    - haematuria
    - recurrent urinary tract infections (for example, three or more infections in the last 6 months)
    - loin pain
    - recurrent catheter blockages (for example, catheters blocking within 6 weeks of being changed)
    - hydronephrosis or kidney stones on imaging
    - biochemical evidence of renal deterioration.

13. Be aware that unexplained changes in neurological symptoms (for example, confusion or worsening spasticity) can be caused by urinary tract disease, and consider further urinary tract investigation and treatment if this is suspected.

14. Refer people with changes in urinary function that may be due to new or progressing neurological disease needing specialist investigation (for example, syringomyelia, hydrocephalus, multiple system atrophy or cauda equina syndrome).

15. Assess the impact of lower urinary tract symptoms on the person's family members and carers and consider ways of reducing any adverse impact. If it is suspected that severe stress is leading to abuse, follow local safeguarding procedures.

URODYNAMIC INVESTIGATIONS

16. Do not offer urodynamic investigations (such as filling cystometry and pressure-flow studies) routinely to people who are known to have a low risk of renal complications (for example, most people with multiple sclerosis).

17. Offer video-urodynamic investigations to people who are known to have a high risk of renal complications (for example, people with spina bifida, spinal cord injury or anorectal abnormalities).

18. Offer urodynamic investigations before performing surgical treatments for neurogenic lower urinary tract dysfunction.

INFORMATION AND SUPPORT

19. Offer people with neurogenic urinary tract dysfunction, their family members and carers specific information and training. Ensure that people who are starting to use, or are using, a bladder management system that involves the use of catheters, appliances or pads:
    - receive training, support and review from healthcare professionals who are trained to provide support in the relevant bladder management systems and are knowledgeable about the range of products available
    - have access to a range of products that meet their needs
    - have their products reviewed, at a maximum of 2 yearly intervals.

20. Tailor information and training to the person's physical condition and cognitive function to promote their active participation in care and self-management.

21. Inform people how to access further support and information from a healthcare professional about their urinary tract management.

22. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in 'Patient experience in adult

NHS services' (NICE clinical guideline 138). Recommendations on shared decision making and information enabling people to actively participate in their care can be found in section 1.5 of NICE clinical guideline 138.

BEHAVIOURAL TREATMENTS

23. Consider a behavioural management programme (for example, timed voiding, bladder retraining or habit retraining) for people with neurogenic lower urinary tract dysfunction:
    - only after assessment by a healthcare professional trained in the assessment of people with neurogenic lower urinary tract dysfunction and
    - in conjunction with education about lower urinary tract function for the person and/or their family members and carers.

24. When choosing a behavioural management programme, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment.

ANTIMUSCARINICS

25. Offer antimuscarinic[b] drugs to people with:
    - spinal cord disease (for example, spinal cord injury or multiple sclerosis) **and**
    - symptoms of an overactive bladder such as increased frequency, urgency and incontinence.

26. Consider antimuscarinic[b] drug treatment in people with:
    - conditions affecting the brain (for example, cerebral palsy, head injury or stroke) **and**
    - symptoms of an overactive bladder.

27. Consider antimuscarinic[b] drug treatment in people with urodynamic investigations showing impaired bladder storage.

28. Monitor residual urine volume in people who are not using intermittent or indwelling catheterisation after starting antimuscarinic treatment.

29. When prescribing antimuscarinics, take into account that:
    - antimuscarinics known to cross the blood-brain barrier (for example, oxybutynin) have the potential to cause central nervous system-related side effects (such as confusion)
    - antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections
    - antimuscarinic treatment may precipitate or exacerbate constipation.

BOTULINUM TOXIN TYPE A

30. Offer bladder wall injection with botulinum toxin type A[c] to adults:
    - with spinal cord disease (for example, spinal cord injury or multiple sclerosis) **and**
    - with symptoms of an overactive bladder **and**
    - in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

[b] At the time of publication (August 2012) not all antimuscarinics had a UK marketing authorisation for this indication or for use in both adults and children. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's 'Good practice in prescribing medicines – guidance for doctors' for further information.

[c] At the time of publication (August 2012), botulinum toxin type A did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance when prescribing a drug without a marketing authorisation for this indication, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's 'Good practice in prescribing medicines – guidance for doctors' for further information.

31. Consider bladder wall injection with botulinum toxin type A[d] for children and young people:
    - with spinal cord disease **and**
    - with symptoms of an overactive bladder **and**
    - in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

32. Offer bladder wall injection with botulinum toxin type A[d] to adults:
    - with spinal cord disease **and**
    - with urodynamic investigations showing impaired bladder storage **and**
    - in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

33. Consider bladder wall injection with botulinum toxin type A[d] for children and young people:
    - with spinal cord disease **and**
    - with urodynamic investigations showing impaired bladder storage **and**
    - in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

34. Before offering bladder wall injection with botulinum toxin type A:
    - explain to the person and/or their family members and carers that a catheterisation regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, **and**
    - ensure that they are able and willing to manage such a regimen should urinary retention develop after the treatment.

35. Monitor residual urine volume in people who are not using a catheterisation regimen during treatment with botulinum toxin type A.

36. Monitor the upper urinary tract in people who are judged to be at risk of renal complications (for example, those with high intravesical pressures on filling cystometry) during treatment with botulinum toxin type A.

37. Ensure that people who have been offered continuing treatment with repeated botulinum toxin type A injections have prompt access to repeat injections when symptoms return.

AUGMENTATION CYSTOPLASTY

38. Consider augmentation cystoplasty using an intestinal segment for people:
    - with non-progressive neurological disorders **and**
    - complications of impaired bladder storage (for example, hydronephrosis or incontinence) **and**
    - only after a thorough clinical and urodynamic assessment and discussion with the patient and/or their family members and carers about complications, risks and alternative treatments.

39. Offer patients life-long follow-up after augmentation cystoplasty because of the risk of long-term complications. Potential complications include metabolic effects, such as the development of vitamin B_{12} deficiency and the development of bladder cancer.

PELVIC FLOOR MUSCLE TRAINING

40. Consider pelvic floor muscle training for people with:
    - lower urinary tract dysfunction due to multiple sclerosis or stroke **or**

[d] At the time of publication (August 2012), botulinum toxin type A did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the 'GMC's Good practice in prescribing medicines – guidance for doctors' for further information.

- other neurological conditions where the potential to voluntarily contract the pelvic floor is preserved.

Select patients for this training after specialist pelvic floor assessment and consider combining treatment with biofeedback and/or electrical stimulation of the pelvic floor.

URETHRAL TAPE AND SLING SURGERY

41. Consider autologous fascial sling surgery for people with neurogenic stress incontinence.

42. Do not routinely use synthetic tapes and slings in people with neurogenic stress incontinence because of the risk of urethral erosion.

ARTIFICIAL URINARY SPHINCTER

43. Consider surgery to insert an artificial urinary sphincter for people with neurogenic stress incontinence only if an alternative procedure, such as insertion of an autologous fascial sling, is less likely to control incontinence.

44. When considering inserting an artificial urinary sphincter:
    - discuss with the person and/or their family members and carers the risks associated with the device, the possible need for repeat operations and alternative procedures
    - ensure that the bladder has adequate low-pressure storage capacity.

45. Monitor the upper urinary tract after artificial urinary sphincter surgery (for example, using annual ultrasound scans) as bladder storage function can deteriorate in some people after treatment of their neurogenic stress incontinence.

ALPHA-BLOCKERS

46. Do not offer alpha-blockers to people as a treatment for bladder emptying problems caused by neurological disease.

MANAGEMENT WITH CATHETER VALVES

47. In people for whom it is appropriate a catheter valve may be used as an alternative to a drainage bag.

[This recommendation is from 'Infection: prevention and control of healthcare-associated infections in primary and community care' (NICE clinical guideline 139).]

48. To ensure that a catheter valve is appropriate, take into consideration the person's preference, family member and carer support, manual dexterity, cognitive ability, and lower urinary tract function when offering a catheter valve as an alternative to continuous drainage into a bag.

49. Consider the need for continuing upper urinary tract surveillance in people who have impaired bladder storage (for example, due to reduced bladder compliance).

MANAGEMENT WITH ILEAL CONDUIT DIVERSION

50. For people with neurogenic lower urinary tract dysfunction who have intractable, major problems with urinary tract management, such as incontinence or renal deterioration:
    - consider ileal conduit diversion (urostomy) **and**
    - discuss with the person the option of simultaneous cystectomy as prophylaxis against pyocystis.

TREATMENT TO PREVENT URINARY TRACT INFECTION

51. Do not routinely use antibiotic prophylaxis for urinary tract infections in people with neurogenic lower urinary tract dysfunction.

52. Consider antibiotic prophylaxis for people who have a recent history of frequent or severe urinary tract infections.

53. Before prescribing antibiotic prophylaxis for urinary tract infection:
    - investigate the urinary tract for an underlying treatable cause (such as urinary tract stones or incomplete bladder emptying)
    - take into account and discuss with the person the risks and benefits of prophylaxis
    - refer to local protocols approved by a microbiologist or discuss suitable regimens with a microbiologist.

54. Ensure that the need for ongoing prophylaxis in all people who are receiving antibiotic prophylaxis is regularly reviewed.

55. When changing catheters in patients with a long-term indwelling urinary catheter:
    - do not offer antibiotic prophylaxis routinely
    - consider antibiotic prophylaxis[e] for patients who:

    -have a history of symptomatic urinary tract infection after catheter change **or**

    -experience trauma[f] during catheterisation.

    [This recommendation is from 'Infection: prevention and control of healthcare-associated infections in primary and community care' (NICE clinical guideline 139).]

MONITORING AND SURVEILLANCE PROTOCOLS

56. Do not rely on serum creatinine and estimated glomerular filtration rate in isolation for monitoring renal function[g] in people with neurogenic lower urinary tract dysfunction.

57. Consider using isotopic glomerular filtration rate when an accurate measurement of glomerular filtration rate is required (for example, if imaging of the kidneys suggests that renal function might be compromised)[g].

58. Offer lifelong ultrasound surveillance of the kidneys to people who are judged to be at high risk of renal complications (for example, consider surveillance ultrasound scanning at annual or 2 yearly intervals). Those at high risk include people with spinal cord injury or spina bifida and those with adverse features on urodynamic investigations such as impaired bladder compliance, detrusor-sphincter dyssynergia or vesico-ureteric reflux.

59. Do not use plain abdominal radiography for routine surveillance in people with neurogenic lower urinary tract dysfunction.

60. Consider urodynamic investigations as part of a surveillance regimen for people at high risk of urinary tract complications (for example, people with spina bifida, spinal cord injury or anorectal abnormalities).

[e] At the time of publication of the guideline (August 2012), no antibiotics had a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information

[f] The GDG for 'Infection: prevention and control of healthcare-associated infections in primary and community care' defined trauma as frank haematuria after catheterisation or two or more attempts of catheterisation.

[g] For more information on the measurement of kidney function, see 'Chronic kidney disease' (NICE clinical guideline 73).

61. Do not use cystoscopy for routine surveillance in people with neurogenic lower urinary tract dysfunction.

62. Do not use renal scintigraphy for routine surveillance in people with neurogenic lower urinary tract dysfunction.

RENAL IMPAIRMENT

63. Discuss with the person and/or their family members and carers the increased risk of renal complications (such as kidney stones, hydronephrosis and scarring) in people with neurogenic urinary tract dysfunction (in particular those with spina bifida or spinal cord injury). Tell them the symptoms to look out for (such as loin pain, urinary tract infection and haematuria) and when to see a healthcare professional.

64. When discussing treatment options, tell the person that indwelling urethral catheters may be associated with higher risks of renal complications (such as kidney stones and scarring) than other forms of bladder management (such as intermittent self catheterisation).

65. Use renal imaging to investigate symptoms that suggest upper urinary tract disease.

BLADDER STONES

66. Discuss with the person and/or their family members and carers the increased risk of bladder stones in people with neurogenic lower urinary tract dysfunction. Tell them the symptoms to look out for that mean they should see a healthcare professional (for example, recurrent infection, recurrent catheter blockages or haematuria).

67. Discuss with the person and/or their family members and carers that indwelling catheters (urethral and suprapubic) are associated with a higher incidence of bladder stones compared with other forms of bladder management. Tell them the symptoms to look out for that mean they should see a healthcare professional (for example, recurrent infection, recurrent catheter blockages or haematuria).

68. Refer people with symptoms that suggest the presence of bladder stones (for example, recurrent catheter blockages, recurrent urinary tract infection or haematuria) for cystoscopy.

BLADDER CANCER

69. Discuss with the person and/or family members and carers that there may be an increased risk of bladder cancer in people with neurogenic lower urinary tract dysfunction, in particular those with a long history of neurogenic lower urinary tract dysfunction and complicating factors, such as recurrent urinary tract infections. Tell them the symptoms to look out for (especially haematuria) that mean they should see a healthcare professional.

70. Arrange urgent (within 2 weeks) investigation with urinary tract imaging and cystoscopy for people with:
    - visible haematuria **or**
    - increased frequency of urinary tract infections **or**
    - other unexplained lower urinary tract symptoms.

ACCESS TO AND INTERACTION WITH SERVICES

71. Provide contact details for the provision of specialist advice if a person has received care for neurogenic lower urinary tract dysfunction in a specialised setting (for example, in a spinal injury unit or a paediatric urology unit). The contact details should be given to the person and/or their family members and carers and to the non-specialist medical and nursing staff involved in their care.

72. Provide people with neurogenic lower urinary tract dysfunction, and/or their family members and carers with written information that includes:
    - a list of key healthcare professionals involved in their care, a description of their role and their contact details
    - copies of all clinical correspondence
    - a list of prescribed medications and equipment.

    This information should also be sent to the person's GP.

73. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in 'Patient experience in adult NHS services' (NICE clinical guideline 138). Recommendations on tailoring healthcare services for each patient can be found in section 1.3 and recommendations on continuity of care and relationships can be found in section 1.4 of NICE clinical guideline 138.

TRANSFER FROM CHILD TO ADULT SERVICES

74. When managing the transition of a person from paediatric services to adult services for ongoing care of neurogenic lower urinary tract dysfunction:
    - formulate a clear structured care pathway at an early stage and involve the person and/or their parents and carers
    - involve the young person's parents and carers when preparing transfer documentation with the young person's consent
    - provide a full summary of the person's clinical history, investigation results and details of treatments for the person and receiving clinician
    - integrate information from the multidisciplinary health team into the transfer documentation
    - identify and plan the urological services that will need to be continued after the transition of care
    - formally transfer care to a named individual(s).

75. When receiving a person from paediatric services to adult services for ongoing care of neurogenic lower urinary tract dysfunction:
    - review the transfer documentation and liaise with the other adult services involved in ongoing care (for example, adult neuro-rehabilitation services)
    - provide the person with details of the service to which care is being transferred, including contact details of key personnel, such as the urologist and specialist nurses
    - ensure that urological services are being provided after transition to adult services.

76. Consider establishing regular multidisciplinary team meetings for paediatric and adult specialists to discuss the management of neurogenic lower urinary tract dysfunction in children and young people during the years leading up to transition and after entering adult services.

5.3 Key research recommendations

Having reviewed the current evidence around several clinical questions, the Guideline Development Group identified areas where there was no evidence at all, where the evidence was inadequate to make a recommendation, or where the evidence that existed was either applicable to only a small subsection of the community, or did not apply to certain subgroups. Subsequently the following clinical questions were proposed and form the research recommendations for the guideline. More information on the rationale for prioritising these topics is listed within the relevant chapters and in Appendix J.

SAFETY AND EFFICACY OF ANTIMUSCARINICS

1. What is the safety and efficacy of more recently developed antimuscarinics compared with (a) placebo/usual care and (b) other antimuscarinics in the treatment of neurogenic lower urinary tract dysfunction?
   - Why this is important:

     No high-quality clinical trials looking at the use of the newer antimuscarinic drugs in people with neurogenic lower urinary tract dysfunction have been carried out. Both placebo-controlled and comparative studies are lacking. This is important because the more recently developed medications are of unknown efficacy, are more expensive and claim (in the non-neurogenic population) to have fewer adverse effects. The adverse effects of antimuscarinics are mostly due to their action at sites other than the bladder (for example, causing a dry mouth) but there is now increasing concern that antimuscarinic effects on the central nervous system may adversely affect cognitive function in both children with brain damage (caused by cerebral palsy or hydrocephalus) and adults with impaired cognition (caused by cerebral involvement in multiple sclerosis or neurodegenerative diseases).

BOTULINUM TOXIN A

2. What is the safety and efficacy of botulinum toxin compared with (a) usual care, (b) antimuscarinics and (c) augmentation cystoplasty in people with neurogenic lower urinary tract dysfunction?
   - Why this is important

     Further research is required to determine whether repeated intradetrusor injections of botulinum toxin type A have long-term efficacy. The efficacy in terms of continence and upper urinary tract preservation should be studied.

     Botulinum toxin injection into the detrusor is an effective means of managing incontinence, and improves urodynamic measures of bladder storage with the potential to protect the kidneys from the effects of high intravesical pressures. It is well tolerated in a spectrum of conditions and ages. However, the longer term efficacy over many injections has not been established.

     A clinical trial is needed to study the outcome in terms of continence and renal preservation over many cycles of repeated injection. Quality of life is an important outcome. A trial should enrol children and adults. The indications for botulinum toxin need not be modified for inclusion, but entrants into a trial must have anatomically normal kidneys (on imaging) and normal renal function.

3. What is the safety and efficacy of botulinum toxin compared with (a) usual care, (b) antimuscarinics and (c) augmentation cystoplasty in people with primary cerebral conditions with lower urinary tract dysfunction?
   - Why this is important

     The effects of intradetrusor botulinum toxin type A injection should be investigated in groups of people with underlying cerebral conditions that are associated with lower urinary tract dysfunction, as well as those with spinal cord injury, spina bifida and multiple sclerosis. Reports of its use in other conditions are limited to small numbers of patients within case series studies that include heterogeneous groups of patients. Potential benefits of successful treatment in cerebral disease may include the avoidance of cognitive impairment, which can be seen as a side effect of antimuscarinic medication.

     A trial should include people with primary cerebral conditions including (but not restricted to) stroke, head injury and cerebral palsy, but excluding multiple sclerosis. Children and adults should be recruited. Tolerability and acceptability are important outcomes, as well as the

primary outcomes of continence, preservation of the upper urinary tracts and quality of life. Measurement of carer burden and quality of life is also important.

TREATMENT TO PREVENT URINARY INFECTION

4. In people with neurogenic lower urinary tract dysfunction, which management strategies (including the use of prophylactic antibiotics and various invasive and non-invasive techniques to aid bladder drainage) reduce the risk of symptomatic urinary tract infections?
   - Why this is important

   Recurrent urinary tract infections in people with neurogenic bladder dysfunction are a cause of considerable morbidity. Urinary tract infections may exacerbate incontinence, cause symptoms of malaise and may progress to involve the upper urinary tract with possible loss of renal function. In the population with neurological diseases such as multiple sclerosis, Parkinson's disease and dementia, the rise in temperature with urinary tract infections can cause deterioration in neurological function and even a relapse of multiple sclerosis. There are therefore numerous reasons why people with neurogenic lower urinary tract dysfunction should avoid urinary tract infections.

   The causes for the high prevalence of urinary tract infections in such people include loss of physiological bladder function and high intravesical pressures. Intermittent or permanent catheterisation inevitably exacerbate the problem, but incomplete bladder emptying is also a predisposing factor for urinary tract infections.

   Research in this area is faced with methodological difficulties, not least because it may be difficult to distinguish between bladder colonisation (asymptomatic bacteriuria) and true infection.

   In view of the considerable clinical burden of urinary tract infections and the global problem of antibiotic resistance, it is important to establish whether or not any infection prevention strategies, including patient training or the provision of information relating to prophylactic antibiotics are effective in reducing symptomatic urinary tract infections.

INTERMITTENT CATHETERISATION, INDWELLING CATHETERS AND PENILE SHEATH URINE COLLECTION

5. What are the long-term risks and effects on quality of life of different bladder management strategies for lower urinary tract dysfunction in people with neurological disease?
   - Why this is important

   The range of bladder management strategies available to manage lower urinary tract dysfunction in neurological disease includes permanent urethral catheterisation and suprapubic catheterisation, intermittent self-catheterisation, penile sheath collection systems and pads. However, there is very sparse evidence about which strategies are most acceptable to patients and/or their family members and carers. The current research base relates mainly to the spinal injury population but may be relevant to people with other neurological diseases.

   Bladder management strategies are a long-term treatment with implications for maintaining health and quality of life. In order to make informed choices about the most appropriate method of bladder management, patients and/or their family members and carers require information about the risks and benefits of the available options. There is currently little evidence about which methods are most likely to produce long-term complications (renal impairment, urinary stones and infections, hydronephrosis, bladder malignancy). The effect on quality of life for patients and/or their family members and carers of different bladder management strategies is not known. There are methodological difficulties due to the heterogeneity of the population with neurological disease, the long time course of treatments and the presence of cognitive impairment in some sub-populations.

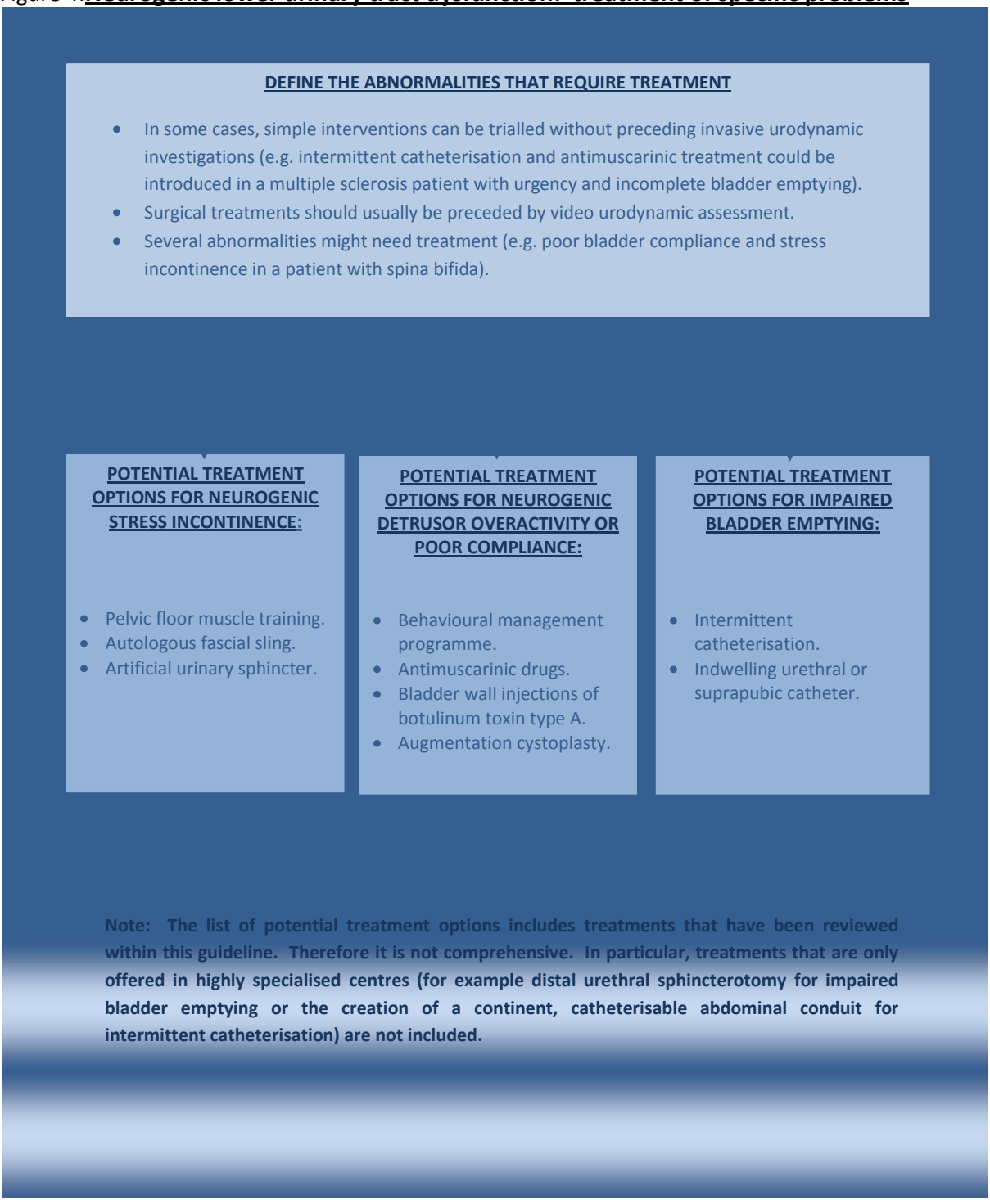
Proposed studies could include prospective cohort studies of disease-specific populations examining the effect of each method on quality of life using both generic and disease-specific assessment methods. In addition, prospective screening for complications including renal impairment, stone formation and infection should be carried out and comparisons made for each bladder management method. Particular emphasis should be placed on quality-of-life outcomes for family members and carers, especially for those looking after people with cognitive impairment.

5.4 Algorithms

Figure 2: Initial care of the patient with neurogenic lower urinary tract dysfunction.

Figure 3:Further care of the patient with neurogenic lower urinary tract dysfunction: management within an appropriate multi-disciplinary team

Figure 4:**Neurogenic lower urinary tract dysfunction: treatment of specific problems**



6 Assessment of lower urinary tract dysfunction in patients with neurological conditions

The assessment of a patient with neurogenic lower urinary tract dysfunction (NLUTD) involves both a clinical evaluation and the use of investigations. This evaluation will inform discussion between the patient, their carers and the clinical team which, in turn, will lead to decisions being made regarding the management approach that is to be used. An inadequate initial assessment can therefore lead to the use of inappropriate treatments and adversely impact on the patient's quality of life, and, in extreme cases, length of life.

The clinical history and examination is the basis of clinical practice and is inevitably the starting point for the assessment process. However, the patient with NLUTD presents a particular challenge to the clinician who has to take into account both specific issues relating to the urinary tract dysfunction and the wider context that is presented by the underlying neurological condition and accompanying social circumstances. NLUTD arises from a wide spectrum of conditions, each of which will affect patients in a variety of ways; this is a field which exemplifies the aphorism that every patient must be seen as an individual.

Assessment of the individual with NLUTD normally begins with simple investigations, which include the completion of a bladder diary (or frequency/volume chart), measurement of residual urine volume and urine testing. A bladder diary records the time when urine is voided, the volume passed and the presence of symptoms such as urinary urgency, incontinence or pain. The timing, type and volume of fluids taken must also be recorded. The measurement of the volume of urine left in the bladder after micturition (the residual volume) can be carried out using portable ultrasound machines or by catheterisation. Urine testing includes the use of urine dip-stick tests and laboratory microbiological studies.

NLUTD can threaten renal integrity as a result of raised bladder pressures, which can lead to the development of hydronephrosis, and infection which can lead to the renal scarring or the development of stones. An indication of current renal function can be gained by biochemical tests such as serum creatinine and calculation of eGFR and further refined by 24 hr endogenous clearance or ^{99m}Tc-DTPA clearance measurements. Upper urinary tract imaging therefore has a role in the assessment of some patients with NLUTD. Ultrasound scanning of the kidneys is widely used in patients with NLUTD both as part of the initial assessment and as a follow-up screening tool for patients who may be at risk of renal complications.

Urodynamic investigations are tests that examine the transport, storage and voiding of urine. The term "urodynamics" covers a range of tests that includes filling cystometry and pressure-flow studies of voiding. X-ray screening can provide additional anatomical information; the combination of radiological screening and cystometry is termed "video-urodynamics". The International Continence Society has been instrumental in producing internationally accepted definitions for the terminology that applies to the function of the LUT and urodynamic investigations [8] as well as setting standards for the conduct of such tests [9]. Urodynamic investigations have been widely employed in the assessment of patients with NLUTD.

Despite the widespread adoption of a urodynamic-based approach to management of NLUTD, there is continuing uncertainty about the precise role of such investigations in this field. For example, expert opinion is divided on the use of urodynamic studies in patients with NLUTD due to multiple sclerosis [10 11]. There is continuing uncertainty about the reproducibility of urodynamic investigations and there is also a need to determine whether urodynamic investigations can provide a reliable prognosis with respect to the long-term risk of renal complications in individuals with NLUTD. In infants and children particularly, urodynamic studies can be confounded by discomfort, lack of

cooperation and changing bladder behaviour during maturation of bladder storage and voiding, and makes cautious interpretation more important.

Given the prevalence and heterogeneity of NLUTD it is apparent that patients will present both to general and specialist services. Patients who are at high risk of serious complications or who might require complex treatments are likely to be seen in specialist centres, such as spinal injury units, although much of their care will actually be delivered in primary care. On the other hand, there are patients with NLUTD who can be assessed and managed successfully by specialist nurses or in a primary care setting. One possible aid to help non-specialist clinicians when they are deciding whether or not to refer a patient to specialist care is the use of "red flags". These can be used to identify key symptoms or findings that should prompt escalation of care to a more specialised service.

6.1 Clinical Assessment

6.1.1 Does the use of clinical assessment, urine culture, a residual urine estimate or a bladder diary/frequency volume chart change the management of patients with neurological disease?

Clinical Methodological Introduction	
Population:	Patients with incontinence due to neurological disease or injury
Intervention:	Clinical assessment Urine culture Residual urine estimate Bladder diary/frequency volume chart
Comparison:	Not applicable
Outcomes:	Change in management

6.1.1.1 Clinical evidence review

We searched for observational studies that reported on changes in clinical management associated with clinical assessment, urine culture, residual urine estimates or bladder diary/frequency volume charts.

No studies were identified for this question.

6.1.1.2 Economic evidence

Literature review

No relevant economic evaluations comparing interventions for patient assessment in neurological incontinence were identified.

Economic considerations

The GDG thought that urine culture is currently performed routinely for many patients with neurological incontinence. Urine culture is low cost and may help to direct patient management if an active UTI is present through determination of the causative organism and drug sensitivity. The GDG judged this intervention to be highly cost-effective when offered to the correct population of patients. Patients with neurological incontinence have a high incidence of both symptomatic UTI and asymptomatic urinary colonisation (asymptomatic bacteriuria). The GDG stated that, if using a catheter, all patients will have bacterial colonisation. A urine dipstick test will therefore exaggerate

the number of UTIs that need to be treated in the catheterised population. Asymptomatic bacteriuria is also common in the non catheterised neuropathic population. In a patient with incontinence, it can be difficult to determine whether urine colonisation represents an active infection which, when treated will reduce or abolish urinary incontinence, or whether the colonisation is truly asymptomatic. Therefore clinical judgements about whether or not to offer antibiotic treatment have to be made when a positive bacterial culture is obtained in a patient with neurogenic lower urinary tract dysfunction. Investigating every single positive dipstick result in the catheterised population with a urine culture is not likely to be cost effective. However, cases of active infection can be missed if bacterial cultures are never taken, so a balance must be found between these two extreme strategies. The most cost effective testing strategy will be one where clinical presentation is considered and testing is done accordingly. However there is no evidence to suggest what that selection should be based on, apart from whether an infection is symptomatic or not. The consensus view of the GDG was that this test should be offered according to the patient's clinical presentation and that the presence or absence of a catheter will have an impact on the decision to perform a urine culture. This may result in a change in current clinical practice for some centres and will likely to lead to cost savings for the NHS.

The use of ultrasonography to assess residual urine estimates involves non-negligible cost (an ultrasound scan of less than 20 minutes costs £55, and more than 20 minutes costs £71 – NHS reference cost 2009-10). This test is currently offered selectively to patients according to clinical presentation. This use is judged likely to be cost-effective by the GDG.

Bladder diary and frequency volume charts are forms filled out by the patient and reported to the clinician during consultation, Whilst it can take some time to explain the use of charts to the patient, the GDG agreed that their use helps by providing objective measurements of parameters such as urinary frequency, voided volumes and frequency of incontinence episodes and the benefit from this is likely to lead to cost savings for the NHS.

Cost of pressure-flow studies: see NHS Reference Costs[12] – Outpatient procedure – Dynamic studies of urinary tract (LB42Z) = £147

6.1.1.3 Evidence statements

Clinical evidence statement

None

Economic evidence statement

The selective use of diagnostic investigations, in addition to clinical assessment, for patients that will benefit from them due to an improvement of their medical management, is likely to be cost-effective.

6.1.2 Recommendations and Link to Evidence

Recommendations:	**CLINICAL ASSESSMENT** **1. When assessing lower urinary tract dysfunction in a person with neurological disease, take a clinical history, including information about:** • **urinary tract symptoms** • **neurological symptoms and diagnosis (if known)** • **clinical course of the neurological disease**

- **bowel symptoms**
- **sexual function**
- **comorbidities**
- **use of prescription and other medication and therapies.**

2. **Assess the impact of the underlying neurological disease on factors that will affect how lower urinary tract dysfunction can be managed, such as:**
   - **mobility**
   - **hand function**
   - **cognitive function**
   - **social support**
   - **lifestyle.**

3. **Undertake a general physical examination that includes:**
   - **measuring blood pressure**
   - **an abdominal examination**
   - **an external genitalia examination**
   - **a vaginal or rectal examination if clinically indicated (for example, to look for evidence of pelvic floor prolapse, faecal loading or alterations in anal tone).**

4. **Carry out a focused neurological examination, which may need to include assessment of:**
   - **cognitive function**
   - **ambulation and mobility**
   - **hand function**
   - **lumbar and sacral spinal segment function.**

5. **Undertake a urine dipstick test using an appropriately collected sample to test for the presence of blood, glucose, protein, leukocytes and nitrites. Appropriate urine samples include clean-catch midstream samples, samples taken from a freshly inserted intermittent sterile catheter and samples taken from a catheter port. Do not take samples from leg bags.**

6. **If the dipstick test result and person's symptoms suggest an infection, arrange a urine bacterial culture and antibiotic sensitivity test before starting antibiotic treatment. Treatment need not be delayed but may be adapted when results are available.**

7. **Be aware that bacterial colonisation will be present in people using a catheter and so urine dipstick testing and bacterial culture may be unreliable for diagnosing active infection.**

8. **Ask people and/or their family members and carers to complete a 'fluid input/urine output chart' to record fluid intake, frequency of urination and volume of urine passed for a minimum of 3 days.**

	9. Consider measuring the urinary flow rate in people who are able to void voluntarily. **10. Measure the post-void residual urine volume by ultrasound, preferably using a portable scanner, and consider taking further measurements on different occasions to establish how bladder emptying varies at different times and in different circumstances.** **11. Consider making a referral for a renal ultrasound scan in people who are at high risk of renal complications such as those with spina bifida or spinal cord injury.** **12. Refer people for urgent investigation if they have any of the following 'red flag' signs and symptoms:** • **haematuria** • **recurrent urinary tract infections (for example, three or more infections in the last 6 months)** • **loin pain** • **recurrent catheter blockages (for example, catheters blocking within 6 weeks of being changed)** • **hydronephrosis or kidney stones on imaging** • **biochemical evidence of renal deterioration.** **13. Be aware that unexplained changes in neurological symptoms (for example, confusion or worsening spasticity) can be caused by urinary tract disease, and consider further urinary tract investigation and treatment if this is suspected.** **14. Refer people with changes in urinary function that may be due to new or progressing neurological disease needing specialist investigation (for example, syringomyelia, hydrocephalus, multiple system atrophy or cauda equina syndrome).** **15. Assess the impact of lower urinary tract symptoms on the person's family members and carers and consider ways of reducing any adverse impact. If it is suspected that severe stress is leading to abuse, follow local safeguarding procedures.**
Relative values of different outcomes	No evidence was found that addressed this clinical question. The GDG made recommendations based on their clinical experience and what they believed to represent current best practice.
Trade off between clinical benefits and harms	Taking a history and conducting a physical examination of patients constitutes usual practice for this group of patients. The GDG considered that it was not possible to treat the patient's NLUTD without having an understanding of how the underlying neurological condition was impacting on them. The GDG considered frequency volume charts, completed by the patient, to be a valuable assessment. It was noted that input charts may provide additional useful information. These investigations are not associated with side effects and, in general, cause only minor inconvenience. The use of portable ultrasound to measure residual urine volume was considered preferable to the use of catheter-measured residual volume measurements in view of

	the reduced discomfort, absence of risk of infection, and patient acceptability. The use of urine testing will be helpful in identifying conditions (such as urinary tract stones) that cause inflammation in the urinary tract and also urinary tract infection. Rarely, an abnormal urine test will result in the diagnosis of a urinary tract malignancy being made. Treatment of such problems can be of major benefit to the patient. However, urine testing can lead to over-investigation and the unnecessary prescription of antibiotics in some patients. These problems can arise if inappropriate samples are analysed or if there is a failure to recognise that, in some patients (such as those using in-dwelling catheters), urine testing will often show abnormal results. Renal assessment by ultrasound examination is of value to the patient who has symptoms that might indicate renal disease (such as loin pain or haematuria) and can be used in screening patients who are believed to be at high risk of developing upper urinary tract complications such as hydronephrosis or stones. Little harm is likely to result from unnecessary scanning although patient inconvenience and, in some patients, anxiety are undesirable consequences.
Economic considerations	The assessment of the clinical history, the assessment of the impact of the neurological condition on several aspects, the general physical examination and the focussed neurological examination are associated with some increase in the clinician's time but they are not expected to increase costs considerably. In addition, these assessments are helpful when deciding the correct management of the patient. (recommendations 1 to 4) There are small costs associated with a urine dipstick test and they are likely to be offset by benefits of the useful information obtained with this test (recommendation 5). The GDG agreed that being selective in offering a urine culture to patients using a catheter, suspected of having a urinary tract infection will reduce the usage of this test and will lead to cost savings for the NHS (recommendation 6). The completion of a volume chart by the patient/carer is associated with some increase in the clinician's time. Whilst it can take some time to explain the use of charts to the patient, the GDG agreed that their use helps by providing objective measurements of parameters such as urinary frequency, voided volumes and frequency of incontinence episodes. This benefit is likely to lead to cost savings for the NHS in the future due to better monitored patients and a better understanding of the patient's condition (recommendation 8). The GDG thought the high cost of pressure-flow studies (£147) would be justified for some patients and therefore decided to recommend this test only, without being prescriptive. It is likely that any cost incurred through this would be offset by better managenent of the patient's condition (recommendation 9).The cost of an ultrasound scan varies from £55 (less than 20 minutes) to £71 (more than 20 minutes).The GDG considered this cost to be justified the benefits of the information obtained by measuring the post-void residual urine volume. Renal ultrasound is associated with additional cost and the GDG thought this test should only be performed in patients who have an increased risk of renal complications. The costs of renal ultrasound would therefore be offset by the savings made through better renal protection. (Recommendation 10).). Referring patients for urgent investigation is associated with some additional costs but the GDG thought these costs would be offset by a prompt diagnosis when the signs indicate some serious conditions requiring immediate treatment (recommendation 11 and 12).
Quality of evidence	No clinical or economic studies were found for this question. The GDG drafted recommendations based on consensus opinion. The GDG agreed that some patients with NLUTD, such as those with spinal dysraphism and spinal cord injury, are at high risk of developing renal damage and that many patients with NLUTD will develop lower urinary tract complications. The group agreed that it was important to make a recommendation for referral for further investigation.

	The GDG discussed the needs of carers and highlighted that it is important to consider and evaluate the impact of a patient's NLUTD on their carers and social circumstances.
Other considerations	The GDG considered that it was important to specify a general examination be undertaken, as treating the urological condition was not possible without an overall assessment of the patient, and if not carried out could lead to inappropriate treatments being offered. The 'red flag' signs and symptoms which would warrant urgent referral were identified by a sub group of the GDG and agreed with the whole group through informal consensus. The GDG noted that the inappropriate prescription of repeated courses of antibiotics for patients with asymptomatic bacteriuria was not uncommon.

6.2 Urodynamics

6.2.1 Does the use of urodynamics (filling cystometry, leak point pressure measurements, pressure-flow studies of voiding, video urodynamics) direct treatment or stratify risk of renal complications (such as hydronephrosis).

Clinical Methodological Introduction	
Population:	Patients with NLUTD
Intervention:	filling cystometry leak point pressure measurements pressure-flow studies of voiding video urodynamics
Comparison:	Not applicable
Outcomes:	Direct treatment Stratify risk

6.2.1.1 Clinical Evidence

We searched for observational studies reporting on the value of filling cystometry, leak point pressure measurements, pressure-flow studies of voiding, and video urodynamics in directing treatment or stratifying risk. The evidence is presented according to whether the patient population is at high or low risk of renal complications. Many studies used terms which no longer reflect current International Continence Society terminology. Where possible, non-standard terms are accompanied by ICS-approved terms [in square brackets].

STUDY POPULATIONS AND METHODOLOGY

<u>Studies on the predictive value of urodynamics in people at high risk, especially regarding renal complications:</u>

Myelodysplasia

Seven studies included patients with myelodysplasia/spinal dysraphism. Four studies looked directly at the predictive value of urodynamics in people at high risk of upper tract deterioration [13] [14] [15] [16]. Three studies looked at scoring systems or statistical models based on urodynamic findings to predict upper tract changes[17] [18] [19].

Spinal cord injury

Two studies examined patients with spinal cord injury[20 21].

Men with multiple sclerosis

One study looked at men with multiple sclerosis [22]

Children and anorectal anomalies

One study reported on children born with anorectal anomalies [23].

Studies on the predictive value of urodynamics in people at lower risk, especially regarding renal complications

Women with multiple sclerosis

One study examined women with multiple sclerosis [24]

Following augmentation cystoplasty

One study looked at children following augmentation cystoplasty[25]

Head injury

One study examined adults following a head injury [26]

Studies on the predictive value of urodynamics in people in known high risk groups actively managed with urodynamic-directed protocols

Five studies reviewed patients managed with urodynamically directed protocols. Two studied children with spinal cord injury [27; 28], two studied children with myelodysplasia [29; 30] and two involved adults with spinal cord injury [31; 20].

Study quality

The majority of the studies reported their findings as a descriptive narrative and did not include any statistical analysis. A number of the studies were retrospective. Some of the studies included only a small proportion of patients with upper tract changes. In addition to the risk of bias from a lack of randomisation, most studies were before and after designs, without an independent comparison group, and so contained additional risks to internal validity.

STUDY RESULTS

Studies on the predictive value of urodynamics in people at high risk, especially regarding renal complications:

Myelodysplasia

One prospective study involved newborns with myelodysplasia [13] (n=36) (follow up 18-24 months). Patients had urodynamic assessment specifically looking for detrusor sphincter dyssynergia with a view to preventing hydronephrosis using intermittent catheterisation. Urodynamic evaluation showed 18 patients had dyssynergia of the detrusor and external sphincter, nine had synergic activity of the sphincter, and nine had no activity of the sphincter. Thirteen (72%) of the group with dyssynergia had, or later were found to have, hydroureteonephrosis, while this was the case in only two (22%) with synergistic and one (11%) with absent sphincter activity.

One study looked at the clinical progress of patients with myelodysplasia (n=42) (age not specified) over a mean follow up of 7.1 yrs (range 3 to 15 yrs) [14]. The patients had serial radiographic studies that included excretory urography (IVP) and voiding cystourethrography. All had undergone

extensive urodynamic evaluation including urethral pressure profilometry, simultaneous determination of urethral pressure, intravesical pressure and external anal or external urethral sphincter electromyography with fluoroscopic voiding cystourethrography. The intravesical pressure at the time of urethral leakage was 40 cm H_20 or less in 20 patients and at a pressure greater than this value in 22 patients. No patient in the low pressure group had vesicoureteric reflux and only two showed ureteric dilation on excretory urography. In contrast, of the patients in the higher pressure group, 15 (68%) showed vesicoureteric reflux and 18 (81%) showed ureteric dilation on excretory urography (see table below). The study demonstrated a strong relationship between both the urethral closure pressure [urethral pressure] and the intravesical pressure at the time of urethral leakage and the clinical course of patients with myelodysplasia.

Table 8: Relationship of urethral opening (leak point) pressure to ureteric complications

	Urethral opening pressure [non-standard term]	
	< 40 cm water No. (%)	> 40 cm water No. (%)
Vesicoureteric reflux	0	15 (68)
Ureteric dilatation	2 (10%)	18 (81)

One cross-sectional study [15] involved 39 patients with myelodysplasia (not newborns, but age not stated) and described the relationship between age, bladder compliance, maximum urethral closure pressure (MUCP), sex, detrusor sphincter dyssynergia (DSD) and detrusor hyperreflexia [neurogenic detrusor overactivity] and the incidence of vesico-ureteric reflux (VUR) and hydronephrosis. The study set out to correlate urodynamic risk factors and upper urinary tract outcomes. The results of the multivariate analysis are presented below (age, sex and bladder compliance were not significant predictors of upper tract deterioration).

Table 9: Multivariate analysis of the incidence of VUR and hydronephrosis

Variables	**Coefficient**	**SEM**	**OR**	**P**
VUR				
MUCP	0.10	0.04	1.10	0.013
DSD	2.93	1.04	18.76	0.005
Hydronephrosis				
MUCP	0.07	0.03	1.08	0.034
DSD	ns	ns	ns	0.074

One prospective study (n=30) [16] aimed to identify neonates with myelomeningocele at risk of changes in the upper urinary tract followed up for a mean on 18.2 months. Initial studies included cystourethrography, excretory urography and urodynamic tests. Follow up consisted of periodic radiographic studies and repeat urodynamic testing if changes were observed. Two groups were identified based on the urodynamic findings: one group (n=9) with detrusor-sphincter dyssynergia and high pressure, decreased-compliance bladders, and a second group (n=21) with atonic or low pressure bladders without dyssynergia. Abnormal radiographic changes were found in 55% and 28.5% of the first and second groups respectively. Anticholinergic medication and clean intermittent catheterisation or vesicostomy reversed the changes in 40% of the children in group 1, 40% remained stable and 20% showed signs of deterioration. Four children in group one with normal neonatal radiographs were treated expectantly and at follow up they all showed signs of deterioration. The neonates in group 2 with normal radiographic findings remained normal at follow up. Of those who initially had changes, 67% reversed to normal without treatment, 17% remained stable and 17% had deterioration.

One study [18] aimed to achieve an objective statistical analysis of the multiple risk factors of renal injury using data from 215 children with myelodysplasia and neurogenic bladder impairment (data collected for 2 yrs). In the regression analysis a constellation of urodynamic and radiographic

parameters influenced the grade of hydronephrosis. The regression coefficient was 0.49. These factors included an elevated urethral pressure, bladder volume smaller than the mean volume for age, presence of detrusor sphincter dyssynergia, and presence and grade of vesicoureteric reflux. Each of these was treated as independent variables in the analysis and reached a significance level of less than 0.05. Elevated urethral pressures on urethral pressure profilometry (p=0.008), bladder volume at or less than the mean for age (p=0.01) and presence of detrusor sphincter dyssynergia (p=0.02) contributed to elevated hydronephrosis grade.

One study (n=103) [19] investigated the possibility of using urodynamic variables to predict upper urinary tract dilation (UUTD) in children with neurogenic bladder-sphincter dysfunction (NBSD) (mean age 10.5 yrs). A urodynamic risk score was calculated with one point being awarded for each of: a detrusor leak-point pressure of >40 cmH2O, bladder compliance of <9 mL/cmH2O and/or evidence of an acontractile detrusor. There was a positive correlation between the urodynamic risk score and changes in the upper urinary tract. A Spearman rank correlation coefficient was 0.634 when a bivariate correlation was used. If a urodynamic risk score of $\geq$ 2 was defined as the urodynamic criterion for predicting upper urinary tract dilation in children with NBSD the study population generated a sensitivity of 68% (70/103) and a specificity of 82% (70/85). The authors conclude that the selective use of urodynamic variables might be valuable for predicting the risk of UUTD in children with NBSD. The main risk factors identified were decreased bladder compliance, increased detrusor leak-point pressure and an acontractile detrusor, and they reciprocally increase the occurrence and grades of UUTD. The relationship between the risk score and degree of upper tract dilatation is illustrated in the table below which uses the following upper tract grading system: group 1- grade 1 hydronephrosis and pelvic dilatation of < 1 cm; group 2 – grade 2-3 hydronephrosis and pelvic dilatation of > 1 cm but < 1.5 cm, and mild dilatation of the renal calyces; and group 3 – grade 4-5 hydronephrosis with pelvic dilatation of > 1.5 cm, mid-range dilatation of the renal calyces and thinning of renal parenchyma. The control group were children with NSBD but no upper urinary tract dilatation or vesicoureteric reflux.

Table 10: Urodynamic risk score and upper urinary tract changes

		Upper urinary tract dilation group (n=103)			
Risk score	Control	1	2	3	Total
0	52 (54)	4	5	1	10 (10)
1	30 (31)	17	3	3	23 (22)
2	11 (11)	7	6	11	24 (23)
3	4 (4)	6	20	20	46 (45)

One study [17] developed an objective scoring system to describe urodynamic findings in myelodysplasia. Scores were calculated for a cohort (n=171) patients with myelodysplasia (mean age at the time of urodynamics was 4.8 yrs and mean follow up of 2.3 yrs). See below for details of the score. Reflux, leak point pressure and bladder compliance were shown to correlate significantly with upper tract changes at the time of urodynamics. Outlet resistance (leak point pressure), bladder compliance, sphincter behaviour and reflux had predictive value with respect to upper tract changes at follow up.

Table 4:Scoring system

		Score	
	0	1	2
Reflux (right and left)	Absent	Grade I-II	Grade III+
Hyperreflexia [neurogenic detrusor overactivity]	Absent	15-50	>50 cm water
Compliance	>20	10-20	<10

		Score	
Leak Pressure [non-standard term]	<25	25-50	>50 cm water
Sphincter	Relaxing	Nonrelaxing	Dyssynergic

Spinal cord injury

The "bladder leak point pressure"[non-standard term] was examined retrospectively in patients with spinal injury and detrusor-external sphincter dyssynergia who had undergone transurethral resection of the external sphincter (n=55; mean age 50 yrs) (follow up performed every one to three years, most recent used) [21]. 36/55 (65%) patients had a bladder leak point pressure greater than 40 cm H_20 and 19/55 (35%) had a pressure less than 40 cm H_20. There was no significant correlation between an elevated bladder leak point pressure and the presence of reflux, stones, bacteriuria or autonomic dysreflexia. There was a significant correlation between elevated bladder leak point pressure and renal damage (p=0.021).

Men with multiple sclerosis

In one prospective study (n=27) [22], men with multiple sclerosis (mean age 41 yrs) underwent synchronous video pressure-flow electromyography studies to explore voiding dysfunction. 18/27 patients had detrusor-external sphincter dyssynergia. 9 of the 18 suffered serious urological complications. Management had included anticholinergics and clean intermittent catheterisation (7/18), condom catheter drainage alone (5/18), indwelling catheter (5/18) or no treatment (1/18). An excretory urography (IVP) revealed normal upper tracts in 21 patients, while 5 with detrusor-external sphincter dyssynergia had bilateral hydronephrosis (grades 3 to 4 in 3 patients with type 3 dyssynergia, and grades 1 to 2 in type 1 and 1 with type 3 dyssynergia). One patient with type 1 dyssynergia had a small caliceal stone. Urological complications correlated strongly with the presence of detrusor-external sphincter dyssynergia.

Children and anorectal anomalies

One study (n=26) [23] investigated children (mean age 25.6 months) with anorectal malformations. All patients were evaluated with leak point pressures (LPP) [non standard term], renal ultrasound scanning, and voiding cystourethrography (urodynamic data collected at different time points). 21/26 demonstrated elevated LPPs above 40 cm H2O; 15 of these children had normal spinal imaging study findings. Uroradiographic findings showed that 12 of the 21 children with elevated LPPs had hydronephrosis or vesicoureteric reflux, with 7 of these having normal spinal cord imaging.

Groups at lower risk especially regarding renal complications:

Women with multiple sclerosis

One study (n=108) [24] investigated the impact of a dyssynergic bladder outlet on intravesical pressures in women with multiple sclerosis (mean follow up 12 yrs). 62/108 (57%) had detrusor overactivity. 30 of these had coexisting bladder outlet dyssynergia. Nonsignificant elevations in detrusor pressures were found in these patients. See table below for urodynamic findings.

Variable	Patients with DO + DSD (n=30)	Patients with DO, no DSD (n=32)	P value
Amplitude at initial DO (cm H2O)	21.93 ± 20.712	21.33 ± 12.863	0.530
Volume at DO (mL)	202.27 ± 146.704	173 ± 150.87	0.788
Pdetmax (cm H2O)	49.77 ± 20.88	41.03 ± 22.590	0.428

Variable	Patients with DO + DSD (n=30)	Patients with DO, no DSD (n=32)	P value
Cystometric capacity	301.52 ± 175.418	272.58 ± 192.582	0.517
Qmax (mL/s)	11.26 ± 5.833	12.96 ± 7.203	0.690
PdetQmax (cm H2O)	35.77 ± 14.429	30.00 ± 14.431	0.566
Voided volume (mL)	208.74 ± 123.729	182.38 ± 129.96	0.800
PVR (mL) Median Range	 50 0-500	 37 0-500	

Pdetmax – maximal detrusor pressure; Qmax – maximal flow rate; PdetQmax – detrusor pressure at Qmax; PVR – postvoid residual urine volume; DO – detrusor overactivity; DSD – detrusor sphincter dyssynergia

With regard to upper tract findings, all patients underwent ultrasonography, and no patients in either group had hydronephrosis. Two of the patients with bladder outlet dyssynergia and three with detrusor overactivity alone had focal caliectasis.

Following augmentation cystoplasty

One study (n=32)[25] assessed clinical and urodynamic outcomes, over a minimum 10-year follow up period, in neuropathic bladder patients (mean age at the end of study 22 years) who had been treated with augmentation cystoplasty. They sought to determine if periodic urodynamic studies are needed in such cases. The authors found that augmentation cystoplasty improved bladder capacity and pressure, and that these changes were maintained over time (see table below). Before augmentation cystoplasty five patients had hydronephrosis compared to none after the procedure; the equivalent numbers for vesicoureteric reflux were 20 and four respectively.

	Preoperative	1 year	P	End	P
MBC	106±52	396±125	<0.0001	507.8±165*	<0.002*
MEFDP	50±32	7±4	<0.0001	10±4	NS*

MBC – mean bladder capacity (ml); MEFDP – mean end-filling detrusor pressure (cm of water); ns – not significant. * Statistical significance between the urodynamic results at 1 yr after augmentation cystoplasty and at the end of follow up.

Head injury

One prospective study (n=11, mean age 40 yrs) [26] explored the use of urodynamic investigations in adults after head injury (time between trauma and urodynamics variable but not specified). 10/11 patients had an indwelling catheter which was then removed after urodynamic assessment. 3/11 (27.3%) patients had an unstable bladder [neurogenic detrusor overactivity] with multiple involuntary contractions in the filling phase. No other abnormalities were found. At one year follow up all three patients had a normal voiding pattern and the upper tracts were normal on ultrasound in all patients. The 8/11 who had normal urodynamics had successful trials without catheter after urodynamic assessment.

Patients in known high risk groups actively managed with urodynamic-directed protocols:

Children with spinal cord injury

In one study (n=40) [27] of children (mean age 9 years) with spinal cord injury the outcome of management based on urodynamic evaluations (mean follow up 46.1 months) was retrospectively

reviewed. Patients having moderate to severe trabeculation of the bladder and correspondingly high intravesical pressures and patients exhibiting detrusor-sphincter dyssynergia on video urodynamics were placed on anticholinergic drugs and intermittent catheterisation. Patients and families desiring continence were also started of intermittent catheterisation, with medications, if indicated. Of the 28 patients with a follow up of more than one year, preservation of the upper urinary tract was observed in 26. Upper tract surveillance showed preservation of the upper tracts in all patients with anatomically normal lower tracts.

One study (n=42) [28] retrospectively reviewed children (mean age at injury 5.3 yrs) with spinal cord injury with one year minimum follow up data (mean 5.5 yrs) from videourodynamics. Bladder management included clean intermittent catheterisation in 40/42 patients and antispasmodics in 37/42. No patient had reflux, hydronephrosis or renal scarring. The results are presented below.

	Cervical	Thoracic	Lumbar
No patients	10	26	6
Average age at injury (yrs)	4.8	5.9	3.4
Clean intermittent catheterisation	80%	96%	100%
Dry	80%	54%	33%
Detrusor sphincter dyssynergia	30%	31%	0
Hyperreflexia [neurogenic detrusor overactivity]*	60%	38%	17%
Anticholinergics	60%	100%	83%
Safe capacity less than expected capacity	80% (8/10)	58% (15/26)	50% (3/6)
Safe capacity increasing with age**	100% (5/5)	76% (13/17)	67% (2/3)

*Includes 2 children who initially had hyperreflexia but subsequently underwent augmentation

** Includes patients with two or more urodynamic studies

Myelodysplasia

In one study (n=123, mean follow up 10 yrs) [29], patients with myelomeningocele had a full history, neurological examination, urinalysis, urine culture, excretory urography, sonography of kidneys and bladder and video urodynamics carried out at birth or 2 weeks after closure of their spinal defect; those at risk of upper tract damage or with abnormal imaging had a nuclear renal scan performed. The treatment strategy was as follows: patients with an overactive sphincter had intermittent catheterisation; those with an overactive detrusor were treated with anticholinergics; when continence was not achieved, surgery was considered (artificial urinary sphincter, augmentation cystoplasty or orthotopic bladder substitution). Urinary continence at last follow-up in relation to the urodynamic pattern at initial evaluation is presented in the table below.

Group 1: overactive detrusor + overactive sphincter (upper urinary tract at risk due to high pressures)

Group 2: overactive detrusor + underactive sphincter

Group 3: underactive detrusor + overactive sphincter

Group 4: underactive detrusor + underactive sphincter

	Group 1 n=43	Group 2 n=37	Group 3 n=8	Group 4 n=35	Total n=123
Continent or socially dry	37 (86%)	21 (57%)	7 (87%)	26 (74%)	91 (74%)
Incontinent	6 (14%)	16 (43%)	1 (13%)	9 (26%)	32 (26%)

One study (n=114) [30] reported on the outcomes of children (newborn to 23 yrs old) with myelodysplasia treated using a urodynamically-based protocol (follow up minimum 18 months maximum 40 months). Patients with bladder filling pressures or pressures at the time of leakage greater than 40 cm H_20 (determined by cystometry) were treated to reduce intravesical pressure. 42% required treatment for high intravesical pressures. None of this group or those with low bladder pressures showed progressive upper urinary tract deterioration. In 8 children (17% of those with high pressure dysfunction) high intravesical pressure persisted despite anticholinergic medication and intermittent catheterisation, and they required an operation to achieve low pressure urine storage.

Spinal cord injury

One retrospective study (n=80) [31] (mean age 29.6 yrs) assessed the long term results of a urodynamic-based treatment regime in patients with neurogenic lower urinary tract dysfunction due to spinal cord injury. All patients had at least one follow up visit a year for a minimum of five consecutive years. At initial presentation 51 patients performed intermittent catheterization, seven had indwelling catheters, 10 utilised reflex voiding, two patients had been implanted with a Brindley stimulator and 10 patients used abdominal straining. At the end of the study no patients had signs of renal damage. This was achieved by patients undergoing sphincterotomy (n=8), augmentation cystoplasty (n=3), Koch pouch (n=1) and botulinum-A-toxin injections (n=12). 22 patients received intravesical anticholinergic therapy. Only three patients did not have their treatment modified during the entire follow up.

One prospective study (n=100) [20] (age range 21-56 yrs) performed urodynamic studies in order to establish a bladder management protocol in patients with spinal cord injury. A total of 82% patients underwent three or four urodynamic studies. At baseline, no urodynamic findings were normal. Findings included detrusor hyperreflexia [neurogenic detrusor overactivity] with detrusor external sphincter dyssynergia (DESD) in 85% of patients with thoracic lesions; detrusor hyperreflexia without DESD in 35% of patients with cervical and lumbar lesions; and detrusor areflexia in 40% of patients with lumbar lesions. The use of clean intermittent catheterisation and anticholinergic medication was instituted in all patients. The table below describes the complications found in this study.

Complication	Number of cases (%)
Upper tract changes (Backpressure)	15 (15)
Autonomic dysreflexia	12 (12)
Chronic renal failure	6 (6)
Stricture urethra	6 (6)
Bladder calculi	4 (4)
Refractory hypotension	1 (1)

6.2.1.2 Economic evidence

No relevant economic evaluations that looked at urodynamic strategies for the assessment of neurological incontinence were identified.

Economic considerations

The GDG thought that in current practice, urodynamic tests are usually used in specific populations of patients. However, these tests are also currently used unnecessarily in some groups of patients (such as patients with multiple sclerosis). The GDG suggested that a better selection of patients for urodynamic tests will lead to a better use of resources and to cost savings for the NHS.

Urodynamic tests involve cost which is not negligible (Dynamic Studies of Urinary Tract = £154 – NHS reference costs 2009-10). This assessment includes both the cost of equipment and the cost of an appointment with a clinician. Other cost implications can also be considered here if the balance is not correct. In some cases, patients who do not undergo urodynamic tests could fail to be classified as high risk, and therefore have an increased likelihood of renal damage due to lack of care. On the other hand if too much urodynamic testing takes place, this leads to wasted time and money on unnecessary tests. However, while these are important issues to consider, the clinical review did not provide any evidence of the number or type of missed cases, therefore classification and costing of these is difficult. The GDG judged that offering urodynamic tests to patients who will benefit from it by an improvement of their medical management is cost-effective use.

6.2.1.3 Evidence statements

Clinical

Studies on the predictive value of urodynamics in people at high risk especially regarding renal complications	
Population	Conclusions of study authors
Myelodysplasia [13] N=36	Infants with dyssynergia of the detrusor-external sphincter are at high risk of deterioration of the urinary tract; they should be followed up closely and intermittent catheterisation should be started early
Myelodysplasia [14] N=42	There is a strong relationship between the urethral closure pressure and intravesical pressure at the time of urethral leakage and the clinical course in patients with myelodysplasia.
Myelodysplasia [15] N=39	There is a significant correlation in patients with myelodysplasia between the degree of upper urinary tract deterioration and abnormal lower urinary tract function, especially for the disordered function of the urethral control mechanisms
Myelodysplasia [16] N=36	Children with detrusor-sphincter dyssynergia and high pressure, decreased-compliance bladders require treatment with anti-cholinergics and intermittent catheterisation. Children with atonic bladders and low pressure, reduced-compliance bladders without dyssynergia do not require such treatment. Both groups require close monitoring
Myelodysplasia [18] N=215	A constellation of urodynamic and radiographic parameters influenced the grade of hydronephrosis
Myelodysplasia [19] N=103	The selective use of urodynamic variables might be valuable for predicting the risk of upper urinary tract damage in children with neurogenic bladder-sphincter dysfunction
Myelodysplasia [17] N=171	An objective score to describe urodynamic findings offers a simple objective measure of lower urinary tract function, which seems to reflect the potential of

Studies on the predictive value of urodynamics in people at high risk especially regarding renal complications	
	the neurogenic bladder to damage the upper tracts
Spinal cord injury [21] N=55	Bladder leak point pressure greater than 40 cm water is a valid indicator of failure of transurethral resection of the external sphincter given that there is a significantly higher incidence of upper tract damage and persisting external detrusor-sphincter dyssynergia in these patients
Men with multiple sclerosis [22] N=27	Urologic complications correlate highly with the presence of detrusor-external sphincter dyssynergia
Children and anorectal anomalies [23] N=26	Patients with anorectal malformations and any uroradiographic or clinical urological abnormality should undergo urodynamic testing even though the spinal studies are normal.
Groups at lower risk especially regarding renal complications	
Population	Conclusion of study authors
Women with multiple sclerosis [24] N=108	Clean intermittent catheterization should not necessarily be dictated by a concern for upper tract damage secondary to increases in intravesical pressure, even among women with dyssynergia
Following augmentation cystoplasty[25] N=32	Repeat urodynamics are only necessary when upper urinary tract dilation or incontinence does not improve
Head injury [26] N=11	Voiding dysfunction is common following head injury. Bladder hyperreflexia is seen with injuries about the pontine micturition centre. The voiding abnormality has good prognosis and resolves spontaneously
Patients in know high risk groups actively managed with urodynamic-directed protocols	
Population	Conclusions of study authors
Children with spinal cord injury [27] N=40	Aggressive follow up is recommended in this group of patients with yearly renal ultrasound and video urodynamics every one to two years
Children with spinal cord injury [28] N=42	Serial urodynamics confirm increasing safe capacity with growth in most children. Close follow up is necessary as bladder characteristics may change with time.
Myelodysplasia [29] N=123	Initial urodynamic pattern is useful for counselling families on the likelihood of achieving continence, and serial urodynamic studies thereafter are a pre-requisite for an adequate treatment strategy
Myelodysplasia [30] N=88	Children, where high intravesical pressure persisted despite anticholinergic medication and intermittent catheterization, require an operation to achieve low pressure
Spinal cord injury [31] N=80	For the protection of the upper urinary tract and maintenance of continence, regular urodynamic follow-up is warranted
Spinal cord injury [20] N=100	Repeated urodynamic studies are an essential aid in managing the evolving nature of bladder dysfunction

Economic evidence statement

The selective use of diagnostic investigations, in addition to clinical assessment, is likely to be cost-effective in patients who will benefit from the additional information provided leading to an improvement in their medical management.

6.2.2 Recommendations and Link to Evidence

Recommendations:	**<u>URODYNAMIC INVESTIGATIONS</u>** **16. Do not offer urodynamic investigations (such as filling cystometry and pressure-flow studies) routinely to people who are known to have a low risk of renal complications (for example, most people with multiple sclerosis).** **17. Offer video-urodynamic investigations to people who are known to have a high risk of renal complications (for example, people with spina bifida, spinal cord injury or anorectal abnormalities).** **18. Offer urodynamic investigations before performing surgical treatments for neurogenic lower urinary tract dysfunction.**
Relative values of different outcomes	The GDG recognised that the use of urodynamic investigations may be of high importance as they have the potential to guide treatments which will impact on very important outcomes which include quality of life, preservation of renal function and improved continence.
Trade off between clinical benefits and harms	The evidence indicated that urodynamic investigations did have a predictive value, particularly in relation to upper tract deterioration, in the following high-risk groups: • Spinal dysraphism • Spinal Cord Injury • Some Male Multiple Sclerosis • Some patients with Anorectal Anomalies Evidence from low-risk groups including: • Female Multiple Sclerosis • Patients after augmentation cystoplasty • Head injury confirmed that these groups had essentially benign urodynamic findings which correlated with preservation of normal upper urinary tracts. The GDG therefore concluded that urodynamic investigations have the potential to provide important benefits to patients through accurate assessment of the precise nature of their NLUTD. However, for patients in low-risk groups who were to be managed using conservative treatments, there is no compelling evidence that demonstrates significant benefit from a urodynamics-driven management approach and any benefit will be offset against the adverse effects, inconvenience and costs of urodynamic investigations. The use of radiological screening in conjunction with urodynamic studies (video-urodynamics) is recommended by the GDG on the basis that several significant abnormalities that are commonly seen in patients with neurogenic LUT dysfunction cannot be diagnosed without the additional anatomical information that X-ray screening provides; these abnormalities include vesico-ureteric reflux and detrusor-sphincter dyssynergia. The GDG noted that there is an international consensus that video-urodynamics should be used when filling cystometry and pressure-flow studies are indicated in patients with neurogenic LUT dysfunction. The possible adverse effects of urodynamic investigations include discomfort, urinary tract infection and psychological upset. Radiation exposure is an additional

	consideration when video-urodynamic investigations are used.
Economic considerations	Since urodynamic studies are fairly expensive, selectively offering these tests to patients at high risk of renal complications will lead to a better use of this resource for the NHS.
Quality of evidence	The studies reported on the predictive value of urodynamic findings for renal outcomes. This study design was appropriate for the clinical question under consideration. A number of the studies reported on findings over a number of years. Longitudinal studies which incorporated urodynamics into management algorithms demonstrated improved renal outcomes in patients with spinal dysraphism and spinal cord injury. The GDG recognised that some of the studies were carried out in an era when urodynamic testing had not been standardised to the extent that it has been today. They also noted that there is an absence of studies that use a control group to look at the alternative strategy of altering management based on the development of complications rather than attempting to pre-empt problems using urodynamic findings. There are many neurological conditions for which the value of urodynamic testing has not been evaluated by appropriate studies. The GDG recognised that the validity of using urodynamic testing/evaluation in patients with NLUTD was not being questioned within the literature. The group recognised that the evidence base rested on a limited number of small case series but that an absence of negative studies helps to support the recommendations. No economic evidence was found on this question.
Other considerations	The GDG believed that urodynamic investigations were currently being undertaken unnecessarily in some patients who would be considered to be at low risk of complications.

7 Information and Support

A clinical service that treats patients with NLUTD will face the need to inform and educate patients and carers. Information might be needed about relatively simple practical issues such as fluid management or may involve education about procedures such as intermittent self catheterisation. However, in some cases, there are complex decisions to be made that involve weighing up benefits and risks. For example, parents of children with NLUTD might need to be involved with decisions about reconstructive surgery that will have life-long implications. In such circumstances decisions aids are likely to be of value.

A further challenge to clinicians who are providing information is the need to adapt the presentation of information to the individual patient's circumstances. Some patients will have significant cognitive and communication impairment due to their underlying neurological condition while others, such as patients after stroke or spinal cord injury, will be coping with major changes to their life of which their NLUTD is only one facet. The need for information to be appropriately presented to patients in the paediatric age group is self-evident.

One of the difficulties facing the patient with NLUTD is that of sifting information that comes from different sources. There are numerous on-line resources that provide information to patients; these include the websites of specialist hospital departments, disease-specific charities, patient groups and commercial organisations. There is a need to help patients and carers interpret information and apply knowledge to their own particular circumstances in an appropriate way.

7.1 Information and Support

7.1.1 Does the provision of information and support regarding the different management systems improve patient outcomes?

Clinical Methodological Introduction	
Population:	Children and adults with NLUTD
Intervention:	Provision of information and support regarding the different management systems
Comparison:	No information
Outcomes:	The outcomes as per the protocol were: • Frequency of voiding by day and night • No. of incontinence episodes per week • Symptoms related to bladder emptying e.g. poor urinary stream • Patient and carer perception of symptoms • Quality of life • Kidney function (hydronephrosis) • Maximum cystometric capacity • Bladder compliance • Residual urine • Treatment adherence • Adverse events Symptomatic urinary tract infection (UTIs)

7.1.1.1 Clinical Evidence Review

Four studies were found. Cardenas 2004[32] was an RCT, but lacked blinding or evidence of allocation concealment, thus being prone to bias. It evaluated effects on areas related to quality of life and patient perception of symptoms, but these outcomes were incompletely reported. For example, data on symptomatic UTIs were presented as episodes rather than counts of subjects affected, and group data were not presented for the other outcomes.

Hagglund 2005[33] and Anderson 1983[34] were trials, but not randomised. In the Hagglund 2005[33] paper, participants were allocated according to geographical area, and although the areas were evaluated for demographic similarity no baseline comparison of the groups were made, except for the outcome variable. Therefore this study was prone to considerable bias. The only relevant outcome reported was UTIs in the past 6 months. In the Anderson 1983[34] study, two cohorts of patients were treated at different times: 1975 and 1979. Although no attempts were made to match the groups, they were reportedly similar in terms of age, sex, proportion of quadriplegics and types of drainage used. Again, the only relevant outcome reported was number of UTIs in the past 6 months.

Barber 1999[35] was a prospective single-group observational study, and thus prone to bias through inevitable threats to internal validity. All patients had experienced $\geq$2 symptomatic UTIs during the 6 month period before intervention, and were deemed to have had a successful outcome if their count of symptomatic UTIs (or significant pyuria/bacteriuria) dropped to <2 in the 6 month period after intervention. Patients not responding after one session in the first 6 months were either offered further education sessions or antibiotic therapy. Those opting for further antibiotic therapy at 6 months (or later) were classified as outcome failures, although of course they may have responded to education sessions eventually had they been given the chance.

All outcomes from all four studies were graded as very low quality with respect to confidence in the effect of the interventions. Table 1 summarises the included papers.

Table 11: Summary of studies included in the clinical evidence review

Study	Study type	Underlying pathology	Age range (yrs)	Follow up (range)	Intervention details	Outcomes reported
Cardenas 2004[32](N=58)	RCT	SCI	Not specified, but adult	5-6 months	**Counselling on IC technique and fluid management** and discussion with the physician on UTI symptoms, the processes of seeking medical treatment for a symptomatic UTI and problems in accessing treatment. All information was backed up by a booklet.	Episodes of symptomatic UTIs; Health beliefs; Locus of control; self efficacy
Hagglund 2005[33](N=60)	Non randomised trial	SCI	Not specified, but probably adult	6 months	**6 hour personal assistance services (PAS) training workshop**. The workshop addressed prevention of common secondary conditions. It was chaired by a SCI physician, who provided information on preventing and treating pressure sores, UTIs, spasms, and autonomic dysreflexia. There was also information on bowel and bladder programs, general nutrition and weight loss strategies. Bladder management topics include types of catheters, proper insertion techniques, sterilisation and handling of reusable catheters, and signs of infection. UTI prevention was discussed alongside the use of an 8 minute video.	Symptomatic UTIs in the past 6 months

Study	Study type	Underlying pathology	Age range (yrs)	Follow up (range)	Intervention details	Outcomes reported
Anderson 1983[34](n=75)	Non randomised trial	SCI	Not specified, but probably adult	6 months post discharge	**A training program of discussion periods followed by practical workshops**. During the rehabilitation phase the patients attended 5 classes of 45 minutes each, on the topics of urinary tract care anatomy and physiology; bacteriology and UTI; monitoring the urinary tract, including danger signs and prevention; modes of urinary drainage, disinfection and appliance care; and trial of voiding and intermittent catheterisation. In addition, an instruction manual was developed for the patients and their families, who were also invited to join the teaching sessions. Patients were expected to follow the information and advice at home.	Symptomatic UTIs in the past 6 months
Barber 1999[35] n=17	Prospective observational study	SCI	Not specified, but probably adult	6 months or longer (not specified)	**Intensive counselling by the clinic nurse** with respect to proper clean intermittent catheterisation (CIC) technique, daily external condom catheter application and care, appropriate cleansing of supplies with dilute sodium hypochlorite solution and daily perineal hygiene. Sessions lasted 15-30 minutes. If the patient continued to exceed the threshold of 2 or more UTIs in the following 6 month period then they were either given further intensive counselling sessions, or placed on antibiotic therapy.	<2 Symptomatic UTIs in a 6 month post intervention period signified a positive outcome.

Incidence of symptomatic UTIs

Hagglund 2005[33] reported that the incidence of symptomatic UTIs was 78% at both baseline and follow up in the control group, but in the intervention group it reduced from 70% at baseline to 41% at follow up (data extrapolated from a figure). The groups did not differ significantly at baseline for the primary outcome, and so the follow up proportions were compared within a meta-analysis. Anderson 1983[34] reported that groups differed in terms of symptomatic UTIs at 6 months follow up, with an incidence of 29% in the Information group and 69% in the control group. However, no reports of baseline incidence were given. The GRADE profile below summarises these results.

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Information versus no intervention	control	Relative (95% CI)	Absolute	
Symptomatic UTIs (follow-up mean 6 months)										
Hagglund 2005[33]; Anderson 1983[34]	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	21/58 (36.2%)	55/77 (71.4%)	RR 0.47 (0.31 to 0.7)	379 fewer per 1000 (from 214 fewer to 493 fewer)	VERY LOW

[1] No blinding and no control for any confounding.

Incomplete reported outcomes

Episodes of symptomatic UTIs

Cardenas 2004[32] reported a trend for a lower number of total episodes of symptomatic UTIs in the intervention group (p=0.097), after adjustment for baseline values. At baseline the intervention group had 41 episodes of UTIs, which reduced to 32 at 6 months follow up, whilst the control group had 27 episodes at baseline and 26 at follow up.

Barber 1999[35] reported that the intervention led to 3/17 patients having a positive outcome (defined as less than a threshold of $\geq$2 UTIs/6 month period) after one intervention session. After an unspecified number of further intervention sessions (one per subsequent 6 month period) the total count of positive responders rose to 11/17. The 6 non-responders opted for antibiotics after one or more interventions, and thus it cannot be assumed they would not have responded to the intervention after more repetitions. Overall, repeated education sessions appeared to be more effective than a single session.

Patient and carer perception of symptoms/ quality of life

Cardenas 2004[32] compared the health beliefs, locus of control and self efficacy across the intervention and control groups, with adjustment for baseline scores. Compared to the control group, the group receiving the information intervention had a significantly increased perception of the severity of their UTIs, a decreased sense of self efficacy, and showed a trend for a higher locus of control. Unfortunately no data were presented apart from the ANCOVA results.

Table 12: Patient and carer perception of symptoms/ quality of life reported by Cardenas 2004[32]

	Information	Usual care	findings
Health beliefs questionnaire	no data provided	no data provided	Increased perception of severity of UTIs in the treatment group, after ANCOVA (p=0.042)
Multidimensional health locus of control	no data provided	no data provided	Trend for higher locus of control in the treatment group, after ANCOVA (p=0.066)
Self efficacy questionnaire	no data provided	no data provided	Decreased self-efficacy in the treatment group, after ANCOVA (p=0.033)

7.1.1.2 Economic evidence

No economic studies were identified on the provision of information and support.

7.1.1.3 Evidence Statements

Clinical Evidence Statements

Two non-randomised trials comprising 135 participants suggested that provision of information might reduce incidence of symptomatic UTIs (6 months) (very low quality).

Evidence statements could not be produced for the following outcomes of the study by Cardenas 2004[32] as results were presented in a way that meant we could not estimate the size of the intervention effect:

- Incidence of UTIs
- Patient and carer perception of symptoms/ quality of life

Evidence statements could not be produced for the following outcomes of the study by Barber 1999[35] as results were presented in a way that meant we could not estimate the size of the intervention effect:

- Incidence of symptomatic UTIs

Economic evidence statement

No economic studies were found on the provision of information and support for patients with NLUTD. The GDG believes that a better informed patient will result in fewer long term costs due to better adherence to treatment and a better understanding of self care. There was recognition of the need for good quality information to be provided and this would incur staff time cost especially when provided through face to face training by clinical staff.

7.1.2 Recommendations and links to evidence

Recommendations:	**INFORMATION AND SUPPORT** **19. Offer people with neurogenic urinary tract dysfunction, their family members and carers specific information and training. Ensure that people who are starting to use, or are using, a bladder management system that involves the use of catheters, appliances or pads:** • **receive training, support and review from healthcare professionals who are trained to provide support in the relevant bladder management systems and are knowledgeable about the range of products available** • **have access to a range of products that meet their needs** • **have their products reviewed, at a maximum of 2 yearly intervals.** **20. Tailor information and training to the person's physical condition and cognitive function to promote their active participation in care and self-management.** **21. Inform people how to access further support and information from a healthcare professional about their urinary tract management.** **22. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in 'Patient experience in adult NHS services' (NICE clinical guideline 138). Recommendations on shared decision making and information enabling people to actively participate in their care can be found in section 1.5 of NICE clinical guideline 138.**
Relative value placed on the outcomes considered	Urinary tract infection and quality of life were the only outcomes of interest reported but both were considered by the GDG to be of importance. In particular, reductions in urinary tract infections were considered to be highly important because urinary tract

	infection is a common problem which usually causes a degree of distress and can have serious health repercussions. If the provision of information was to demonstrate a reduction in UTIs this would be of clinical significance.
Quality of evidence	The GDG found the evidence to be limited in scope and of poor quality. The outcomes from all four studies were graded as being of very low quality due to limitations in study design. All of the studies reported a reduction in the incidence of symptomatic urinary tract infections; however, the outcomes were incompletely reported in two studies [32] and[35] and it was therefore not possible to estimate the size of the effect of the intervention. The GDG agreed that limited weight could be placed on the findings of the studies, but that they indicated a favourable trend in favour of the hypothesis that the provision of information helps patients to manage their condition successfully.
Trade-off between clinical benefits and harms	The provision of information for both patients and carers was considered important and likely to be beneficial. The GDG also recognised that ongoing support was needed for people with life long conditions. The provision of information was felt, in general, to be unlikely to cause significant harm.
Economic considerations	The GDG recognises that there are costs attached to training and information delivery but that these are likely to be offset by health gains due to improvements in patient wellbeing. A better informed patient might lead to fewer long term costs due to better adherence to treatment and a better understanding of self care.
Other considerations	The GDG believes that the current provision of information in this area is very variable, both in terms of quality and quantity. The types of interventions described in the studies ranged from counselling on intermittent catheterisation technique and fluid management to structured training programmes or workshops. Although it was not possible to recommend what form the information provision should take, the GDG agreed that information on treatment plans, self management techniques, and education on the management of urinary tract infections were areas where information provision was likely to be particularly beneficial for both patients and carers. The GDG agreed that the recommendations made on information provision in the Patient Experience guideline were highly relevant to this population and should be incorporated in the guideline. The stakeholder consultation process generated comments on the difficulties faced by some patients in accessing catheters, appliances and other products that effectively met their needs. The experience of the GDG members was that the quality of life of a person with neurogenic lower urinary tract dysfunction could be seriously affected if appropriate products were not available and if the staff who were giving advice had poor knowledge of the range and nature of available products.

8 Treatment to improve bladder storage

Dysfunction of the urinary bladder during the storage phase of the micturition cycle can take the form of either involuntary contractions of the bladder (neurogenic detrusor overactivity), or a loss of receptive relaxation of the bladder wall leading to a progressive increase in pressure as the bladder fills (reduced bladder compliance).

Both neurogenic detrusor overactivity and impaired bladder compliance can lead to symptoms, such as increased urinary frequency, urinary urgency and incontinence. In both conditions deterioration in renal function may occur due to an inability of the upper urinary tract to expel urine in the face of high pressures within the bladder. Patients may be deemed to be at high risk of renal deterioration either because their neurological condition is known to carry a high risk or as a result of the findings of urodynamic investigations. Conditions that are associated with a high risk of renal deterioration include spinal cord injury and spinal dysraphism while adverse urodynamic features include impaired bladder compliance and neurogenic detrusor overactivity in the face of an uncoordinated urethral sphincter (detrusor sphincter dyssynergia).

Incontinence and urinary frequency in patients with neurological disease also occur in the context of cognitive impairment as a result of difficulties with the interpretation of urinary tract sensations and a loss of the appreciation of the social context of micturition.

There are a number of treatment options available that seek to improve continence through improving the ability of the bladder to store urine. These include behavioural, drug and surgical treatments.

Behavioural Treatments to improve bladder storage

Behavioural treatments encompass a range of approaches that seek to train or re-train the neurological processes that control micturition in a way which promotes urine storage. For example, a patient might be prompted to empty the bladder at regular intervals in order to pre-empt episodes of urinary incontinence. Behavioural approaches in those with neurological disease are used for people with significant cognitive impairments such as dementia, often in the care home or hospital environment and also may be used in the early stages after acute neurological injury or illness as a means of re-establishing continence as the micturition cycle recovers. The treatment does not necessarily aim to alter the neural control of micturition, rather to manage toileting regimes to promote continence.

Types of Behavioural Treatments

Timed voiding – consists of taking the patient to the toilet at set time intervals, for example every 2 hours.

Prompted voiding – this is used to encourage people to initiate their own toileting. It usually involves positive reinforcement. It involves the use of a carer to take the person with incontinence to the toilet, and so involves education of both the person with incontinence and their carer

Habit re-training – involves working out an individual's toileting pattern and then developing a personalised toileting schedule to prevent involuntary voiding.

Behavioural treatments are not fully standardised, which hampers evaluation of their effectiveness. However, such evaluation is important as these treatments are widely used and can involve considerable use of resources in the form of staff time.

Drug Treatments to improve bladder storage

Acetylcholine is the neurotransmitter which has the primary role in stimulating contraction of the urinary bladder. The detrusor muscle of the bladder wall is rich in muscarinic receptors which, when activated by acetylcholine, trigger bladder contraction. Antimuscarinic drugs are muscarinic receptor antagonists and have the potential to reduce or abolish bladder contractile activity. They have long been established as the first line treatment for detrusor overactivity and symptoms of an overactive bladder. Antimuscarinic drugs may also have effects on bladder sensory mechanisms as muscarinic receptors are also found in the sub-epithelial neural plexus of the bladder [36]. The majority of these compounds are administered orally, although some intravesical antimuscarinic preparations have been developed. Early forms of antimuscarinics had a number of troublesome side effects, which newer compounds have sought to ameliorate. Antimuscarinics drugs were formerly known as "anti-cholinergics".

Antimuscarinic drugs have been used for many years to treat patients with neurogenic detrusor overactivity although the response of an individual patient to antimuscarinic treatment is variable. There are also important outstanding questions about the ability of antimuscarinic drugs to protect the upper urinary tract in the face of a high pressure, overactive bladder.

There are seven different types of botulinum toxin (A-G) but it is botulinum toxin type A which has become widely used in clinical practice, although Botulinum toxin type B has also been the subject of clinical trials. Botulinum toxin type A (BTX) acts by blocking the release of acetylcholine and other neurotransmitters from nerve terminals. Injection of the drug into the detrusor muscle using an endoscopic technique was described in Schurch et al in 2000[37] since then the use of BTX for treating neurogenic detrusor overactivity has become widespread. However, a number of questions have yet to be definitively answered so that the duration and adequacy of the response to the treatment in different patient groups has not been fully elucidated. It is also unclear whether or not the drug is sufficiently effective to prevent the development of hydronephrosis in the patient with high pressure urine storage due to either neurogenic detrusor overactivity or reduced bladder compliance. Finally, the cost of the drug and the requirement for injection via a cystoscope mean that the treatment is associated with significant costs which have to be balanced against clinical benefit; there is a lack of published data looking at economic issues in relation to BTX therapy.

Surgical Treatments to improve bladder storage

In cases where the functional capacity of the bladder is severely compromised and where drug therapies have proved ineffective, augmentation cystoplasty can be considered as a means of increasing bladder capacity and maintaining low storage pressures. Augmentation cystoplasty is a surgical procedure which involves opening the abdomen and exposing the bladder. The bladder is opened widely and a patch, made out of an isolated and de-tubularised length of intestine, is sewn into the defect in the bladder wall thereby increasing the capacity of the organ.

The principle of auto augmentation involves denuding (but not breaching) the urotheial lining of the bladder, in what is effectively an excision of detrusor muscle. This has sometimes been described with the adjunct of overlaying omentum or of a demucosalised intestinal patch in order to support the exposed bladder mucosa.

Augmenting a bladder usually impairs its intrinsic ability to empty to completion, and recourse to intermittent catheterisation is usually expected. This can be per urethra or via a continent, catheterisable abdominal conduit. This type of conduit consists of a narrow tube (the appendix is often used as the conduit) one end of which is anastomosed to the bladder while the other end is brought to the skin surface to form a small stoma. The bladder can be drained by passing a catheter through the conduit into the bladder. Urine is prevented from refluxing into the conduit, and leaking onto the skin surface, by creating a flap valve at the site of the anastomosis of the conduit into the bladder. Continent, catheterisable abdominal conduits are often called Mitrofanoff conduits, after the surgeon who helped to establish the principles of the surgical procedure.

Augmentation cystoplasty has been in routine use for treating selected patients with NLUTD for over two decades [38] but is known to be associated with significant morbidity. It is therefore important that the use of augmentation cystoplasty in patients with NLUTD is accompanied by careful consideration of the risks and benefits of the operation. The evaluation of the cost-effectiveness of augmentation cystoplasty has received little attention to date.

8.1 Behavioural treatments

8.1.1 Do behavioural management programmes (timed voiding, voiding on request, prompted voiding, bladder retraining, habit retraining, urotherapy) compared with a) each other b) usual care, improve outcomes?

Clinical Methodological Introduction	
Population:	Neurological disease
Intervention:	Prompted voiding Habit retraining Timed voiding Voiding on request Bladder retraining Urotherapy
Comparison:	To each other Treatment as usual
Outcomes:	Quality of life Frequency of voiding by day and night No. of incontinence episodes per week Patient and carer perception of symptoms Adverse events Treatment adherence

8.1.1.1 Clinical evidence

We searched for RCTs and systematic reviews comparing the effectiveness of behavioural management programmes for improving the outcomes of incontinence in patients with neurological disease or injury. We looked for any RCT studies that compared the effectiveness of one or more type of behavioural management programme with another behavioural management programme, or treatment as usual.

No RCTs or systematic reviews were found concerning behavioural therapy for incontinence in neurological disorders. However, two Cochrane systematic reviews and one RCT (which was not included in the Cochrane reviews) which were focussed on behavioural therapy for elderly adults with incontinence were found. It is possible that elderly people might respond differently to behavioural treatment, compared to patients with neurological disorders, because of a different aetiology of incontinence and differing levels of mobility. However, it was felt that in the absence of direct findings, the findings for elderly people might have some relevance, and that the findings could be downgraded for indirectness to account for the differing populations, according to GRADE guidelines. These three studies are summarised in table 9.

Table 13: Characteristics of the included studies

Study	Type of study	Population	Intervention	Comparator	Follow up
[39]	Cochrane review N=9	Average age was 84 years, and women	Prompted voiding.	No prompted	Interventions lasted from 20

Study	Type of study	Population	Intervention	Comparator	Follow up
	trials	predominated. Many were from nursing homes, and some were cognitively impaired and/or not independent in ADLs.		voiding. These patients were not given any placebo treatment or alternative treatment.	days to 32 weeks, but only two studies looked at longer term effects after cessation of intervention (12 and 22 weeks).
[40]	Cochrane review N=4 trials	Mean age was 80 years, and they were all physically and/or mentally impaired. They were mostly in nursing homes and dependent in ADLs.	Habit retraining + other treatment. Other treatments included: education to staff and caregivers, toileting prompt, electronic monitoring devices, fluid manipulation, and environmental modification and support.	Usual care	Interventions lasted from 6 weeks to 6 months. Only 1 study stated any longer term follow up: at 12 weeks.
[41]	RCT	Dependent elderly women >65 years with a mild or moderate mobility disorder who were suffering from chronic urinary incontinence (incontinence episodes 2x per week for at least 3 months). Participants were recruited from nursing homes, homes for the elderly and day care centres for non-demented elderly people.	Intervention provided by PTs or OTs on an individual basis, and aimed at training mobility and toileting skills. The therapy was focussed on those aspects of toileting that took longer than a threshold time. The tasks were practiced 3x per week for 30 mins, for a minimum of 1 week and a maximum of 8 weeks. Once the participant could achieve all tasks under the threshold time the intervention was allowed to be terminated.	Usual care	Up to 8 weeks (immediately post intervention). No long term follow up

The two identified systematic reviews and single RCT assessed the behavioural interventions of **prompted voiding, habit retraining and training mobility and toileting skills** (see Table 1 for details of these interventions). The first two behavioural interventions were the only practices contained in the protocol for which we found evidence. Training mobility and toileting skills was also included as a behavioural intervention as the GDG felt it potentially relevant.

The outcomes for **prompted voiding** which the GDG agreed were closely related to the proposed outcomes listed in 1.2:

- Numbers with no improvement of wet episodes
- Proportion of hourly checks that were wet
- Reduction in the mean proportion of hourly checks

- Incontinent episodes in 24 hours
- Self initiated toileting

The outcomes for **habit retraining** which the GDG agreed were closely related to the proposed outcomes listed in 1.2:

- Incontinent episodes in 24 hours
- Voided volume and incontinent volume
- Prevalence of bacteriuria
- Prevalence of skin rash*
- Prevalence of skin breakdown*
- Impact on caregivers*

The outcomes for **Training Mobility and Toileting skills** which the GDG agreed were closely related to the proposed outcomes listed in 1.2:

- Average weight of pads over 24 hours*
- Micturitions on toilet compared to total micturitions*
- Change from dependent to independent toileting*
- Change from independent to dependent toileting*

Most of the outcomes in the 12 RCTs included in the two Cochrane reviews were analysed in GRADE using the data and study quality information provided by the reviews. Separate GRADE profiles were created for the prompted voiding and habit retraining interventions. Those outcomes marked with an asterix (*) were not appropriate for meta-analysis or GRADE, and are described in a narrative account in the appropriate section.

Comparison of prompted voiding to no prompted voiding

Outcomes appropriate for GRADE

Table 14: Grade profile for outcomes relating to prompted voiding versus no voiding

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Prompted voiding Frequency (proportions) or Mean (sd)	no prompted voiding Frequency (proportions) or Mean (sd)	Relative (95% CI)	Absolute	
Number of people with no improvement in wet episodes										
Hu 1989 [39]	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	serious[c]	16/65 (24.6%)	24/68 (35.3%)	RR 0.7 (0.41 to 1.19)	106 fewer per 1000 (from 208 fewer to 67 more)	⊕OOO VERY LOW
Proportion of hourly checks that were wet (Better indicated by lower values)										
Schnelle 2003 [39]	randomised trials	Serious[a]	no serious inconsistency	very serious[b]	no serious imprecision	Mean (sd):23 (21)	Mean (sd): 35 (21)	MD: -12 (-18.79, -5.21)	MD 12 lower (18.79 to 5.21 lower)	⊕OOO VERY LOW
Reduction in mean proportion of hourly checks that are wet (Better indicated by higher values)										
Engberg 2002 [39]	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	very serious[d]	Mean (sd):40.6 (44.3)	Mean (sd): 23 (22.7)	MD: +17.6 (-14.58, +49.78)	MD 17.6 higher (14.58 lower to 49.78 higher)	⊕OOO VERY LOW
Incontinent episodes in 24 hours (Better indicated by lower values)										
Hu 1989 Schnelle 1989 [39]	randomised trials	very serious[a]	very serious[e]	very serious[b]	no serious imprecision	Hu: Mean (sd):1.65 (1.61) Schnelle: Mean (sd):2.1 (1.6)	Hu: Mean (sd): 1.9 (1.29) Schnelle: Mean (sd): 4.1 (2)	MD: -0.92 (-1.32, -0.53)	MD 0.92 lower (1.32 to 0.53 lower)	⊕OOO VERY LOW

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Prompted voiding Frequency (proportions) or Mean (sd)	no prompted voiding Frequency (proportions) or Mean (sd)	Relative (95% CI)	Absolute	
Self initiated toileting (Better indicated by higher values)										
Schnelle 1989 [39]	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	no serious imprecision[c]	Mean (sd):2.7 (1.2)	Mean (sd): 0.8 (1)	MD: +1.9 (+1.51, +2.29)	MD 1.9 higher (1.51 to 2.29 higher)	⊕OOO VERY LOW

[a] Although all of the studies described their randomisation procedure, allocation concealment was lacking or unclear in all. Only one study (Schnelle 2003) reported blinding of researchers, and so the outcome from that study was graded as having serious limitations, rather than the very serious limitations attributed to the other outcomes from the other studies. Downgrading for attrition bias was not carried out as insufficient detail was available from the review.
[b] The population in this outcome is potentially different to the population having incontinence secondary to neurological disorders.
[c] Upper 95% CI crosses the MID for clinically significant benefit
[d] Upper and lower 95% CIs cross the MIDs for clinically significant benefit and harm
[e] I squared was >75% so downgraded to very serious.

Narrative summary (for outcomes that are not appropriate for GRADE due to insufficient information given, such as a lack of variance data, or the presentation of numbers of episodes rather than cases)

Reporting of the outcome of *proportion of hourly checks that were wet* was not reported adequately to allow meta-analysis in 4 RCTs (Ouslander 2005, Schnelle 1983, Smith 1992, Surdy 1992) [39], as they lacked measures of variance and some used medians. These studies all found that the median or mean number of hourly checks that were wet were numerically greater in the control group, weakly suggesting a beneficial effect of prompted voiding (table 3). No statistical analysis was performed, but it can be seen that the probability of all 4 studies showing this trend by chance alone is only 6.25% (50% raised to the fourth power).

Table 15: Mean or median proportion of hourly checks that were wet

Study	Prompted voiding	No prompted voiding
Ouslander 2005	25%	50%
Schnelle 1983	15%	25.5%
Smith 1992	21%	85%
Surdy 1992	13.25%	49.95%

Incontinent episodes in 24 hours were reduced by 60% - 80% in the intervention group compared to 20-37% in the control group (Engberg 2002, Smith 1992) [39]. Linn (1995) [39] noted that treatment group incontinence reduced from 42% at baseline to 17% after treatment (Table 4). These results were incomplete and so could not be meta-analysed.

Table 16: Incontinent episodes in 24 hours – changes during the course of the study

	Prompted voiding	**No prompted voiding**
Engberg 2002	↓60%	↓37%
Smith 1992	↓80%	↓20%
Linn 1995	↓59%	No data

Self initiated toileting increased in the intervention group more than the control group in 3 studies (Scnelle 1983, Engberg 2002, Linn 1995) [39] and was greater in the intervention group for the final four weeks in one study (Hu 1989) [39], but these data did not include standard deviations (Table 5).

Table 17: Self initiated toileting – changes during the course of the study

	Prompted voiding	**No prompted voiding**
Schnelle 1983	↑ from 0.3 to 2 per day	↓to 0.2 per day
Engberg 2002	↑ from 2 to 3.3 per day	No change
Linn 1995	↑ from 0.38 to 2.3 per day	No change
Hu 1989	2.65 self-initiated episodes/day in final 4 weeks	1.12 self-initiated episodes/day in final 4 weeks

Comparison of habit retraining plus another treatment to usual care

Outcomes appropriate for GRADE

Table 18: Grade profile for outcomes relating to habit training + other treatment versus usual care

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Habit retraining plus another treatment Frequency (proportions) or Mean (sd)	Usual care Frequency (proportions) or Mean (sd)	Relative (95% CI)	Absolute	
Number of incontinent episodes per 24 hours (Better indicated by lower values)										
Colling 2003 Jirovec 2001 [40]	randomised trials	Serious[a]	Serious[b]	very serious[c]	very serious[d]	Colling:Mean (sd):4 (2.63) Jirovec: Mean (sd): 0.37 (0.28)	Colling:Mean (sd):3.43 (2.59) Jirovec: Mean (sd): 0.49 (0.36)	SMD: -0.12 (-0.47, +0.23)	SMD 0.12 lower (0.47 lower to 0.23 higher)	⊕OOO VERY LOW
Incontinent volume (Better indicated by lower values)										
Colling 2003 [40]	randomised trials	Serious[a]	no serious inconsistency	very serious[c]	Serious[e]	Mean (sd):292 (202)	Mean (sd): 193 (233)	MD: +99 (-17.57, +215.57)	MD 99 higher (17.57 lower to 215.57 higher)	⊕OOO VERY LOW
prevalence of bacteriuria (E coli)										
Colling 2003[40]	randomised trials	Serious[a]	no serious inconsistency	very serious[b]	very seriousd	5/32 (15.6%)	2/24 (8.3%)	RR 1.88 (0.4 to 8.85)	73 more per 1000 (from 50 fewer to 654 more)	⊕OOO VERY LOW

[a] No blinding reported. Colling 2003 may have used a blinded outcome assessor, though this is unclear.
[b] I squared was between 50 and 75% so graded as serious.

[c]The population in this outcome are potentially different to the population having incontinence secondary to neurological disorders.
[d] Upper and lower 95% CIs cross the MIDs for clinically significant benefit and harm
[e] Lower 95% CI crosses the MID for clinically significant benefit

Narrative summary (for outcomes that are not appropriate for GRADE due to insufficient information given, such as a lack of variance data, or the presentation of numbers of episodes rather than cases)

The following outcomes were not presented in a form that was appropriate for meta-analysis.

Number of incontinent episodes
Colling 1992[40] showed a significant reduction in the number of episodes of urinary incontinence during the treatment period in the treatment group.

Prevalence of skin rash

Colling 2003 [40] reported a significant decrease in skin rash prevalence from 17.7% at baseline to 9.4% at the end of the intervention period. No data are provided for the usual care group, other than the information that a non-significant increase occurred.

Prevalence of skin breakdown

Colling 2003 [40] reported a significant decrease in skin breakdown prevalence from 11.6% at baseline to 2.3% at the end of the study period in the intervention group. In the control group two patients had skin breakdown at baseline and none at the end of the study period. The prevalence figures for the intervention group appear to be counts of the episodes of skin breakdown rather than counts of participants having at least one episode, as 11.6% of the group size of 32 and 2.3% of the control group size of 24 yield non-whole numbers (3.7 and 0.6 respectively). Thus they cannot be analysed with a meta-analysis.

Impact on caregivers

Colling 2003 [40] reported that caregivers found management of incontinence less stressful at the end of the intervention. A greater number of carers felt more prepared to care for their patient's incontinence needs than at baseline. No statistically significant changes were reported.

Comparison of training mobility and toileting skills to no treatment in achievement of Independent toileting

Outcome data to which GRADE cannot be applied

No outcomes were appropriate for GRADE.

Narrative summary (for outcome data to whichGRADE cannot be applied due to incomplete outcome reporting, for example means and standard deviations, or equivalent, were unavailable).

Average weight of pads over 24 hours

The intervention group had a trend (p=0.07) for an 8% lower weight of pads over 24 hours compared to the comparison group. No further data were given in the paper [41].

Micturitions on toilet compared to total micturitions

The intervention had no significant effect on the number or percentage of micturitions on the toilet. No data were given in the paper [41].

Change from dependent to independent toileting

In the intervention group 6 changed from dependent to independent, compared to 2 in the comparison group (p=0.14). The lack of data on the number who were initially dependent in each group makes this data inappropriate for GRADE [41].

Change from independent to dependent toileting

In the intervention group 4 changed from independent to dependent, compared to 3 in the comparison group (p=0.70). The lack of data on the number who were initially independent in each group makes this data inappropriate for GRADE [41].

8.1.1.2 Economic evidence

No relevant economic evaluations comparing behavioural management programmes with each other or with usual care were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 19: Unit Costs

Item	Cost	Source/Assumptions
Specialist Community Nurse	**£77 per hour**	**PSSRU 2011**
Travel	**£1.40 per visit**	**PSSRU 2011**
Total	**£159**	**Assuming 1/2 hour visits, 1 a week for 1 month**

Source: Unit Costs of Health and Social Care 2010 compiled by Lesley Curtis (PSSRU)[42]

Economic considerations

No evidence could be found that suggested that behavioural management programmes are cost-effective in neuropathic patients with urological incontinence. The cost of behavioural management advice and programmes is unlikely to be high, as shown in the unit costs above. While the costs of these programmes are not negligible, the GDG felt that, if effective, their cost may be offset by the cost savings associated with a reduction in the use of incontinence aids.

Other NICE guidance, Urinary Incontinence (CG40) 2006, and Lower Urinary Tract Symptoms CG97 2010, recommend behavioural management programmes where cases of incontinence are mild and where conservative management is likely to lead to an improvement in continence.

8.1.1.3 Evidence Statements

Clinical Evidence Statement

<u>Comparison between prompted voiding and no prompted voiding</u>

- One study comprising 133 participants found that that there was no significant difference between prompted voiding and no prompted voiding for the proportion of people with no improvement in wet episodes (22 weeks)(very low quality).
- One study comprising 147 participants found that a statistically significant lower proportion of hourly checks that were wet in the prompted voiding group (8 weeks) (very low quality).
- One study comprising 19 participants found that that there was no significant difference between prompted voiding and no prompted voiding for the reduction in the mean proportion of hourly checks that are wet (8 weeks) (very low quality).
- Two studies comprising 257 participants found that a statistically significant lower number of incontinent episodes per 24 hours in the prompted voiding group (8-22 weeks)(very low quality).

- One study comprising 126 participants found that a statistically significant higher amount of self initiated toileting in the prompted voiding group (8 weeks) (very low quality).

Evidence statements could not be produced for the following outcomes of the systematic review [39] as results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect

- Proportion of hourly checks that were wet
- Incontinence episodes in 24 hrs
- Self initiated toileting

Comparison between habit training with one other treatment to usual care

- Two studies comprising 130 participants found that that there was no significant difference between habit retraining with one other treatment and usual care for the number of incontinent episodes per 24 hours (12 – 26 weeks) (very low quality).
- One study comprising 56 participants found that that there was no significant difference between habit retraining with one other treatment and usual care for incontinent volume (12 weeks)(very low quality).
- One study comprising 56 participants found that that there was no significant difference between habit retraining with one other treatment and usual care for prevalence of bacteriuria (12 weeks)(very low quality).
- Evidence statements could not be produced for the following outcomes of the study by Ostaszkiewicz [40] as results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect
  - Skin rash
  - Skin breakdown

Comparison of training mobility and toileting skills to no treatment in achievement of Independent toileting

Evidence statements could not be produced for the following outcomes of the study by van Houten[41] as results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect

- Weight of pads over 24 hr
- Percentage of micturations on the toilet
- Dependent to independent toileting
- Independent to dependent toileting

Economic evidence statements

- While the costs of these programmes are not inegligible, if effective their cost may be offset by the cost savings associated with a reduction in the use of incontinence aids (including catheters and pads).

8.1.2 Recommendations and links to evidence

Recommendations:	**BEHAVIOURAL TREATMENTS** **23.Consider a behavioural management programme (for example, timed**

	voiding, bladder retraining or habit retraining) for people with neurogenic lower urinary tract dysfunction: • **only after assessment by a healthcare professional trained in the assessment of people with neurogenic lower urinary tract dysfunction and** • **in conjunction with education about lower urinary tract function for the person and/or their family members and carers.** **24. When choosing a behavioural management programme, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment.**
Relative value placed on the outcomes considered	The GDG considered the outcomes reported to be important but noted the lack of data on quality of life and impact on family and carers. Any improvements in continence would lead to improvements in quality of life.
Economic considerations	The GDG considered costs in relation to staff training, provision of prompted voiding and behavioural management programmes in both 24 hour care provision and community settings. The GDG agreed that provision of staff training was likely to be cost effective given the relatively low cost of providing training. The GDG concluded that there were negligible additional costs associated with the use of behavioural management programmes which may be offset by the reduction in the use of incontinence aids and skin care in 24 hour care provision. The GDG noted the burden of implementing behavioural therapies in the community setting is likely to fall on family members and carers.
Quality of evidence	There was very limited very low quality evidence showing that prompted voiding reduced the number of hourly checks that were wet and the number of incontinence episodes in 24 hrs. There was no evidence of improved continence outcomes associated with habit retraining. There was very limited very low quality evidence that toileting mobility and toileting skills improved continence and toileting outcomes. The GDG considered the evidence presented to be of very low quality. The evidence, which was from the United States, was not directly related to the UK neuropathic population but was of some relevance, due to the inclusion of cognitively impaired individuals in the majority of the studies. However, the lack of subgroup analysis that specifically looked at patients with neurological disease prevented more detailed analysis. There were no studies that looked at a paediatric population. The GDG noted that these interventions may be suitable for people who are regaining bladder function after acute neurological insult, and some patients with cognitive impairment (e.g. elderly people with dementia) in a setting with appropriate family or carer support . Although the studies had relatively short-term follow-up, based on GDG experience it was felt that improvements in outcomes would be maintained over time
Trade-off between clinical benefits and harms	The GDG agreed that the interventions had the potential for clinical benefit in individual cases with very limited risk of harm. The GDG noted that assessment is needed to exclude potentially treatable causes of incontinence such as urinary tract infection, diabetes mellitus, and structural abnormalities.
Other considerations	In current practice a behavioural intervention might be considered if a person with incontinence has a degree of cognitive impairment significant to suggest a mis-interpretation of bladder sensations or a lack of social awareness. The person's physical condition and mobility also need to be considered. Carer support and education is essential to any programme as the process is time-consuming. The GDG agreed that well trained staff were required to provide the necessary training and education for patients and carers.

8.2 Antimuscarinics

8.2.1 What is the safety and efficacy of antimuscarinics compared with a) placebo or treatment as usual b) other antimuscarinics for the treatment of incontinence due to neurological disease/ overactive bladder due to neurological disease?

Clinical Methodological Introduction	
Population:	Neurological disease Patients with neurogenic detrusor over-activity Patients with reduced bladder compliance
Intervention:	Antimuscarinics
Comparison:	Placebo or treatment as usual Other antimuscarinics
Outcomes:	• Quality of life. • Patients and carers' perception of symptoms. • Frequency of voiding by day and night. • Number of incontinence episodes per week. • Maximum cystometric capacity • Bladder compliance • Residual urine • Kidney function (hydronephrosis) • Adverse events, including urinary tract infections, renal complications and unscheduled hospital admissions. • Treatment adherence

8.2.1.1 Clinical evidence

We searched for RCTs in adults and RCTs and observational studies in children, comparing the effectiveness of antimuscarinics for improving outcomes for patients with neurogenic detrusor overactivity (formerly called “detrusor hyperreflexia”)or patients with reduced bladder compliance.

This review compares antimuscarinics with either placebo/treatment as usual or with other antimuscarinics. For the adult population RCTs only were included. The within-subject drug comparisons from each RCT are presented separately. For children and young people RCT and observational studies were included. Studies with a sample size of 20 or less were excluded. For the adult population five RCTs were included in the review [43 44 45 46 47]. For children and young people, thirteen observational studies were included in the review [48 49 50 51 52 53 54 55 56 57 58 59 60]. Table 1 summarises the population, intervention and comparison.

Table 20: Summary of studies included in the clinical evidence review

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
Adults				
FADER (2007)[43]	Adults with multiple sclerosis who (i) had previously benefited from or were using oral antimuscarinic treatment for overactive bladder (ii)	Intravesical atropine or placebo 6.67 mg in 20 ml 0.9% saline to provide 6 mg in 18 ml x 4 times daily	Oral oxybutynin or placebo Dose was the equivalent to what the patient was on before the study began Mode dose in 26 patients was 5 mg oxybutynin IR	2 weeks

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
	were performing intermittent catheterisation at least twice daily		twice daily (range 2.5 mg twice to 5 mg 4 times daily)	
GAJEWSKI 1986[44]	Patients with multiple sclerosis with urinary symptoms Proportion of patients using catheters not stated	Oxybutynin 5 mg three times daily N=19	Propantheline 15 mg three times daily N=15	6 to 8 weeks (duration of treatment)
MADERSBACHER 1995[45]	Patients with detrusor hyperreflexia with spinal cord injury aged 18 yrs or older. Proportion of patients using catheters not stated	Trospium chloride 20 mg twice daily (plus one placebo dummy) N=52	Oxybutynin 5 mg three times daily N=43	3 weeks (one week without treatment and two weeks on treatment)
STOHRER 1999[46]	In-patients over the age of 18 yrs with detrusor hyperreflexia and suprasacral spinal cord injury. Clean intermittent catheterisation used by all patients implied	Oral propiverine 15 mg tid N=60	Placebo N=53	14 days (length of treatment)
STOHRER 2007[47]	Patients 18 yrs or over with known neurological disorder and demonstrable detrusor activity at urodynamic assessment. Maximum cystometric capacity was restricted to 300 ml. "Most patients practising intermittent catheterisation"	Oral propiverine 15 mg tid N=70	Oral oxybutynin 5mg tid (immediate release) N=61	21 days (length of treatment)
Children				
AMARK 1998[61]	Children with myelodysplasia, neurogenic bladder disturbance with detrusor hyperreflexia	Intravesical oxybutynin 0.1mg/kg twice daily Plus clean	No comparator	0.66 to 5 years (mean 2.25 years)

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
	(detrusor contractions >10cm water over a period of >10s) and/or high bladder pressure (>40cm water) during bladder filling All using clean intermittent catheterisation	intermittent catheterisation		
BASKIN 1990[49]	Children with myelomeningocoele and neurogenic bladder dysfunction Patients using clean intermittent catheterisation	Oxybutynin 0.1mg/kg three times daily (n=35) (Spastic or hypertonic bladder and significant sphincter dyssynergia) In combination with clean intermittent catheterisation	Observation group (n=13) (Extremely lax external sphincter)	Treatment group: 6-72 months (mean 39 [18] months) Observation group: 20 to 60 months (mean 44 [16] months)
CONNOR 1994[50]	Children with myelodysplasia and severe neurogenic bladder dysfunction; incontinent; could not tolerate, or had an inadequate response to, oral oxybutinin	Intravesical oxybutynin 5mg twice daily for minimum of 3 months	No comparator	4-9 months
FERRARA 2001[51]	Children who had undergone surgical repair for meningomyelocele (MMC) within 24-48 h after birth and a neurogenic bladder 34/101 clean intermittent catheterisation Inclusion criteria: Those at high risk of upper urinary tract deterioration	Oxybutynin orally or intravesically mean dose 0.1 to 0.2 mg/kg two to three times daily Oral N=67 Intravesical N=34 plus clean intermittent catheterisation	Before treatment	3 yrs
FRANCO (2005)[52]	Children aged 6 to 15 yrs with documented	Oxybutynin	Before treatment/ baseline	24 weeks

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
	diagnosis of detrusor hyperreflexia due to neurogenic conditions, and were using a total daily dose of 10 or 15 mg oral oxybutynin chloride with clean intermittent catheterisation	Extended release tablets 5-20 mg per day Tablets 7.5 to 15 mg 2 to 4 times daily Syrup 5 to 30 mg per day Total daily dose ranged from 0.20 to 0.40 mg/kg (46% patients) 0.40 to less than 0.60 mg/kg (35%) in the majority of patients		
GOESSL (1998)[53]	Consecutive children with myelomeningocele (MMC) identified with previously untreated detrusor hyperreflexia. Detrusor hyperreflexia was defined as maximal detrusor pressures exceeding 40 cm H2O Patients using clean intermittent catheterisation	Oxybutynin 0.2 to 0.3 mg/kg/day oral combined with clean intermittent catheterisation four times daily	No comparator	Urodynamic investigation repeated at 3 mths, 2 yr clinical follow-up
HEHIR 1985[54]	Children with spina bifida (lumbosacral meningomyelocoele) with neuropathic bladder; incontinent. All using clean intermittent catheterisation	Intravesical oxybutynin 5mg three times daily for 4 weeks	Placebo	4 weeks on each treatment plus washout period
KAPLINSKY 1996[55]	Children with neurogenic bladder refractory to, or who could not tolerate oral therapy; incontinence and/or elevated bladder pressures refractory to intermittent catheterisation and oral anticholinergic medication	Intravesical oxybutynin 5mg twice daily for 4 weeks	Placebo	21 continuing treatment followed for mean of 35 months (range 3 to 67 months)

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
MADERBACHER 2009[56]	Children and adolescents Inclusion criteria: i) confirmed neurogenic detrusor overactivity due to MMC or spinal cord injury confirmed by the history of the patients and a urodynamic assessment (ii) aged 1 to 18 yrs (iii) treatment periods ≥ 12 months (v) urodynamic assessment either at ≥ 12 months of treatment or al last follow-up Intermittent catheterisation 80.4%	Propiverine 5 mg, or of higher body weight, 15 mg Immediate release	Oral oxybutynin Immediate release	Urodynamic assessment either at ≥ 12 months of treatment or al last follow-up
PAINTER (1996)[57]	Children with myelodysplasia and neurogenic bladder who could not tolerate, or had no response to, oral anticholinergics, or had high pressures on initial urodynamic studies and intravesical oxybutinin was first line therapy.	Intravesical oxybutynin 5mg twice daily	No comparator	2-26 months (mean 13months, median 12 months)
PALMER 1997[58]	Children with myelodysplasia and neurogenic bladder dysfunction with inadequate response to, or intolerable side effects of, oral therapy	Intravesical oxybutynin 1.25mg three times daily, increased as necessary for satisfactory response	No comparator	5 years
REDDY 2008[59]	Subjects who successfully completed one of three 12-week open-label dose-escalation studies of oral tolterodine; stable neurological disease and neurogenic detrusor overactivity	Oral tolterodine (4 months-4 years 0.2-2mg twice daily; 5-10 years 0.5-4mg twice daily; 11-16 years 2, 4 or 6mg once daily (starting dose according to response in original study dose adjustments within these ranges for efficacy or safety	No comparator	12 months

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
		reasons).		
SCHULTE_BAUKLOH 2006[60]	Children with neurogenic detrusor overactivity due to an upper motor neurone lesion; inclusion criteria 3 months to 18 years 18/20 using clean intermittent catheterisation	Propiverine hydrochloride 0.4mg/kg body weight twice daily; increased as appropriate	No comparator	3-6 months

Propiverine vs placebo

Adults - spinal cord injury

Table 21: antimuscarinics (propiverine vs placebo) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Clinical symptoms										
1 [A]	RCT	Propiverine n=60	Placebo N=53	Propiverine vs placebo Patient assessment % improved 63.3 vs 22.6% Physician assessment 53% were 'very good' or 'good' under vs 11%	S (iii)	N	N	N (iv)	N	Very Low
Outcome: Maximum cystometric capacity										
1 [A]	RCT	Propiverine n=60	Placebo N=53	Mean (SD) ml Propiverine 366 (143) Placebo 289 (163) Propiverine vs placebo Final value scores MD77.00 (95%CI 20.12 to 133.88)	S (i)	N	N	Y (ii)	N	Low
Outcome: Residual urine										
1 [A]	RCT	Propiverine n=60	Placebo N=53	Mean (SD) ml Propiverine 86.5 (109.3) Placebo 60.8 (91.9) Propiverine vs placebo Final value scores MD25.70 (-11.41 to 62.81)	S (i)	N	N	Y (ii)	N	Low
Outcome: Bladder compliance (detrusor coefficient)										
1 [A]	RCT	Propiverine n=60	Placebo N=53	Mean (SD) ml/cmH2O Propiverine 21.8 (15.8) Placebo 17.2 (11.9) Propiverine vs placebo MD4.60 (-0.52 to 9.72)	S (i)	N	N	Y (ii)	N	Low
Outcome: drop-outs due to adverse events										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	RCT	Propiverine n=60	Placebo N=53	Propiverine vs placebo 5/60 vs 1/53 RR 4.42 (95%CI 0.53 to 36.61)	S (i)	N	N	S (ii)	N	Low

S serious N none MD mean difference RR relative risk CI confidence interval

(i) No details of randomisation or allocation concealment
(ii) The 95%CI crossed the minimally importance difference (MID) for benefit or harm
(iii) No details of randomisation or allocation concealment, incomplete outcome reporting – downgraded two levels
(iv) Imprecision could not be assessed

[A] Stohrer et al. (1999)[46]

Propiverine vs oxybutynin

Adults – spinal cord injury

Table 22: Propiverine vs oxybutynin - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: 24-hr incontinence episodes										
1 [A]	RCT	Propiverine N=46	Oxybutynin N=45	Mean difference (baseline – follow-up) (SD) Propiverine vs Oxybutynin -1.6 (2.3) vs -1.3 (2.0); MD -0.30 (95%CI -1.19 to 0.59)	N	N	N	N	N	High
Outcome: 24 hr micturition frequency										
1 [A]	RCT	Propiverine N=46	Oxybutynin N=45	Mean difference (baseline – follow-up) (SD) Propiverine vs Oxybutynin -2.9 (2.9) vs -2.5 (3.3); MD -0.40 (95%CI -1.68 to 0.88)	N	N	N	N	N	High
Outcome: Maximum cystometric capacity										
1 [A]	RCT	Propiverine N=46	Oxybutynin N=45	Mean (SD) ml Propiverine 309 (166) Oxybutynin 298 (125) MD11.00 (95%CI -49.29 to 71.29)	N	N	N	S (i)	N	Moderate
Outcome: Bladder compliance										
1 [A]	RCT	Propiverine N=46	Oxybutynin N=45	Mean (SD) ml/cm H2o Propiverine 22.7 (24.3) Oxybutynin 37.8 (48.3) Propiverine vs oxybutynin MD-15.10 (95%CI-30.86 to 0.66)	N	N	N	S (i)	N	Moderate
Outcome: Residual urine										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	RCT	Propiverine N=46	Oxybutynin N=45	Mean (SD) ml Propiverine 140.9 (167) Oxybutynin 149 (133) MD -8.10 (95%CI-70.06 to 53.86)	N	N	N	S (i)	N	Moderate
Outcome: Adverse events										
1 [A]	RCT	Propiverine N=70	Oxybutynin N=61	Propiverine vs oxybutynin 48/70 vs 48/61 RR 0.87 (0.71 to 1.07)	N	N	N	S (i)	N	Moderate

S serious N none MD mean difference CI confidence interval RR relative risk
(i) The 95%CI crossed the minimally important difference (MID) for either benefit or harm

[A] Stohrer et al. (2007)[47]

Table 23: Propiverine (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: 24hr Incontinence episodes mean (SD)										
1 [A]	Observational	Propiverine N=46 Before treatment	After treatment	Before vs after Difference mean (SD) –1.6 (15.6); p<0.05	S (i)	N	N	N (ii)	N	Very Low
Outcome: Maximum cystometric capacity										
1 [A]	Observational	Propiverine N=46 Before treatment	After treatment	Before vs after Mean (SD) ml 198 (110) vs 309 (166) MD 111	S (i)	N	N	N (ii)	N	Very Low
Outcome: Bladder compliance										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Observational	Propiverine N=46 Before treatment	After treatment	Before vs after Mean (SD) ml/cm H^2O 10.8 (13.8) vs 22.7 (24.3) MD 11.9	S (i)	N	N	N (ii)	N	Very low
Outcome: Residual urine										
1 [A]	Observational	Propiverine N=46 Before treatment	After treatment	Before vs after Mean (SD) ml 72.6 (115) vs 140.9 (167) MD 68.3	S (i)	N	N	N (ii)	N	Very low
S serious N none MD mean difference CI confidence interval RR relative risk (i) Before vs after data (ii) Imprecision not assessed, data at high risk of bias [A] Stohrer et al. (2007)[47]										

Table 24: Oxbutynin (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: 24-hr incontinence episodes										
1 [A]	Observational	Oxybutynin N=45 Before treatment	After treatment	Before vs after Difference mean (SD) -1.3 (13.4)	S (i)	N	N	N (ii)	N	Very low
Outcome: Maximum cystometric capacity										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Observational	Oxybutynin N=45 Before treatment	After treatment	Before vs after Mean (SD) ml 164 (64) vs 298 (125) MD 134	S (i)	N	N	N (ii)	N	Very low
Outcome: Bladder compliance										
1 [A]	Observational	Oxybutynin N=45 Before treatment	After treatment	Before vs after Mean (SD) ml/cm H^2O 12.7 (12.1) vs 37.8 (48.3) MD25.1	S (i)	N	N	N (ii)	N	Very low
Outcome: Residual urine										
1 [A]	Observational	Oxybutynin N=45 Before treatment	After treatment	Before vs after Mean (SD) ml 65.3 (78) vs 149 (133) MD83.7	S (i)	N	N	N (ii)	N	Very low
S serious N none MD mean difference CI confidence interval RR relative risk (i) Before vs after data (ii) Imprecision not assessed, data at high risk of bias [A] Stohrer et al. (2007)[47]										

Trospium vs oxybutynin

Adults – spinal cord injury

Table 25: Trospium vs oxybutynin - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										
1 [A]	RCT	Trospium N=52	Oxybutynin N=43	Mean (SD) ml Trospium 311.9 (139) Oxybutynin 350.9 (154) Trospium vs oxybutynin MD -39.00 (95%CI-95.09 to 17.09)	Y (i)	N	N	Y (ii)	N	Low
Outcome: Residual urine										
1 [A]	RCT	Trospium N=53	Oxybutynin N=43	mean (SD) mL Trospium 128.32 (168) Oxybutynin 154.36 (210) Trospium vs oxybutynin MD-26.04 (95%CI-98.44 to 46.36)	Y (i)	N	N	Y (ii)	N	Low
Outcome: Adverse events (antiparasympathetic side effects)										
1 [A]	RCT	Trospium N=53	Oxybutynin N=43	Trospium vs oxybutynin 26/53 vs 22/43 RR 0.96 (95%CI 0.64 to 1.43) Differences in the 'severity' grading - dryness of mouth deteriorated to 'severe' in 4% trospium but 23% oxybutynin	Y (i)	N	N	Y (ii)	N	Low
Outcome: Treatment adherence (withdrawals)										
1 [A]	RCT	Trospium N=53	Oxybutynin N=43	Trospium vs oxybutynin 7/53 vs 3/43 RR 1.89 (95%CI 0.52 to 6.89)	Y (i)	N	N	Y (iii)	N	Low

S serious N none MD mean difference CI confidence interval RR relative risk NS not significant

(i) No details of allocation concealment or randomisation
(ii) The 95%CI crossed the minimally important difference (MID) for either benefit or harm
(iii) No details of allocation concealment or randomisation, incomplete outcome reporting
(iv) Imprecision could not be assessed

[A] Maderbacher et al. (1995)[45]

Table 26: Trospium (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										
1 [A]	Observational	Trospium N=52 Before treatment	After treatment	Before vs after mean (SD) mL Trospium 215.2 (132) vs 311.9 (139); p<0.001 MD96.7	Y (i)	N	N	N (ii)	N	Very low
Outcome: Residual urine										
1 [A]	Observational	Trospium N=53 Before treatment	After treatment	Before vs after mean (SD) mL Trospium 49.22 (92) vs 128.32 (168); p<0.001 MD 79.08	Y (i)	N	N	N (ii)	N	Very low

S serious N none MD mean difference RR relative risk CI confidence interval NS not significant

(i) Before vs after data
(ii) Imprecision could not be assessed, data at high risk of bias

[A] Maderbacher et al. (1995)[45]

No evidence was reported for the following outcomes:

- Frequency of voiding by day and night, no. of incontinence episodes per week, quality of life, patients and carers' perception of symptoms, adverse events, treatment adherence, kidney function or bladder compliance

Table 27: Oxybutynin (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										
1 [A]	Observational	Oxybutynin N=43 Before treatment	After treatment	Before vs after mean (SD) mL Oxybutynin 187.8 (110) vs 350.9 (154); p<0.001 MD 163.1	Y (i)	N	N	N (ii)	N	Very low
Outcome: Residual urine										
1 [A]	Observational	Oxybutynin N=43 Before treatment	After treatment	Before vs after mean (SD) mL Oxybutynin 48.14 (83) vs 154.36 (210); p<0.001 MD 106.22	Y (i)	N	N	N (ii)	N	Very low

S serious N none MD mean difference CI confidence interval RR relative risk NS not significant

(i) Before vs after data
(ii) Imprecision not assessed, data at high risk of bias

[A] Maderbacher et al. (1995)[45]

Oxybutynin vs propantheline

Adults – multiple sclerosis

Table 28: Oxybutynin vs propantheline - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	RCT	Oxybutynin N=19	Propantheline N=15	Mean (SD) ml Oxybutynin 282.5 (117.9) Propantheline 198.3 (129) Oxybutynin vs propantheline MD 84.20 (95%CI 0.10 to 168.30)	S (i)	N	N	S (ii)	N	Very low
S serious N none MD Mean difference CI confidence interval (i) No details of allocation concealment, randomisation or blinding (ii) The 95%CI crossed the minimally important difference (MID) for benefit or harm [A] Gajewski et al. (1986)[44]										

Table 29: Oxbutynin (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										
1 [A]	Observational data	Oxybutynin N=19 Before treatment	After treatment	Before vs after Mean (SD) ml Oxybutynin 138.3 (64) vs 282.5 (117.9); p<0.05 MD 144.2	S (i)	N	N	S (ii)	N	Very low
S serious N none MD Mean difference CI confidence interval (i) Before vs after data (ii) Imprecision not assessed, data at high risk of bias [A] Gajewski et al. (1986)[44]										

Table 30: Propantheline (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										
1 [A]	Observational	Propantheline N=15 Before treatment	After treatment	Before vs after Mean (SD) ml Propantheline 163.3 (77.6) vs 198.3 (129); ns MD 35	S (i)	N	N	S (ii)	N	Very low

S serious N none MD Mean difference CI confidence interval

(i) Before vs after data
(ii) Imprecision not assessed, data at high risk of bias

[A] Gajewski et al. (1986)[44]

Atropine vs oxybutynin

Table 31: Atropine vs oxybutynin- Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Incontinence										
1 [A]	Randomised crossover trial	Atropine N=57	Oxybutynin N=57	Mean (SD) vs Mean change(SD) Baseline vs oxybutynin 1.7 (2.1) vs -0.9 (1.6) Baseline vs atropine 1.7 (2.1) vs -0.9 (1.7)	N	N	N	N (i)	N	Low
Outcome: Maximum cystometric capacity										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Randomised crossover trial	Atropine N=57	Oxybutynin N=57	Mean (SD) vs Mean change(SD) Baseline vs oxybutynin 221.9 (106.9) vs 55.5 (67.2) Baseline vs atropine 221.9 (106.9) vs 79.6 (89.6) Oxybutynin vs atropine p=0.053	N	N	N	N (ii)	N	Low
Outcome: Adverse events (dry mouth)										
1 [A]	Randomised crossover trial	Atropine N=57	Oxybutynin N=57	Odds of a worse score on oxbutynin compared to atropine 9 (95%CI 4 to 22); p<0.0001.	N	N	N	N (ii)	N	Low
S serious N none MD Mean difference CI confidence interval (i) Imprecision not assessed [A] Fader et al. (2007)[43]										

Oxybutynin vs placebo

Children and young people

Table 32: Oxybutynin vs placebo - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Crossover trial	Oxybutynin (24)	Placebo	Symptoms on oxybutynin dry 4/24 improved 12/24 wet 8/24	Y (i)	N	N	N (ii)	N	Very low
1 [B]	Crossover trial	Oxybutynin (21)	Placebo	Symptoms on oxybutynin dry day and night 12/28 daytime continence between catheterisation 5/28 unchanged 4/28	Y (i)	N	N	N (ii)	N	Very low
Outcome: Maximum cystometric capacity										
1 [A]	Crossover trial	Oxybutynin (24)	Placebo	Mean (SD) Baseline 197 (24) vs oxybutynin 299 (32) mL; p=0.001 vs placebo 218 (29) ; ns	Y (i)	N	N	N (ii)	N	Very low
1 [B]	Crossover trial	Oxybutynin (21)	Placebo	Increased 17/21, mean increase 237% from pre-treatment values; p<0.0001	Y (i)	N	N	N (ii)	N	Very low
Adverse events (side effects)										
1 [A]	Crossover trial	Oxybutynin (24)	Placebo	Dry mouth oxybutynin 3/24 placebo 1/24 RR 3.00 (CI 0.34 to 26.84)	N	N	N	S (iii)	N	Very low
1 [B]	Crossover trial	Oxybutynin (28)	Placebo	Anticholinergic side effects 7/28 unable to tolerate	Y (i)	N	N	N (ii)	N	Very low

S serious N none RR relative risk CI confidence interval ns not significant

(i) Incomplete outcome reporting
(ii) Imprecision could not be assessed
(iii) The 95%CI crossed the minimally important difference for both benefit and harm – downgraded two levels

[A] Hehir et al 1985[54]
[B] Kaplinsky et al. 1996[55]

Oxybutynin (pre vs post treatment)

Children and young people

Table 33: Oxybutynin (pre vs post treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										
1 [A]	Observational	Oxybutynin (41)	-	No. incontinent Before vs after 35/41 vs 11/35 RR 2.72 (1.64 to 4.50)	S (i)	N	N	N	N	Very low
1 [B]	Prospective open label trial	Oxybutynin (111)	-	% catheterisation without intermittent leaking accident Increase from baseline 21.5%; p<0.001	S (i)	N	N	N (iI)	N	Very low
1 [C]	Observational	Oxybutynin (37)	-	Before vs after Regularly dry 1/37 vs 18/37 Always wet between micturations 18/37 vs 3/37	S (i)	N	N	N	N	Very low
1 [D]	Observational	Oxybutynin (35)	-	Virtually dry between catheterisations 25/35 Significant wetting 8/35	S (i)	N	N	N (ii)	N	Very low
1 [E]	Observational	Oxybutynin (13)	-	Mostly continent 5/13 Significant improvement 3/13 No improvement 5/13	S (i)	N	N	N (ii)	N	Very low
1 [F]	Observational	Oxybutynin (30)	-	Of the 29 incontinent 3 achieved continence and 19 decreased use of pads	S (i)	N	N	N (ii)	N	Very low
Outcome Maximum cystometric capacity										
1 [A]	Observational	Oxybutynin (41)	-	Before vs after mean (SD) mL 141 (96) vs 197 (99); p<0.01 MD 56	S (i)	N	N	N (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [G]	Observational	Oxybutynin Oral (67)	Intravesical (34)	Before vs after mean (SD) mL oral 128 (107) vs 214 (110) MD 86 -49.26) Intravesical 132 (103) vs 226 (118) MD 94	S (i)	N	N	N (ii)	N	Very low
1 [B]	Prospective open label trial	Oxybutynin (111)	-	Before vs after mean (SD) mL 196.9 (122.3)) vs 260.5 (126.111.97) ; p<0.001MD 63.6	S (i)	N	N	N (ii)	N	Very low
1 [E]	Observational	Oxybutynin (13)	-	Increased capacity 10/13 mean increase 41% (range -24 to + 95%)	S (i)	N	N	N (ii)	N	Very low
1 [F]	Observational	Oxybutynin (30)	-	Before vs after mean (SD) mL 209 (103) vs 282 (148); p<0.01 MD 73	S (i)	N	N	N (ii)	N	Very low
Outcome: Bladder compliance										
1 [A]	Observational	Oxybutynin (41)	-	Before vs after mean (SD) mL/cmH20 6.5 (5.6) vs 16.8 (13.7); p<0.01 MD 10.3	S (i)	N	N	N (il)	N	Very low
1 [G]	Observational	Oxybutynin Oral (67)	Intravesical (34)	Before vs after mean (SD) mL/cmH20 Oral 8.1 (6.3) vs 14.8 (11.6) MD 6.7 Intravesical 8.5 (6.1) vs 16.0 (11.0) MD 7.5	S (i)	N	N	N (il)	N	Very low
1 [E]	Observational	Oxybutynin (13)	-	Improved compliance 12/13	S (i)	N	N	N (ii)	N	Very low
Outcome: Adverse events (side effects)										
1 [A]	Observational	Oxybutynin (41)	-	13/41	S (i)	N	N	N (ii)	N	Very low
1 [C]	Observational	Oxybutynin (39)	-	2/39	S (i)	N	N	N (ii)	N	Very low
1 [D]	Observational	Oxybutynin (35)	-	2/35	S (i)	N	N	N (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [F]	Observational	Oxybutynin (30)	-	0/30	S (i)	N	N	N (ii)	N	Very low
Outcome: Urinary tract infections (UTI)										
1 [G]	Observational	Oxybutynin Oral (67)	Intravesical (34)	Experienced a decrease 70/101	S (i)	N	N	N (ii)	N	Very low
1 [C]	Observational	Oxybutynin (33)	-	Before vs after Asymptomatic bacteriuria 10/33 vs 14/33 Lower UTI 11/33 vs 21/33 Upper UTI 9/33 vs 8/33 Use of prophylactic antibiotics 15/33 vs 15/33	S (i)	N	N	N (ii)	N	Very low
1 [D]	Observational	Oxybutynin (35)	Observation (13)	Treament vs observation Gp UTI 2/35 vs 0/13 asymptomatic bacteriuria 21/35 vs 0/13	N	N	N	N (ii)	N	Very low
Outcome: Treatment adherence (Discontinuations)										
1 [G]	Observational	Oxybutynin Oral (67)	Intravesical (34)	Oral 11/67 Intravesical 6/34	S (i)	N	N	N (ii)	N	Very low
1 [C]	Observational	Oxybutynin (39)	-	7/39	S (i)	N	N	N(ii)	N	Very low
1 [D]	Observational	Oxybutynin (35)	-	2/35	S (i)	N	N	N (ii)	N	Very low
1 [E]	Observational	Oxybutynin (28)	-	15/28	S (i)	N	N	N (ii)	N	Very low
1 [H]	Observational	Oxybutynin (23)	-	15/23	S (i)	N	N	N (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none RR relative risk MD mean difference CI confidence interval (i) Before vs after data (ii) Imprecision could not be assessed, data at high risk of bias [A] Goessl et al. (1998)[53] [B] Franco et al. (2005)[52] [C] Amark et al. (1998)[61] [D]Baskin et al. (1990)[49] [E]Connor et al. (1994)[50] [F]Painter et al. (1996)[57] [G] Ferrara et al. (2001)[51] [H] Palmer et al. (1997)[58]										

Tolterodine (before vs after treatment)

Children and young people

Table 34: Tolterodine (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										
1 [A]	Prospective open label trial	Tolterodine N=30	-	Mean no. of episodes decreased by approximately 45%	S (i)	N	N	S (ii)	N	Very low
Outcome: Functional bladder capacity										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Prospective open label trial	Tolterodine N=30	-	Functional bladder capacity increased in the first month children aged 6 mths-4 yrs and 5-10 yrs	S (i)	N	N	S (ii)	N	Very low
Outcome: Adverse events										
1 [A]	Prospective open label trial	Tolterodine N=30	-	29/30 most mild to moderate	S (i)	N	N	S (ii)	N	Very low
Outcome: Treatment adherence (withdrawals)										
1 [A]	Prospective open label trial	Tolterodine N=30	-	1/30	S (i)	N	N	S (ii)	N	Very low

S serious N none

(i) Incomplete outcome reporting – downgraded two levels
(ii) Imprecision could not be assessed

[A] Reddy et al. (2008)[59]

Propiverine (before vs after treatment)

Children and young people

Table 35: Propiverine (before vs after treatment) - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Observational	Propiverine N=20	-	Mean no. of incontinence episodes decreased by approximately 45%	S (i)	N	N	N (ii)	N	Very low
Outcome: Maximum cystometric capacity										
1 [A]	Observational	Propiverine N=20	-	Mean (SD) Before vs after mL 166 (28.8) to 231 (34.8); p<0.005; MD 65	S (i)	N	N	N (ii)	N	Very low
Outcome: Bladder compliance										
1 [A]	Observational	Propiverine N=20		Mean (SE) Before vs after mL/cm water 11.2 (2.8) to 30.6 (9.7); p<0.01 MD 19.4	S (i)	N	N	N (ii)	N	Very low
Outcome: Adverse events										
1 [A]	Observational	Propiverine N=20	-	2/20	S (i)	N	N	N (ii)	N	Very low

S serious N none

(i) No comparator group/ before vs after data
(ii) Imprecision not assessed, data at high risk of bias

[A] Schulte-Baukloh et al. (2006)[60]

Propiverine vs oxybutynin

Children and young people

Table 36: Propiverine vs oxybutynin - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Observational	Propiverine N=127	Oxybutynin N=128	% continent Before vs after Propiverine 7.7 vs 31.6 Oxybutynin 20.8 vs 50.4	S (i)	N	N	N (ii)	N	Very low
Outcome: Maximum cystometric capacity										
1 [A]	Observational	Propiverine N=127	Oxybutynin N=128	Before vs after mL Propiverine 145.9 vs 242.3 Oxbutynin 221.8 vs 310.0	S (i)	N	N	N (ii)	N	Very low
Outcome: Adverse events										
1 [A]	Observational	Propiverine N=127	Oxybutynin N=128	Propiverine 11/127 Oxybutynin 22/128 RR 0.50 (95%CI 0.26 to 1.00)	N	N	N	Y (iii)	N	Very low

S serious N none

RR relative risk CI confident interval

(i) Differences at baseline
(ii) Imprecision not assessed, data at high risk of bias
(iii) The 95%CI crosses the minimally important difference (MID) for either benefit or harm

[A] Madersbacher et al. (2009)[56]

8.2.1.2 Economic Evidence

No studies could be found that assessed the cost effectiveness of antimuscarinic agents in the neurogenic population.

In order to aid evaluation of cost effectiveness, unit costs are provided below:

Table 37: Unit Costs of antimuscarinics contained in clinical review

Antimuscarinic	Dose	Pack size	Pack cost (£)	Pill cost (£)
Oral Atropine Sulphate (Oral)	600 mg	28	20.82	0.74
Atropine Sulphate (Intravesical)	600 mg/mL	1 ampoule	0.55	0.55
Oxybutynin Hydrochloride	2.5mg	56	5.86	0.10
	3mg	56	14.00	0.25
	5mg	56	6.11	0.11
	5mg	84	11.60	0.14
Trospium Chloride	20mg	60	18.20	0.30
Propiverine Hydrochloride	15mg	56	18.00	0.32
Tolterodine Tartrate	1mg	56	29.03	0.52
	2mg	56	30.56	0.55
Propantheline Bromide	15 mg	56	18.00	0.32

The clinical review shows antimuscarinics to be effective in reducing incontinence. The treatments are also low cost. CG40 provides evidence to suggest that antimuscarinics, particularly non-proprietry oxybutynin, are cost-effective in people with non-neurogenic incontinence. While this evidence is lacking in applicability to the neurogenic population, it is suggestive of cost effectiveness. The GDG also suggested that even better results can be achieved in neurogenic populations to non-neurogenic populations. The GDG considered on the basis of these factors combined these treatments are likely to be cost effective in patients with neurogenic lower urinary tract dysfunction.

Due to the fact that there is no high quality evidence to choose between the treatments and it is therefore not possible to recommend one treatment over another, in terms of side effects or effectiveness. All of the treatments are very low cost, with no treatment costing more than 80p per pill, therefore balancing the side effect profile with the cost of the pill is more important than making sure the pill is the lowest cost. Of course, where there is nothing to choose between the two, the lowest cost treatment should be provided.

8.2.1.3 Evidence Statements

Clinical Evidence Statements

Adults

Propiverine vs placebo

Adults - Spinal cord injury

One study of 113 participants found a statistically significant improvement for patients receiving propiverine compared to placebo for

- Maximum cystometric capacity (14 days) (low quality)

One study of 113 participants found no significant difference for propiverine compared with placebo for

- Residual urine (14 days) (low quality)
- Bladder compliance (14 days) (low quality)
- Drop-outs due to adverse events (low quality)

Evidence statements could not be produced for the following outcomes of the study by Stohrer [46] as results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect

Clinical symptoms

Propiverine vs oxybutynin

Adults - Spinal cord injury

One study comprising 91 participants found no significant difference for propiverine compared with oxybutynin for

- 24-hr incontinence episodes (21 days) (high quality)
- 24-hr micturition frequency (21 days) (high quality)
- maximum cystometric capacity (21 days) (moderate quality)
- bladder compliance (21 days) (moderate quality)
- residual urine (21 days) (moderate quality)
- adverse events (21 days) (moderate quality)

Properverine (before vs after treatment)

One study comprising 91 participants suggested a difference in favour of propiverine for

- 24 hr incontinence episodes (21 days) (very low quality)
- Maximum cystometric capacity (21 days follow up) (very low quality)
- Bladder compliance (21 days) (very low quality)

One study comprising 91 participants suggested a difference against (increase) propiverine for

- Residual urine (21 days follow up) (very low quality)

Oxybutynin (before vs after treatment)

One study comprising 91 participants suggested a difference in favour of oxybutynin for

- 24 hr incontinence episodes (21 days) (very low quality)
- Maximum cystometric capacity (21 days follow up) (very low quality)
- Bladder compliance (21 days) (very low quality)

One study comprising 91 participants suggested a difference against (increase) propiverine for

- Residual urine (21 days) (very low quality)

Trospium vs oxybutynin

Adults – spinal cord injury

One study comprising 95 participants found no significant difference for trospium compared with oxybutynin for

- maximum cystometric capacity (3 weeks) (low quality)

- residual urine (3 weeks) (low quality)
- treatment adherence (3 weeks) (low quality)
- adverse events (3 weeks) (low quality)

Trospium (before vs after treatment)

One study comprising 95 participants suggested a difference in favour of trospium for

- Maximum cystometric capacity (3 weeks) (very low quality)

One study comprising 95 participants suggested a difference against (increase) trospium for

- Residual urine (3 weeks) (very low quality)

Oxybutynin (before vs after treatment)

One study comprising 95 participants suggested a difference in favour of oxybutynin for

- Maximum cystometric capacity (3 weeks) (very low quality)

One study comprising 95 participants suggested a difference against (increase) trospium for

- Residual urine (3 weeks) (very low quality)

Oxybutynin vs propantheline

Adults – multiple sclerosis

One study comprising 34 participants found a significant improvement in favour of oxybutynin compared with propantheline for

- maximum cystometric capacity (6 to 8 weeks) (very low quality)

Oxybutynin (before vs after treatment)

One study comprising 34 participants suggested an improvement in favour of oxybutynin for

- Maximum cystometric capacity (6 to 8 weeks) (very low quality)

Propantheline (before vs after treatment)

One study comprising 34 participants suggested there was no difference for propantheline (before vs after treatment) for

- Maximum cystometric capacity (6 to 8 weeks) (very low quality)

Atropine vs oxybutynin

Adults – multiple sclerosis

Evidence statements could not be produced for the following outcome of the study by Fader [43] as results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect

- Incontinence
- Maximum cystometric capacity
- Adverse events

Oxybutynin vs placebo

Children and young people

Two studies of 45 participants suggested that, compared to placebo, oxybutynin

- Improved continence (4 weeks to 21 months) (very low quality)
- Increased maximum cystometric capacity (4 weeks to 21 months) (very low quality)
- Increased adverse events (4 weeks to 21 months) (very low quality)

Oxybutynin (before vs after treatment)

Children and young people

Six studies of 267 participants suggested that oxybutynin improved

- Continence (2 to 60 months)(very low quality)

Five studies of 296 participants suggested that oxbutynin increased

- Maximum cystometric capacity (2 to 36 months) (very low quality)

Three studies of 155 participants suggested that oxybutynin improved

- bladder compliance (3 to 36 months) (very low quality)

Four studies of 145 participants suggested that oxybutynin increased

- adverse events (2 to 60 months) (very low quality)

Two of three studies of 182 participants suggested that oxybutynin increased

- urinary tract infections (36 to 60 months) (very low quality)

Five studies of 226 participants reported discontinuations ranging from 6% to 65%

Tolterodine (before vs after treatment)

Children and young people

One study of 30 participants suggested that tolterodine

- Improved continence (12 months) (very low quality)
- Improved functional bladder capacity (12 months) (very low quality)
- Increased adverse events (12 months) (very low quality)

The withdrawal rate was 3%

Propiverine (before vs after treatment)

Children and young people

One study of 20 participants suggested that propiverine

- Improved continence (3 to 6 months) (very low quality)
- Improved maximum cystometric capacity (3 to 6 months) (very low quality)
- Improved bladder compliance (3 to 6 months) (very low quality)
- Increased adverse events (3 to 6 months) (very low quality)

Propiverine vs oxybutynin

Children and young people

One study comprising 255 participants suggested that propiverine and oxybutynin

- Improved continence (12 months or longer) (very low quality)
- Improved maximum cystometric capacity (12 months or longer) (very low quality)
- Increased adverse events (12 mths of longer follow up) (very low quality)

8.2.1.4 Economic Evidence Statements

- Antimuscarinic agents are likely to be cost-effective for the treatment of patients with urinary incontinence from neurological cause.

8.2.2 Recommendations and links to evidence

Recommendations:	**ANTIMUSCARINICS** **25. Offer antimuscarinic[h] drugs to people with:** • **spinal cord disease (for example, spinal cord injury or multiple sclerosis) *and*** • **symptoms of an overactive bladder such as increased frequency, urgency and incontinence.** **26. Consider antimuscarinic[h] drug treatment in people with:** • **conditions affecting the brain (for example, cerebral palsy, head injury or stroke) *and*** • **symptoms of an overactive bladder.** **27. Consider antimuscarinic[h] drug treatment in people with urodynamic investigations showing impaired bladder storage.** **28. Monitor residual urine volume in people who are not using intermittent or indwelling catheterisation after starting antimuscarinic treatment.** **29. When prescribing antimuscarinics, take into account that:** • **antimuscarinics known to cross the blood-brain barrier (for example, oxybutynin) have the potential to cause central nervous system-related side effects (such as confusion)** • **antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections** • **antimuscarinic treatment may precipitate or exacerbate constipation.**
Relative values of different outcomes	For both children and adults the outcomes of renal protection, reduced urinary frequency and improved continence were felt to be of high importance by the GDG
Trade off between clinical benefits and harms	Children and young people The GDG was confident that the available evidence supported a firm recommendation for the use of antimuscarinic drugs when symptoms suggestive of impaired bladder storage were present. However, the value of these drugs is less convincingly established where urodynamic criteria alone were used as the trigger to initiate treatment. This was felt to be an important issue since the potential renal protective effect of treatment with antimuscarinic drugs may be of importance in some patients. However, it is also recognised that long-term therapy with these drugs can be associated with side effects. Side effects can include problems such as dry mouth and constipation, but, perhaps of most concern, is the possibility that drug treatment can impact on cognitive function.

[h] At the time of publication (August 2012) not all antimuscarinics had a UK marketing authorisation for this indication or for use in both adults and children. The prescriber should follow relevant professional guidance when prescribing a drug without a marketing authorisation for this indication, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's 'Good practice in prescribing medicines – guidance for doctors' for further information.

	The GDG noted that the frequency of urinary tract infections was seen to increase with the use of antimuscarinic drugs but the group questioned whether this was due to patients being started on intermittent catheterisation at the same time as drug therapy was started. The infections might therefore relate to increased residual urine volumes occurring as a direct result of drug treatment, or could be unrelated to antimuscarinic therapy and be arising because catheterisation was being introduced as an independent aspect of neurogenic LUT dysfunction management. The GDG noted that treatment with antimuscarinics as a first line treatment is the established practice for both adults and children. <u>Adults</u> The potential for antimuscarinic drugs to reduce symptoms, notably incontinence, was felt to be of importance. There is less certainty as to the extent that drug treatment is capable of protecting the kidneys from the effects of a hostile bladder. The GDG recognised that antimuscarinic drugs can be associated with troublesome side effects such as a dry mouth and constipation. The group was particularly concerned that these drugs might have an adverse effect on cognitive function, particularly in those patients with an element of pre-existing cognitive impairment. It was acknowledged that oxybutynin in particular is believed to be a drug that has the potential to impact on cognition. It was noted that some RCTs in the spinal cord injury group showed a benefit when treatment was compared to placebo and in before and after comparisons for bladder capacity The GDG agreed that based on the evidence reviewed and consensus expert opinion the treatment should be offered to this group of patients. The evidence showed a consistent increase in residual urine which was regarded as being of no significance for those patients who are established on intermittent catheterisation but might be associated with problems such as an increased incidence of urinary tract infections in those who do not use catheter drainage.
Economic considerations	The clinical review shows antimuscarinics to be effective in reducing incontinence. The treatments are also low cost. CG40 provides evidence to suggest that antimuscarinics, particularly non-proprietry oxybutynin, are cost-effective in people with non-neurogenic incontinence. While this evidence is lacking in applicability to the neurogenic population, it is suggestive of cost effectiveness. The GDG also suggested that there is a strong clinical perception that better results are seen when treating the neuropathic population with antimuscarinics than is seen in the non-neuropathic populations. It is therefore likely that these treatments are cost effective. However, there is no high quality evidence to choose between them and it is therefore not possible to recommend one treatment over another, in terms of side effects or effectiveness. All of the treatments are very low cost, with no treatment costing more than 80p per pill, therefore balancing the side effect profile with the cost of the pill is more important than making sure the pill is the lowest cost. Of course, where there is nothing to choose between the two, the lowest cost treatment should be provided.
Quality of evidence	<u>Children and young people</u> The evidence was from observational studies comparing outcomes before and after treatment. However, the GDG agreed that the evidence is consistent in demonstrating increased bladder capacity and improvement in continence with antimuscarinic treatment in children with spina bifida. The GDG noted the absence of data on quality of life. <u>Adults</u> The studies compared outcomes before and after treatment in the same group of patients. The studies therefore lacked internal validity due to an absence of a matched comparison group. The RCTs on adults had a small sample size but had adequate follow-up times. There was a lack of data on quality of life. The GDG expressed concern that the available data related to an era before some of the newer

	antimuscarinic drugs had been introduced. The GDG agreed that the evidence wasn't strong enough to consider recommending the use of particular drugs and agreed that recommendations should be made on the basis of the antimuscarinic agents as a generic group. The choice of drug should be left to the treating clinician based on side effect profile and cost. The evidence on Intravesical Atropine compared to Oral Oxybutynin was considered. While atropine did show evidence of a potential clinical benefit, the GDG noted that the use of intravesical atropine had received relatively little attention in clinical trials and clinical practice in the UK, and it was agreed that there is inadequate data to support the use of atropine. The majority of the evidence that was available related to patients with impaired bladder storage in association with spinal cord disease. There is a paucity of data relating to patients with brain lesions and neurogenic LUT dysfunction. Given the evidence in the able-bodied population and in patients with spinal cord disease, the GDG believes that it's reasonable to consider the use of antimuscarinic treatment in other neurogenic groups with symptoms of bladder over-activity. The economic evidence considered was partially applicable to our population as studies were conducted in non-neurogenic population. The GDG thought results could be applicable to the neurogenic population too.
Other considerations	Children and young people The terminology relating to congenital spinal anomalies is the source of possible confusion. "Spina bifida" describes the vertebral anomaly which is associated with open and closed myelomeningocoele. However, there are other forms of spinal malformation which are also associated with neurogenic LUT dysfunction which will be treated using similar methods to those employed in meningomyelocoele patients; spinal dysraphism includes both myelomeningocoele and the other congenital spinal anomalies that are associated with neurogenic LUT dysfunction. Children with neurogenic LUT dysfunction and raised bladder storage pressures (particularly those with spina bifida) have been managed using one of two strategies. Some clinicians use a pre-emptive approach and introduce a combination of antimuscarinic drugs and intermittent catheterisation before any evidence of upper urinary tract dilatation is present. The alternative strategy is to monitor the upper urinary tracts and introduce these treatments if hydronephrosis develops. <u>Adults</u> The GDG discussed the suggestion that antimuscarinic agents might be more effective in the neurogenic population than in patients with idiopathic bladder overactivity. This was felt to be a possibility but the only evidence to support this hypothesis was anecdotal. The GDG agreed further research was required on the efficacy of the newer antimuscarinics in comparison with the older well established drugs.

8.2.3 Research recommendations

Safety and efficacy of antimuscarinics

1. **What is the safety and efficacy of more recently developed antimuscarinics compared with (a) placebo/usual care and (b) other antimuscarinics in the treatment of neurogenic lower urinary tract dysfunction?**

- **Why this is important:**

  No high-quality clinical trials looking at the use of the newer antimuscarinic drugs in people with neurogenic lower urinary tract dysfunction have been carried out. Both placebo-controlled and comparative studies are lacking. This is important because the more recently developed medications are of unknown efficacy, are more expensive and claim (in the non-

neurogenic population) to have fewer adverse effects. The adverse effects of antimuscarinics are mostly due to their action at sites other than the bladder (for example, causing a dry mouth) but there is now increasing concern that antimuscarinic effects on the central nervous system may adversely affect cognitive function in both children with brain damage (caused by cerebral palsy or hydrocephalus) and adults with impaired cognition (caused by cerebral involvement in multiple sclerosis or neurodegenerative diseases).

8.3 Botulinum toxin

8.3.1 What is the safety and efficacy of detrusor injections of botulinum toxin type A[i] or B compared with a) usual care b) antimuscarinics in neurological disease

Clinical Methodological Introduction	
Population:	Patients with NLUTD
Intervention:	Botulinum toxin type A Botulinum toxin type B
Comparison:	Usual care Antimuscarinics Augmentation cystoplasty
Outcomes:	Quality of life Frequency of voiding by day and night. Number of incontinence episodes Urgency Increased bladder capacity Residual urine Kidney function Adverse events, including urinary tract infections, unscheduled hospital admissions, generalised muscle weakness Treatment continuance

8.3.1.1 Clinical evidence

We searched for RCTs comparing the short-term effectiveness of botulinum toxin type A or B compared to usual care, antimuscarinics or augmentation cystoplasty in adults and for observational studies comparing the longer-term effectiveness (two or more injections of botulinum toxin type A or B) in adults. For children we searched for RCTs or observational studies comparing the short-term or long-term effectiveness of botulinum toxin type A or B, usual care, antimuscarinics or augmentation cystoplasty. All of the searches were on interventions for improving incontinence in neurological disease or injury

Adults

No relevant studies were found on botulinum toxin type B. No studies were found comparing botulinum toxin type A with augmentation cystoplasty. The majority of studies comprised patients who were either on antimuscarinics, or antimuscarinics had failed to control their symptoms.

[i] At the time of publication (August 2012), botulinum toxin type A did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's 'Good practice in prescribing medicines – guidance for doctors' for further information.

Studies on the shorter-term (one cycle of treatment) efficacy compared botulinum toxin type A with placebo and were on adults with neurogenic detrusor overactivity [62], neurogenic detrusor overactivity secondary to spinal cord injury or multiple sclerosis [63 64 65 66 67].

Eight longer-term (two or more cycles of treatment) observational studies were identified comparing before and after botulinum toxin type A in adults with neurogenic detrusor overactivity [63 68 69 70 71] neurogenic detrusor overactivity due to spinal cord lesions[72 73 74] neurogenic lower urinary tract dysfunction [75].

The botulinum toxin type A preparations are individual and not interchangeable so the results are reported by preparation (Botox (Allergan), Dysport (Ipsen), unclear/both preparations).

Tables 33 and 34 summarise the population, intervention, comparison and outcomes for each of the studies. Table 35 summarises the number of injections the adults received in the longer-term efficacy studies.

Children

No studies were identified on botulinum toxin type B. No studies were identified comparing botulinum toxin with augmentation cystoplasty.

The majority of patients were either on antimuscarinics or antimuscarinics had failed to control their symptoms.

One RCT (N=23) in children with neuropathic bladder after repair of myelomeningocele was identified comparing botulinum type A (preparation not specified) plus continued oxybutynin with discontinuation of oxybutynin [76].

The observational studies compared before and after botulinum toxin type A in children with myelomeningocele or spina bifida [77; 78; 79; 80], myelodysplasia [81]; spinal cord lesions [82] and neurogenic detrusor overactivity/ hyper-reflexia [83; 84; 85; 86].

The results are reported by preparation (Botox, Dysport, unclear/both preparations)

Tables 2 summarise the population, intervention, comparison and outcomes for each of the studies.

Table 38: Summary of studies included in the clinical evidence review - Adults

STUDY	POPULATION	INTERVENTION	COMPARISON	FOLLOW-UP
Shorter term efficacy				
Cruz 2011 [63]	Patients with incontinence due to neurogenic detrusor overactivity (included patients with multiple sclerosis and spinal cord injury only)	Botulinum toxin type A (Botox) 200U N=92 300U N=91 Injections were performed with no anaesthesia, local anaesthetic, or under general anaesthesia	Placebo N=92	12 weeks
Ehren 2007 [62]	Inclusion criteria: age ≥18 years; urodynamically verified detrusor over-activity with	500 U Botulinum toxin type A (Dysport) Allowed to use a maximum of 4mg (2 tabs) of tolterodine daily.	Placebo Allowed to use a maximum of 4mg (2 tabs) of tolterodine daily.	26 weeks

STUDY	POPULATION	INTERVENTION	COMPARISON	FOLLOW-UP
	urinary leakage for at least 1 year; inadequate response to oral antimuscarinics; ability to perform clean intermittent catheterisation.	N=17	N=14	
Herschorn 2011, 2009 [64]; ; [65]	Patients with neurogenic detrusor overactivity and urinary incontinence secondary to spinal cord injury or multiple sclerosis	Botulinum toxin type A (Botox) 300U injected into 30 sites N=28 At 36 weeks all subjects were offered open label Botulinum toxin A	Placebo N=29 At 36 weeks all subjects were offered open label Botulinum toxin A	36 weeks
Schurch 2005A, 2007 [66]; [67].	Patients with urinary incontinence caused by neurogenic detrusor overactivity with spinal cord injury (n=53) or multiple sclerosis (n=6). Inclusion criteria: aged 18 yrs or over, urinary incontinence of > 6 wk duration and regularly performed CIC	Botulinum toxin type A (Botox) 200 U (n=19) or 300 U (n=19) Patients performing clean intermittent catheterisation (CIC). Also, they had experienced inadequate response to oral antimuscarinics, however concomitant use of these agents was during the study	Placebo (n=21) Patients performing CIC. Also, they had experienced inadequate response to oral antimuscarinics, however concomitant use of these agents was allowed during study	26 wks
Longer-term efficacy				
del Popolo 2008 [72]	Patients with spinal cord lesions with neurogenic detrusor overactivity (September 1999 and December 2005) resistant to conventional antimuscarinic therapy	Botulinum toxin type A (Dysport) 1000, 750, 500 IU N=199	**Before 1st injection** Resistant to conventional antimuscarinic therapy. Practising clean intermittent catheterisation **Following injections** Gradually reducing antimuscarinic therapy from the first week until the third week after the drugs, until the complete suspension of the drugs. Therapy reintroduced if deterioration despite injection	Variable range after 1 to 8 injections

STUDY	POPULATION	INTERVENTION	COMPARISON	FOLLOW-UP
			N=199	
Giannantoni 2009 [73]	Patients with neurogenic detrusor overactivity. Subgroup of spinal cord injury followed up for > 6 yrs	300 U Botulinum toxin type A (Botox) N=17	BASELINE N=8 oral antimuscarinics N=9 had stopped taking antimuscarinics due to intolerable side effects	Quality of Life 4 mths and every year during follow-up Urodynamics 4 mths, 1, 3 and 6 yr Voiding diary for 2 days/per week during follow up
Grosse 2005 [75]	Patients with repeat BTX-A injections for neurogenic lower urinary tract dysfunction (detrusor overactivity, low compliance, reduced bladder capacity – with or without incontinence), unmanageable by antimuscarinic treatment and able to practice intermittent (self) catheterisation	Initially 200 UI Botulinum toxin type A or 250 UI (Botox) (n=5) and 500 UI (Dysport) (n=7) Then 300 UI (Botox) and 750 or 1000 UI (Dysport) N=66	BASELINE Intermittent self catheterisation 53/66 (24 also had spontaneous or triggered voiding) Antimuscarinic medication 53/66. 13/66 did not antimuscarinics because of adverse effects or ineffectiveness N=66	Variable
Karsenty 2006 [68]	Patients with neurogenic detrusor overactivity and incontinence Patients had to have received at least two repeat injections.	300 U Botulinum toxin type A (Botox) N=17	BASELINE Antimuscarinic use not specified N=17	Mean no. of injections 5.4 (range 3 to 9)
Khan 2011 [69]	Patients with multiple sclerosis and neurogenic detrusor overactivity. Patient must have been willing to perform CIC.	300 U Botulinum toxin type A (Botox) Injected into 30 sites on outpatient basis Injections repeated on return of symptoms (no minimum period) 1st injection N=137 2nd injection N=99 3rd injection N=47 4th injection N=25 5th injection N=14 6th injection N=5	Pre-treatment Patients had not responded to behavioural therapy or to pharmacotherapy of at least two medications.	Mean 29 mths (range 9 to 80 mths)

STUDY	POPULATION	INTERVENTION	COMPARISON	FOLLOW-UP
		N=137		
Kuo 2011 [74]	Patients with more than one year history of chronic suprasacral cord injury. All patients were diagnosed with detrusor sphincter dyssynergia by videourodynamic study. In addition, all patients voided by reflex or abdominal stimulation with or without clean intermittent catheterisation, were free of indwelling catheter or cystostomy, and were free of urinary tract infection.	200 U Botulinum toxin type A (Botox) Injected into 40 sites under light general anasthesia Injections repeated every 6 mths N=33 (completed treatment)	All patients had been treated with antimuscarinics for at least one year and failed to resolve their urinary incontinence.	24 months
Pannek 2009B [70]	Patients with neurogenic detrusor overactivity due to spinal cord lesions Inclusion criteria: minimum of five treatments of BoNT-A	Botulinum toxin type A (preparation unclear) Mean no. of treatments 7.1 (range 5 to 11) N=27	BASELINE All patients failed to respond sufficiently to antimuscarinic treatment N=27	Not specified Mean no. of treatments 7.1 (range 5 to 11)
Reitz 2007 [71]	Patients with neurogenic detrusor overactivity Patients who received at least five intradetrusor injections and who were followed by clinical and urodynamic evaluation after at least four injections	Botulinum toxin type A (Botox) N=20	BASELINE Concomitant antimuscarinic medications were allowed N=20	For a minimum of 4 injections

Table 39: Summary of studies included in the clinical evidence review - Children

STUDY	POPULATION	INTERVENTION	COMPARISON	Follow-up
Neel 2007 [76]	Children with neuropathic bladder after repair of	Botulinum toxin type A 12 IU/kg (Dysport)	Botulinum toxin type A 12 IU/kg (Dysport)	Six mths

STUDY	POPULATION	INTERVENTION	COMPARISON	Follow-up
	myelomeningocele.	N=12 **Plus oxybutynin** continued at the same pre-injection dose	N=11 **Oxybutynin was discontinued** on the day of the BTX-A injection	
Altaweel 2006 [77]	Children and young adults with neurogenic bladder due to myelomeningocele	Botulinum toxin type A (Unclear manufacturer) 5 IU/kg to a maximum of 300 IU N=20	BASELINE N=20	Mean 17.2 mths (SD 2 months)
Akbar 2007A [81]	Patients with myelodysplasia	Botulinum toxin type A (Dysport) injections in conjunction with clean intermittent catheterisation (CIC). Antimuscarinics tapered. 20 units/kg to a maximum of 400 units N=19	BASELINE CIC plus antimuscarinics if tolerated N=19	Up to 12 mths
Deshpande 2010 [78]	Patients with neurogenic bladder caused by spina bifida and had uncontrolled incontinence while on clean intermittent catheterisation (CIC) and antimuscarinic therapy	Botulinum toxin type A (Botox) 10 IU/kg to a maximum dose of 300 IU N=7	BASELINE All patients included in the study had uncontrolled incontinence whilst on clean intermittent catheterisation and oxybutynin N=7	9 mths
Do 2009 [82]	Patients with neurogenic detrusor overactivity due to spinal cord lesions in children (n=3 sacral birth defects, n=4 acquired thoracic lesions)	Botulinum toxin type A (Botox) 6-11 IU/kg to a maximum of 300 UI N=7	BASELINE 6/7 patients using CIC and oxybutynin 1/7 intolerant to oxybutynin and continuously incontinent N=7	Variable
Kajbafzadeh 2006 [79]	Children with urodynamically proven detrusor hyperreflexia	Botulinum toxin type A (Botox) BTX-A 10 IU/kg	BASELINE All patients had been taking antimuscarinic	4 months

STUDY	POPULATION	INTERVENTION	COMPARISON	Follow-up
	caused by myelomeningocele.	Antimuscarinic medication was discontinued at least 10 days before urodynamic assessment N=26	medications since birth and underwent clean intermittent catheterisation every 3 to 4 hrs, with unacceptable adverse effects or little or no success from treatment N=26	
Riccabona 2004 [80]	Children with myelomeningocele (MMC).	Botulinum toxin type A (preparation unclear) 10 U/kg N=15	BASELINE All patients had been on antimuscarinic medication since birth and received clean intermittent catheterisation every 4 hrs, showing little or no success	12 months
Schulte-Baukloh 2005A [83]	Children with neurogenic detrusor overactivity who had received at least three BTX-A injections.	Botulinum toxin type A (Botox) 12 U/kg N=10	BASELINE Bladder emptying occurred through intermittent catheterisation four or five times daily plus antimuscarinics N=10	Initially 1, 3 and 6 mths then twice yearly Outcomes compared 3rd vs 1st (3TI group) (all 10 children) 5th vs 1st injection (5TI group) (n=4 children)
Schulte-Baukloh 2003 [84]	1-16 years old; neurogenic bladder and detrusor hyper-reflexia; respond poorly to antimuscarinic drugs	Botulinum toxin type A (Botox) 12 U/kg up to a maximum of 300U N=20	BASELINE All but one had to use CIC at least 4 times a day. N=13 had anticholingergic therapy stopped on receiving botulinum toxin. N=7 remained on antimuscarinic therapy N=20	6 months
Schulte-Baukloh 2002 [85]	1-16 years; detrusor hyperreflexia and high intravesical pressure >40cm H_20 or unacceptable side effects of antimuscarinic medication.	Botulinum toxin type A (Botox). 12U/kg of body weight, up to a maximum of 300 U, Antimuscarinic medication was stopped at least 10 days before the injection	BASELINE All but one child emptied their bladder with clean intermittent catheterisation at least four times a day. Antimuscarinic medication was stopped at least 10	Unclear (Probably 2-4 weeks)

STUDY	POPULATION	INTERVENTION	COMPARISON	Follow-up
		N=17	days before baseline urodynamic measurements, except that in 1 case antimuscarinic medication was maintained before and after injection N=17	
Schurch 2006 [86]	Children with neurogenic bladder, who required clean intermittent catheterisation (CIC) and were at high risk of impaired kidney function due to neurogenic detrusor overactivity and high bladder pressure despite maximum antimuscarinic medication	Botulinum toxin type A (Botox) 12 U/kg to a maximum dose of 300 U N=24	BASELINE Clean intermittent catheterisation and maximum doses of antimuscarinic medication N=24	6 months

Table 40: Summary of the No. of injections for longer-term observational studies in adults

STUDY	NO. OF INJECTIONS
Cruz 2011 [63]	Total number of injections 2 N=74
Giannantoni 2009 [73]	Mean no. of injections 7.2 (SD1.3) mean interval between injections 11.0 mths
del Popolo 2008[72]	No. of injections: 1 n=199 2 n=160 3 n=90 4 n=51 5 n=49 6 n=12 7 n=6 8 n=2 9 n=1
Grosse 2005 [75]	No. of injections: 2 or more n=66 3 or more n=34 4 or more n=17 5 or more n=5 6 or more n=3 7 n=1

STUDY	NO. OF INJECTIONS
Karsenty 2006 [68]	Mean no. of injections: 5.4 (range 3 to 9)
Khan 2011 [69]	No. of injections: 1 n=137 2 n=99 3 n=47 4 n=25 5 n=14 6 n=5
Kuo 2011 [74]	N=33 Injections repeated every 6 mths for 24 mths
Pannek 2009 [70]	Mean no. of treatments 7.1 (range 5 to 11)
Reitz 2007 [71]	Minimum of 4 injections. Injections repeated every 7 months

Adults shorter term safety and efficacy

Botulinum toxin type A (Botox 200 U) versus placebo

Table 41: Botulinum toxin A (Botox 200 U) versus placebo - Clinical study characteristics and clinical summary of findings

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Botulinum toxin 200 U N, mean (SD)/ freq. count	Placebo N, mean(SD)/ freq. count	Relative (95% CI))/ p value	Absolute	
I-QoL (mean change score (no SD)) 6 weeks (Better indicated by higher values)										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[b]	92 24.4	92 11.7	p<0.001	Botulinum 24.4 Placebo 11.7 p<0.001	HIGH
I-QoL (final median score) 6 weeks (Better indicated by higher values)										
Schurch 2007 [67].	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	19 84.1	21 56.3	p<0.01	Botulinum 84.1 Placebo 56.3 p<0.01	MODERATE
I-QoL (final median score) 24 weeks (Better indicated by higher values)										
Schurch 2007 [67].	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	19 86.4	21 44.3	p<0.05	Botulinum 86.4 Placebo 44.3 p<0.05	MODERATE
Incontinence episodes/week (mean change score) 6 weeks (Better indicated by lower values)										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	92 -21.8 (18.1)	92 -13.2 (20.0)	MD 8.6 (-14.11 to -3.09)	MD 8.6 lower (14.11 to 3.09 lower)	MODERATE
Incontinence episodes/day (mean change score) 6 weeks (Better indicated by lower values)										
Schurch 2005 [66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	19 -0.9 (1.84)	21 -0.2 (1.45)	MD -0.7 (-1.73 to 0.33)	MD -0.7 lower (1.73 lower to	LOW

Quality assessment						No of patients		Effect		Quality
									0.33 higher)	
Incontinence episodes/day (mean change score) 24 weeks (Better indicated by lower values)										
Schurch 2005 [66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	19 -1.1 (1.92)	21 -0.1 (1.09)	MD 1 (-1.98 to -0.02)	MD 1 lower (1.98 to 0.02 lower)	LOW
Maximum bladder capacity ml (mean change score) 6 weeks (Better indicated by higher values)										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	92 157.0 (164.8)	92 6.5 (144.8)	MD 150.5 (105.67 to 195.33)	MD 150.5 higher (105.67 to 195.33 higher)	HIGH
Maximum bladder capacity ml (mean change score (no SD)) 6 weeks (Better indicated by higher values)										
Schurch 2005 [66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[d]	19 448.8 (182.1)	21 299.6 (45.0)	ns	ns	MODERATE
Maximum bladder capacity ml (mean change score (no SD)) 24 weeks (Better indicated by higher values)										
Schurch 2005 [66]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[d]	19 174.2	21 41.6	Botulinum p<0.05	Botulinum p<0.05	MODERATE
All adverse events end of scheduled follow-up[e]										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	79/91 86.80%	67/90 (74.40%)	RR 1.17 (1.01 to 1.35)	126 more per 1000 (from 7 more to 260 more)	MODERATE
Muscle weakness end of scheduled follow-up[e]										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	6/91 6.60%	1/90 (1.10%)	RR 5.93 (0.73 to 48.31)	54 more per 1000 (from 3 fewer to 520 more)	MODERATE
Urinary tract infections end of scheduled follow-up[e]										
Cruz 2011 [63]; Schurch 2005 [66]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	seriousc	57/110 51.80%	39/111 (27.10%)	RR 1.46 (1.08 to 1.98)	125 more per 1000 (from 22 more to 266 more)	MODERATE

[a] Unclear allocation concealment
[b] Imprecision could not be assessed, no estimate of effect/median value reported
[c] The 95%CI crosses the minimally important difference for either benefit or harm
[d] Imprecision could not be assessed, no estimate of effect reported
[e] Cruz data covers treatment period for cycle 1 of the intervention
ns not significant

Botulinum toxin type A (Botox 300 U) versus placebo

Table 42: Botulinum toxin A (Botox 300 U) versus placebo - Clinical study characteristics and clinical summary of findings

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Botulinum toxin 300 U N, mean (SD)/ freq count	Placebo N, mean(SD)/ freq count	Relative (95% CI))/ p value	Absolute	
I-QoL (mean change scores) 6 weeks (Better indicated by higher values)										
Herschorn 2009	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	28 19.52 (22.93)	29 -2.23 (13.24)	MD 21.75 (11.98 to 31.52)	MD 21.75 higher (11.98 to 31.52 higher)	HIGH
I-QoL (mean change score) 24 weeks (Better indicated by higher values)										
Herschorn 2009	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	28 16.27 (22.72)	29 0.44 (16.73)	MD 15.83 (5.44 to 26.22)	MD 15.83 higher (5.44 to 26.22 higher)	MODERATE
I-QoL (mean change score (no SD)) 6 weeks (Better indicated by lower values)										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[b]	91 24.3	92 11.7	p<0.001	p<0.001[g]	HIGH

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Botulinum toxin 300 U N, mean (SD)/ freq count	Placebo N, mean(SD)/ freq count	Relative (95% CI))/ p value	Absolute	
I-QoL (final median score) 6 weeks (Better indicated by higher values)										
Schurch 2007 [67].	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision[d]	19 77.3	21 56.3	p<0.01	p<0.01	MODERATE
I-QoL (final median score) 24 weeks (Better indicated by higher values)										
Schurch 2007	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision[d]	19 67.0	21 44.3	p<0.05	p<0.05	MODERATE
Incontinence episodes/week (mean change score) 6 weeks (Better indicated by lower values) [e]										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	91 -19.4 (25.7)	92 -13.2 (20.0)	MD -6.2 (-12.88 to 0.48)	MD 6.2 lower (12.88 lower to 0.48 higher)	MODERATE
Incontinence episodes/day (mean final score) 6 weeks (Better indicated by lower values)										
Herschorn 2011 [64];	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	28 1.31 (1.25)	29 4.76 (2.92)	MD -3.45 (-4.61 to -2.29)	MD 3.45 lower (4.61 to 2.29 lower)	HIGH
Incontinence episodes/day (mean final score) 24 weeks (Better indicated by lower values)										

Treatment to improve bladder storage

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Botulinum toxin 300 U N, mean (SD)/ freq count	Placebo N, mean(SD)/ freq count	Relative (95% CI))/ p value	Absolute	
Herschorn 2011 [64];	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	28 1.56 (1.52)	29 3.98 (2.71)	MD - 2.42 (-3.56 to -1.28)	MD 2.42 lower (3.56 to 1.28 lower)	HIGH
Incontinence episodes/day (mean change score) 6 weeks (Better indicated by lower values)										
Schurch 2005 [66]	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	serious[a]	19 -1.5 (2.33)	21 -0.2 (1.45)	MD - 1.30 (-2.52 to -0.08)	MD 1.30 lower (2.52 to 0.08 lower)	LOW
Incontinence episodes/day (mean change score) 24 weeks (Better indicated by lower values)										
Schurch 2005 [66]	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	serious[a]	19 -0.9 (1.34)	21 -0.1 (1.09)	MD - 0.80 (-1.56 to -0.04)	MD 0.80 lower (1.56 to 0.04 lower)	LOW
Maximum bladder capacity ml (mean change score) 6 weeks (Better indicated by higher values)										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	91 157.2 (185.2)	92 6.5 (144.8)	MD 150.7 (102.5 to 198.9)	MD 150.7 higher (102.5 to 198.9 higher)	HIGH
Maximum bladder capacity ml (final median score) 6 weeks (Better indicated by higher values)										
Herschorn 2011 [64];	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[d]	28 521.5 (IQR 384 to 703.5)	29 241.0 (143.o to 358.0)	p=0.0002	p=0.0002	HIGH
Maximum bladder capacity ml (final median score) 24 weeks (Better indicated by higher values)										

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Botulinum toxin 300 U N, mean (SD)/ freq count	Placebo N, mean(SD)/ freq count	Relative (95% CI))/ p value	Absolute	
Herschorn 2011 [64];	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[d]	28 374.5 (IQR 227.5 to 661.5)	29 246.0 (129.0 to 418.0)	p=0.031	p=0.031	HIGH
Maximum bladder capacity ml (mean change score (no SD)) 6 weeks (Better indicated by higher values)										
Schurch 2005	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	19 169.1	21 45.0	p<0.05	p<0.05	MODERATE
Maximum bladder capacity ml (mean change score (no SD)) 24 weeks (Better indicated by higher values)										
Schurch 2005 [66]	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	19 92.9	21 41.6	p<0.05	p<0.05	MODERATE
All adverse events end of scheduled follow up[f]										
Cruz 2011 [63]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	79/89 88.80%	67/90 (74.40%)	RR 1.19 (1.03 to 1.37)	141 more per 1000 (from 22 more to 275 more)	MODERATE
Muscle weakness end of scheduled follow up[f]										
Cruz 2011 [63] Herschorn 2011 [64];	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	7/117 6%	1/119 (0.60%)	RR 5.1 (0.9 to 28.82)	25 more per 1000 (from 1 fewer to 167 more)	MODERATE
Urinary tract infection end of scheduled follow up[f]										
Curz 2011 [63] Herschorn 2011 [64];	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	77/136 56.60%	55/140 (40%)	RR 1.43 (1.12 to 1.83)	172 more per 1000 (from 48 more to 332 more)	MODERATE

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Botulinum toxin 300 U N, mean (SD)/ freq count	Placebo N, mean(SD)/ freq count	Relative (95% CI))/ p value	Absolute	
Schurch 2005 [66]										

[a] The 95%CI crosses the MID for either benefit or harm
[b] Imprecision could not be assessed, no estimate of effect reported
[c] Unclear allocation concealment
[d] Imprecision could not be assessed, median values reported
[e] The final value and change scores when combined resulted in heterogeneity (I^2> 80%). These outcomes are presented separately
[f] Cruz data covers the treatment period for cycle 1 of the intervention

Dysport

Table 43: Botulinum toxin type A (Dysport) versus placebo Quality of life - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Quality of life - Qualiveen										
1 [A]	RCT	Botulinum toxin type A (Dysport) N=17	Placebo N=14	"Significant improvement seen on many quality of life parameters" 6 weeks (counts) Placebo slightly or not adversely affected 30 Extremely or not adversely affected 98 Treatment slightly or not adversely affected 176 Extremely or moderately affected 42 26 weeks (counts) Placebo slightly or not adversely affected 24 Extremely or not adversely affected 100 Treatment slightly or not adversely affected 148 Extremely or moderately 68	VS (i)	N	N	N (ii)	N	Low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
VS very serious N none (i) No details of randomisation or allocation concealment, incomplete outcome reporting (ii) Imprecision could not be assessed – no estimates of effect [A] Ehren et al. 2007 [62]										

Table 44: Botulinum toxin type A (Dysport) versus placebo Continence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Continence										
1 [A]	RCT	Botulinum toxin type A (Dysport) N=17	Placebo N=14	Number of days with urinary leakage The botulinum toxin type A group had significantly fewer days with leakage compared to placebo at 0 to 6 weeks (p<0.001), 7 to 12 weeks (p=0.002) and 13 to 26 weeks (p=0.010)	VS (i)	N	N	N (ii)	N	Low
VS very serious N none (i) No details of randomisation or allocation concealment, incomplete outcome reporting. (ii) Imprecision could not be assessed – no estimates of effect [A] Ehren et al 2007 [62]										

Table 45: Botulinum toxin type A (Dysport) versus placebo Maximum cystometric capacity - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Maximum cystometric capacity										
1 [A]	RCT	Botulinum toxin type A(Dysport) N=17	Placebo N=14	The botulinum-A toxin group had a significantly higher bladder capacity than placebo at 6 (p<0.001) and 12 weeks (p=0.026) but not at 26 weeks (ns)	VS (i)	N	N	N (ii)	N	Low
VS very serious N none (i) No details of randomisation or allocation concealment, incomplete outcome reporting (ii) Imprecision could not be assessed – no estimates of effect [A] Ehren et al. 2007 [62]										

Both/ unclear preparations

No studies identified

Adults longer-term follow up data

Botox

Table 46: Botulinum toxin type A (Botox) (pre vs post treatment) Quality of life - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Quality of life										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Prospective observational study	Botulinum toxin type A (Botox) N=42 200 U N=32 300 U	Baseline N=42 200 U N=32 300 U	Incontinence-Specific Quality of Life, total summary score (lower the score the better) 200 U Baseline 34.6 (20.7) vs Week 6 21.2 (25.3) 300 U Baseline 36.6 (21.6) vs Week 6 20.2 (30.4)	S (i)	N	N	N (i)	N	Very low
1 [B]	Prospective observational study	Botulinum toxin type A (Botox) N=17 Mean no. of injections 7.2 (SD 1.3)	Baseline N=17	Higher the score the better) mean (SD) Baseline 22.4 (18.6) vs 4 mths 77.7 (20.9) vs 12 mths 85.7 (16.8) vs 24 mths 83.5 (22.1) vs 36 mths 80.6 (15.4) vs 72 mths 83.9 (17);	S (i)	N	N	N(ii)	N	Very low
1 [C]	Prospective observational study	Botulinum toxin type A (Botox) N=137 1 to 6 injections	Baseline N=137	Urogenital Distress Inventory (UDI) UDI (lower the score the better) mean (SD) before vs after 1st injection 61.8 (1.4) 1 vs 23.0 (1.7) 2nd injection 55.5 (2.2) vs 24.0 (2.3) 3rd injection 56.4 (3.4) vs 8.6 (1.6) 4th injection 57.2 (5.0) vs 19.8 (3.6) 5th injection 54.6 (5.8) vs 8.6 (4.0) 6th injection 67 (3.4) vs 12.2 (7.5) Similar results reported for Incontinence Impact Questionnaire (IIQ)	S (ii)	N	N	N (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [D]	Prospecitve observational study	Botulinum toxin type A (Botox) N=33 4 injections (1 every 6 mths)	Baseline N=33	Quality of life index Mean (SD) (higher the score the better) p<0.05 for all comparisons Baseline vs 6 mths vs 12 mths vs 18 mths vs 24 mths 207.1 (111) vs 306.4 (186) vs 376.9 (180) vs 369.7 (129) vs 411.7 (32.9)	S (ii)	N	N	N (ii)	N	Very low

S serious N none SD standard deviation

(i) Before vs after data
(ii) Data at high risk of bias (very low quality), imprecision not assessed

[A] Cruz et al (2011) [63]
[B] Giannantoni et al (2009) [73]
[C] Khan et al (2011) [69]
[D] Kuo et al (2011) [74]

Table 47: Botulinum toxin type A (Botox) (pre vs post treatment) Continence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Prospective observational study	Botulinum toxin type A (Botox) N=42 200 U N=32 300 U	Baseline N=42 200 U N=32 300 U	No. of incontinence episodes per week Baseline vs change at week 6 mean (SD) 200 U 37.2 (20.0) vs -20.4 (26.4) 300 U 31.5 (16.6) -19.7 (20.2)	S (i)	N	N	N (i)	N	Very low
1 [B]	Prospective observational study	Botulinum toxin type A (Botox) N=17 Mean no. of injections 7.2 (SD 1.3)	Baseline N=17	No. of incontinence episodes per day mean (SD) Baseline 4.8 (2.7) vs 4 mths 2.4 (1.0) vs 1 yr 2.1 (2.1) vs 3 yr 1.8 (0.9) vs 6 yr 1.8 (1.1); baseline vs 6 yr p=0.01	S (i)	N	N	N(ii)	N	Very low
1 [C]	Prospective observational study	Botulinum toxin type A (Botox) N=17 Mean no. of injections 5.4 (range 3 to 9)	Baseline N=17	Incontinence mean no. of episodes per day First injection 2.6 vs last injection 0	S (ii)	N	N	N (ii)	N	Very Low
1 [D]	Prospective observational study	Botulinum toxin type A (Botox) N=137 1 to 6 injections	Baseline N=137	Continence Before versus after treatment (1st injection implied) 17% versus 76%	S (ii)	N	N	N (ii)	N	

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before vs after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Cruz et al (2011) [63] [B] Giannantoni et al 2009A [73] [C] Karsenty et al. (2006) [68] [D] Khan et al (2011) [69]										

Table 48: Botulinum toxin type A (Botox) (pre vs post treatment) Maximum cystometric capacity - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Maximum cystometric capacity ml										
1 [A]	Prospective observational study	Botulinum toxin type A (Botox) N=42 200 U N=32 300 U	Baseline N=42 200 U N=32 300 U	Baseline vs change at week 6 mean (SD) 200 U 221.7 (151.1) vs 123.5 (154.4) 300 U 232.4 (159.3) vs 147.3 (156.3)	S (i)	N	N	N (i)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [B]	Prospective observational study	Botulinum toxin type A (Botox) N=17 Mean no. of injections 7.2 (SD 1.3)	Baseline N=17	Baseline 243 (64.7) vs 4 mths 390 (51.8) vs 1 yr 389.4 (45.9) vs 3 yrs 439.4 (41.6) vs 6 yrs 420.8 (55.7) baseline vs 6 yr p=0.001	S (i)	N	N	N(ii)	N	
1 [C]	Prospective observational study	Botulinum toxin type A (Botox) N=17 Mean no. of injections 5.4 (range 3 to 9)	Baseline N=17	mL (SD) Baseline 348.8 (115.8) vs first injection 499.1 (3.6)	S (i)	N	N	N(ii)	N	Very low
1 [D]	Prospective observational study	Botulinum toxin type A (Botox) N=20 For a minimum of 4 injections	Baseline N=20	Mean (95%CI) Baseline 216.5 (187.5 to 395) vs Injection 1 500 (500 to 576.5) vs Injection 2 500 (500 to 520) vs Injection 3 490 (415 to 500) vs Injection 4 500 (402.5 to 512.5) vs Injection 5 500 (435 to 500)	S (i)	N	N	N(ii)	N	Very low
1 [E]	Prospecitve observational study	Botulinum toxin type A (Botox) N=33 4 injections (1 every 6 mths)	Baseline N=33	Mean (SD) p<0.05 for all comparisons Baseline vs 6 mths vs 12 mths vs 18 mths vs 24 mths 4.51 (1.34) vs 2.31 (1.28) vs 2.29 (1.49) vs 2.30 (1.23) vs 2.26 (1.68)	S (ii)	N	N	N (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before vs after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Cruz et al (2011) [63] [B] Giannantoni et al (2009) [73] [C] Karsenty et al. (2006) [68] [D] Reitz et al. (2007) [71] [E} Kuo et al (2011) [74]										

Table 49: Botulinum toxin type A (Botox) (pre versus post treatment) Adverse events - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Adverse events										
1 [A]	Prospective observational study	Botulinum toxin type A (Botox) N=17 Mean no. of injections 7.2 (SD 1.3)	Baseline N=17	**Urinary tract infections** Baseline 6.7 (2.1) vs 4 mths 1.6 (1.3) vs 1 yr 3.3 (2.1) vs 3 yrs 1.7 (2.0) vs 6 yrs 1.8 (0.5) baseline vs 6 yr p=0.001	S (i)	N	N	N(ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [B]	Prospective observational study	Botulinum toxin type A (Botox) N=137 1 to 6 injections	Baseline N=137	**Urinary tract infections** Antibiotics required after 30/327 treatment sessions Long term antibiotics treatment was required 23/137 (17%) **Exacerbations of MS** 8/137 (5.8%)	S (i)	N	N	N(ii)	N	Very low
S serious N none (i) Before vs after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Giannantoni et al (2009) [73] [B] Khan et al (2011) [69]										

Dysport

Table 50: Botulinum toxin type A (Dysport) (pre vs post treatment) Maximum cystometric capacity - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Retrospective observational study	Botulinum toxin type A (Dysport) N=199 1 injection N=90 3 injections N=49 5 injections	Baseline, post 1st, 3rd and 5th injections N=199	Mean ml (SD) Baseline 226.04 (22) Vs 1 yr 407.69 (26.8) vs 3 yrs 400.4 (34.4) vs 5 yrs 405.6 (35.6)	S (i)	N	N	N(ii)	N	Very low
S serious N none (i) Before versus after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] del Popolo et al. (2008) [72]										

Table 51: Botulinum toxin type A (Dysport) (pre vs post treatment) Patient satisfaction - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Patient satisfaction										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Retrospective observational study	Botulinum toxin type A (Dysport) N=199 1 injection N=90 3 injections N=49 5 injections	Baseline, post 1st, 3rd and 5th injections N=199	A significant improvement in patient satisfaction was found after each retreatment (VAS), with an improvement of a mean of 4 points (median 5, range 2 to 8 points).	S (i)	N	N	N (ii)	N	Very low
S serious N none (i) Before versus after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] del Popolo et al. 2008 [72]										

Table 52: Botulinum toxin type A (Dysport) (pre vs post treatment) Treatment adherence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Treatment adherence										
1 [A]	Retrospective observational study	Botulinum toxin type A (Dysport) N=199 1 injection N=90 3 injections N=49 5 injections	Baseline, post 1st, 3rd and 5th injections N=199	Non-responders: 20/199 (15 after the first injection and 5 after repeated injections) showed poor clinical improvement	S (i)	N	N	N (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before versus after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] del Popolo et al. 2008 [72]										

Both/unclear preparations

Table 53: Botulinum toxin type A (pre vs post treatment) Continence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Continence										
1 [A]	Retrospective case series	Botulinum toxin type A N=27 Mean no. of treatments 7.1 (range 5 to 11)	Pre injection N=27	No. continent Baseline vs after 1 injection N (%) 4/27 vs 25/27 Before final injection vs after final injection 5/27 vs 20/27	S (i)	N	N	N(ii)	N	Low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before vs after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Pannek et al (2009) [70]										

Table 54: Botulinum toxin type A (pre vs post treatment) Adverse events - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Adverse events										
1 [A]	Prospective observational study	Botulinum toxin type A No. of injections: 2 or more N=66 3 or more N=34 4 or more N=17 5 or more N=5 6 or more N=3 7 N=1	Post injection	Adverse events Four patients observed transient muscular weakness in the trunk and/or extremities, all after Dysport	S (i)	N	N	N (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [B]	Retrospective observational study	Botulinum toxin type A N=27 Mean no. of treatments 7.1 (range 5 to 11)	Post injection	Adverse events 4/27 complained about temporary muscular weakness either localised in the limbs (two patients) or generalised (two patients).	S (i)	N	N	N (ii)	N	Very low
S serious N none (i) Before versus after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Grosse et al. (2005) [75] [B] Pannek et al. (2009) [70]										

Table 55: Botulinum toxin type A (pre vs post treatment) Patient satisfaction - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Patient satisfaction										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Prospective observational study	Botulinum toxin type A No. of injections: 2 or more N=66 3 or more N=34 4 or more N=17 5 or more N=5 6 or more N=3 7 N=1	Post injection	Major improvement (%) (satisfied plus very satisfied) Post 1st injection 73 vs 2nd injection 71 vs 3 rd injection 96 vs 4th injection 89	S (i)	N	N	N (ii)	N	Very low
S serious N none (i) Before vs after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Grosse et al. (2005) [75]										

Table 56: Botulinum toxin type A (pre versus post treatment) Treatment adherence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Treatment adherence										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Prospective observational study	Botulinum toxin type A No. of injections: 2 or more N=66 3 or more N=34 4 or more N=17 5 or more N=5 6 or more N=3 7 N=1	Post injection	Non-responders: Eight patients were injected for the second time within three months since the first injection (one Dysport, seven Botox). Four patients refused a second injection for a period of 2 to 4 yrs because of lack of effect of the first injection.	S (i)	N	N	N (ii)	N	Very low

S serious N none

(i) Before versus after data

(ii) Data at high risk of bias (very low quality), imprecision not assessed.

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[A] Grosse et al. (2005) [75]

Children

Botox

Table 57: Botulinum toxin type A plus oxbutynin versus botulinum toxin type A with discontinuation of oxybutynin - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										
1 [A]	RCT	Botulinum toxin type A plus oxybutynin N=12	Botulinum toxin type A plus oxybutynin discontinued N=11	**BTX-A plus oxybutynin** before 4/12 vs after 9/12 **BTX-A before** 4/11 after 8/11	S (i)	N	N	S (ii)	N	
Outcome: Maximum bladder capacity ml										
1 [A]	RCT	Botulinum toxin type A plus oxybutynin N=12	Botulinum toxin type A plus oxybutynin discontinued N=11	**BTX-A plus oxybutynin** Mean (SD) Before vs one month 96 (66) vs 155 (73) Before vs six months 96 (66) vs 141 (62) **BTX-A** Before vs one month 96 (71) vs 172 (119); Before vs Six months 96 (71) vs 143 (72) The difference between the groups was not statistically significant	S (i)	N	N	S (ii)	N	Low
Outcome: Side effects										
1 [A]	RCT	Botulinum toxin type A plus oxybutynin N=12	BTX-A oxybutynin discontinued N=11	No side effects reported	S (i)	N	N	S (ii)	N	

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none SD standard deviation; CI confidence interval. (i) No details/unclear randomisation, allocation concealment, blinding. (ii) Data at high risk of bias (very low quality), imprecision not assessed. [A]Neel et al. 2007 [76]										

Table 58: Botulinum toxin type A (Botox) (pre versus post treatment) Continence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										
1 [A]	Prospective observational study	Botulinum toxin type A (Botox) N=7	Baseline N=7	Continence score (No. of pads used per day) median (range) Pre Botox 3 (1-5) vs 1 mth 1 (0-3) vs 6 mth 3 (0 to 5) vs 9 mths 3 (1-7)	S (i)	N	N	S (ii)	N	Very low
1 [B]	Prospective observational study	Botulinum toxin type A (Botox) N=26	Baseline N=26	Incontinence score (maximum score 3, 3 = wet for more than 50% of the time between catheterisations) pre versus 4 months 2.5 vs 0.3 (p<0.001) Of the 26 patients, 19 (73%) became completely dry between two consecutive clean intermittent catheterisations	S (i)	N	N	S (ii)	N	Very low
1 [C]	Prospective observational study	Botulinum toxin type A(Botox) N=20	Baseline N=20	Incontinence score (maximum 3, 3= wet more than 50% of episodes between catheterisation) Pre-treatment versus 4 weeks, versus 3 months 2.4 (0.80) versus 1.1 (1.2)	S (i)	N	N	S (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [D]	Prospective observational study	Botulinum toxin type A (Botox) N=17	Baseline N=17	Incontinence score (maximum 3, 3= wet more than 50% of episodes between catheterisation) pre-treatment versus post-treatment 2.36 (0.74) versus 1.43 (1.02); ns (SE or SD not stated in the paper)	S (i)	N	N	S (ii)	N	Very low
1 [E]	Prospective observational study	Botulinum toxin type A (Botox) N=24	Baseline N=24	Incontinence score % (lower the score the better) 1 versus 3 versus 6 mths 46 versus 15 versus 13	S (i)	N	N	S (ii)	N	Very low

S serious N none SD standard deviation; SE standard error

(i) Before versus after data
(ii) Data at high risk of bias (very low quality), imprecision not assessed

[A] Deshpande et al. 2010 [78]
[B] Kajbafzadeh et al. 2006 [79]
[C] Schulte-Baukloh et al. 2003 [84]
[D} Schulte-Baukloh et al. 2002 [85]
[E] Schurch et al. 2006 [86]

Table 59: Botulinum toxin type A (Botox) (pre vs post treatment) Maximum cystometric capacity - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	Prospective observational study	Botulinum toxin type A (Botox) N=7	Baseline N=7	Bladder capacity mean mL (% improvement and range) Baseline 257 (140-400) versus 1 mth 344 (134%, 180-700) versus 3-6 mths 312 (121%, 200-390) versus 9 mths 306 (119%, 170 to 400)	S (i)	N	N	S (ii)	N	Very low
1 [B]	Prospective observational study	Botulinum toxin type A (Botox) N=26	Baseline N=26	Mean (SD) ml pre versus post 4 mths 102.8 (32.1) versus 270.2 (48.4)	S (i)	N	N	S (ii)	N	Very low
1 [C]	Retrospective observational study	Botulinum toxin type A (Botox) N=10 (3 injections) N=4 (5 injections)	Baseline N=10 (3 injections) N=4 (5 injections)	Maximal bladder capacity mL Mean (SD) Three times injected group Baseline versus after 1st injection 111.9 (48.4) versus 231.3 (128.1) Before and after 3rd injection 214.6 (124.3) versus 220.8 (202.7) Five times injected group Baseline versus after 1st injection 160.3 (56.3) versus 301.0 (157.5) Before and after 5th injection 235.3 (146.7) versus 403.7 (201.1)	S (i)	N	N	S (ii)	N	Very low
1 [D]	Prospective observational study	Botulinum toxin type A (Botox) N=20	Baseline N=20	ML Mean (SD) Pre-treatment 163.05 (93.4) vs 4 wks 219.85 (134.5), versus 3 mths 200.60 (10.8.5), versus 6 mths 222.38 (166.9)	S (i)	N	N	S (ii)	N	Very low
1 [E]	Prospective observational study	Botulinum toxin type A (Botox) N=17	Baseline N=17	Mean mL pre-treatment Pre-treatment versus post-treatment 137.53 (59.96) versus 215.25 (96.36); p<0.05 (SD or SE not stated in the paper)	S (i)	N	N	S (ii)	N	Very low
1 [F]	Prospective observational study	Botulinum toxin type A (Botox) N=24	Baseline N=24	% Increase from baseline 1 mth 35 versus 3 mth 23 versus 6 mths 36	S (i)	N	N	S (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none SD standard deviation; SE standard error (i) Before vs after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Deshpande et al. 2010 [78] [B] Kajbafzadeh et al. 2006 [79] [C] Schulte-Baukloh et al. 2005A [83] [D] Schulte-Baukloh et al. 2003 [84] [E] Schulte-Baukloh et al. 2002 [85] [F] Schurch et al. (2006) [86]										

Table 60: Botulinum toxin type A (Botox) (pre vs post treatment) Kidney - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Kidney function										
1 [A]	Prospective observational study	Botulinum toxin type A (Botox) N=26	Baseline N=26	Mean vesciouteral reflux (VUR) grade Mean Pre-treatment versus 4 months 1.7 versus 0.7; p<0.01 VUR grade decreased in 11 patients (73%)	S (i)	N	N	S (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before versus after data. (ii) Small study sample, uncertainty in terms of precision – no information on estimations of effect. [A] Kajbafzadeh et al. 2006 [79]										

Table 61: Botulinum toxin type A (Botox) (pre vs post treatment) Side effects and urinary tract infection - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Side effects and urinary tract infection										
1 [A]	Prospective observational study	Botulinum toxin type A) N=7	Baseline N=7	Side effects One case of mild microscopic haematuria for several hours after cystoscopy and injection. This did not have any clinical consequences. Urinary tract infection One patient suffered a single urinary tract infection during follow up	S (i)	N	N	S (ii)	N	Very low
1 [B]	Retrospective observational study	Botulinum toxin type A (Botox) N=7	Baseline N=7	Urinary tract infections “The only side effects were urinary tract infections” Adverse events None of the patients experienced generalised muscle weakness	S (i)	N	N	S (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [C]	Prospective observational study	Botulinum toxin type A (Botox) N=26	Baseline N=26	Urinary tract infection None reported Systemic muscle weakness None reported	S (i)	N	N	S (ii)	N	Very low
1 [D]	Retrospective observational study	Botulinum toxin type A (Botox)	Baseline	Serious side effects During 5 yrs of experience no patient experienced any serious side effects (one epileptic attack in known epileptic but no further problems with later injections)	S (i)	N	N	S (ii)	N	Very low
1 [E]	Prospective observational study	Botulinum toxin type A (Botox) N=24	Baseline N=24	Side effects None reported including muscle weakness. One epileptic seizure in known epileptic Urinary tract infections 2/24	S (i)	N	N	S (ii)	N	Very low

S serious N none

(i) Before versus after data
(ii) Data at high risk of bias (very low quality), imprecision not assessed

[A] Deshpande et al. 2010 [78]
[B] Do et al. 2009 [82]
[C] Kajbafzadeh et al. 2006 [79]
[D] Schulte-Baukloh et al. 2005A [83]
[E] Schurch et al. 2006 [86]

Dysport

Table 62: Botulinum toxin type A (Dysport) (pre versus post treatment) Continence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										
1 [A]	Retrospective observational study	Botulinum toxin type A (Dysport) N=19	Baseline N=19	3/19 stopped BTX-A treatment due to persisting incontinence and underwent augmentation surgery	S (i)	N	N	S (ii)	N	Very low

S serious N none

(i) Before versus after data.

(ii) Data at high risk of bias (very low quality), imprecision not assessed.

[A] Akbar et al. 2007 [81]

Table 63: Botulinum toxin type A (Dysport) (pre versus post treatment) Maximum cystometric capacity - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										
1 [A]	Retrospective observational study	Botulinum toxin type A (Dysport) N=19	Baseline N=19	Pre-treatment 180.58 (128.60) versus after 1 injection 290.42 (169.47) versus after 2 injections 292.68 (169.29) versus after 3 injections 346.81 (147.79) (n=16)	S (i)	N	N	S (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before versus after data. (ii) Data at high risk of bias (very low quality), imprecision not assessed. [A] Akbar et al. 2007 [81]										

Both/unclear preparations

Table 64: Botulinum toxin type A (pre vs post treatment) Continence - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Continence										
1 [A]	Prospective observational study	Botulinum toxin type A N=15	Baseline N=15	Incontinence score (Maximum score 3, 3 = wet for more than 50% of the time between catheterisations) Treatment 1 Pre-treatment 2 versus 3 mths 0.47 vs 9 mths 0.67 versus 12 mths 2.7 Treatment 2 Pre-treatment 2.7 versus 3 mths 0.45 versus 9 mths 0.64 versus 12 mths 2.7	S (i)	N	N	S (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before versus after data (ii) Data at high risk of bias (very low quality), imprecision not assessed [A] Riccabona et al. 2004 [80]										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Maximum cystometric capacity										
1 [A]	Prospective observational study	Botulinum toxin type A N=20	Baseline N=20	Maximal bladder capacity cc mean (SD) Before versus after 1st injection Continent (n=13) 215.6 (58.8) vs 338.3 (98.4) Incontinent (n=7) 146 (44.4) versus 164.2 (48.2)	S (i)	N	N	S (ii)	N	Very low
1 [B]	Prospective observational study	Botulinum toxin type A N=15	Baseline N=15	Mean ml Treatment 1 Baseline 136.34 versus 3 mths 297.02 versus 9 mths 284 versus 12 mths 154 Treatment 2 Baseline 154 versus 3 mths 295 versus 9 mths 241 versus 12 mths 161	S (i)	N	N	S (ii)	N	Very low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none (i) Before versus after data. (ii) Data at high risk of bias (very low quality), imprecision not assessed. [A] Altaweel et al. 2006 [77] [B] Riccabona et al. 2004 [80]										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Hydronephrosis										
1 [A]	Prospective observational study	Botulinum toxin type A N=20	Baseline N=20	There were no observed changes	S (i)	N	N	S (ii)	N	Very low
S serious N none (i) Before versus after data. (ii) Small study sample, uncertainty in terms of precision – no information on estimations of effect. [A] Altaweel et al. 2007 [77]										

8.3.1.2 Economic Evidence

Three studies[87-89] were found but excluded on the basis of potentially serious limitations and partial applicability that (see list of excluded studies).

This area was identified as important for economic evaluation given the uncertainty over the trade-off between cost and effectiveness. Therefore an original cost-effectiveness analysis was conducted to answer this question.

Novel Cost Effectiveness Analysis

In order to explore the cost effectiveness of botulinum toxin for the treatment of NLUTD, a full cost effectiveness analysis was carried out. The key methodology and results are written up here but the full report can be found in appendix I.

Model Overview

Comparators

The model compares the cost effectiveness of four strategies for the management of incontinence due to neurogenic lower urinary tract dysfunction (NLUTD):

Augmentation Cystoplasty (AC) is a well established major open surgical technique where the bladder is made larger or 'augmented' by incorporating a bowel segment into the bladder. Most commonly an ileal segment is used but alternatives include a section of the large intestine. The incorporation of intestine into the bladder prevents effective bladder contractions from occurring and patients usually cannot void completely following the surgery, therefore needing to perform clean intermittent self catheterisation.

The second intervention is the injection of *botulinum toxin* type A *(BTX)* into the bladder wall. BTX is currently not licensed for this indication but various trials have shown it to be effective in reducing the frequency of incontinence episodes[63,65,66] in patients with incontinence due to NLUTD. The protocol for administration of BTX varies but the method used in this model is 30 endoscopic injections of 300u or 200u into the bladder wall. The operation will take less than 1 hour. Patients with NLUTD will mostly need to use intermittent catheterisation to empty the bladder effectively following treatment.

The third strategy is where BTX is administered for two variable cycles (6-12 months) and then AC is conducted in 100% of those that do not respond to BTX (BTX100AC). BTX continues to be administered in those that do respond.

The final comparator is no treatment or "best supportive care" (No-Rx). This comparator is included as an arm where patients opt to manage their incontinence with a mixture of incontinence appliances: pads, indwelling catheters, sheaths and suprapubic catheters.

Population

The population in this model is made up of patients with NLUTD (Myelomeningocele, Spinal Cord Injury, Multiple Sclerosis etc.) and bladder over-activity who are unresponsive or intolerant to antimuscarinic medication. The patients in the base case are considered to be adults as the paucity of data on children prevents an adequate analysis for the paediatric age group. However the cost effectiveness in children will be tested in a sensitivity analysis. Patients had an average age of 49 with a sex distribution of 53% female and 47% male. Mortality data was adjusted using a standardised

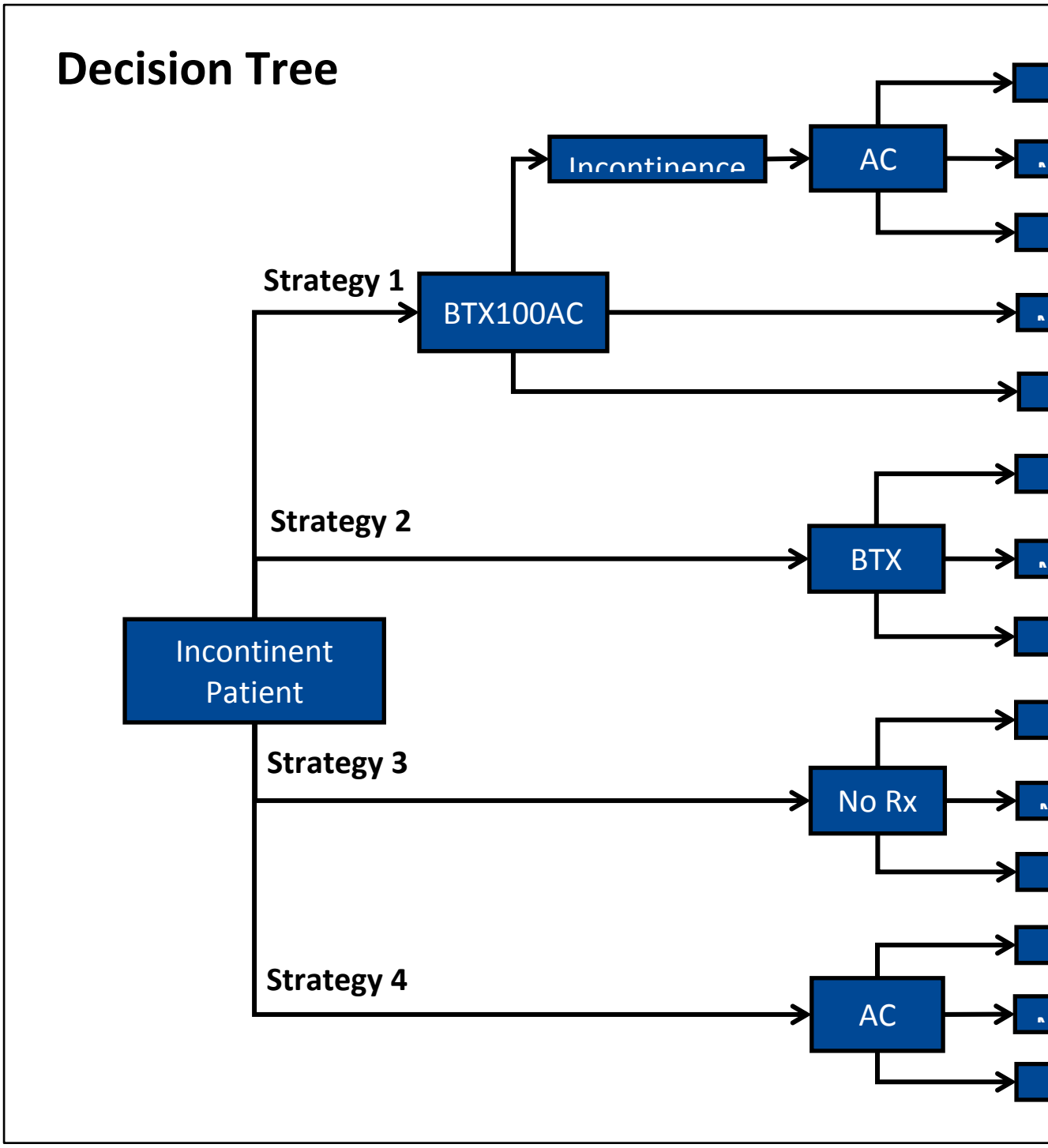
mortality ratio from a group of patients with spinal cord injury[90]. Subgroup analysis was carried out on different groups of patients to determine cost effectiveness in a paediatric population.

However, not all of the comparators are relevant in every situation. For some patients, such as multiple sclerosis patients, the AC comparator is not relevant as they are not suitable for this surgical option. There are therefore two base case comparisons. Base case 1 is all the comparators compared together. The second base case analysis is simply BTX compared with No-Rx.

Model Structure and approach to modelling

A decision tree was constructed in Windows Excel® to model the comparison of cost and effectiveness of the interventions. Upon receiving treatment a patient could end up in one of three possible health states: incontinent, mildly incontinent or continent. Once in any of these health states, they would remain there for the duration of the model. In order to model the long term effects and survival, life tables were then attached to each of the final health states in the tree and a hypothetical cohort of a thousand patients was run through the model. The trials that were used to inform the model used frequency of incontinence episodes as the main outcome. Quality of Life weights were attached to being either incontinent, continent or having mild incontinence on the basis of the frequency of episodes. As adverse events and the presence or absence of urinary tract infections have important quality of life and cost implications, these were also included. The cost components included costs of the treatment itself, the ongoing costs associated with adverse events and any monitoring or follow up treatments. A diagram of the model can be found in Figure 5.

Figure 5 Decision Tree.



Outcomes

As outlined previously, with each of the four strategies, an incontinent patient will either become continent, meaning that the treatment was effective; they will have improved continence but will not be fully continent - mild incontinence; or they will remain incontinent. Each of these options is determined by the effectiveness of each treatment. The frequency of incontinence episodes is used

as the main outcome. Due to the inconstant reporting of the effectiveness of treatments between studies, assumptions had to be made about the frequency of incontinence episodes that constituted each outcome. This was done so that costs and effects could be calculated. It was assumed that in the continent group a patient would suffer from one incontinence episode per week; in the mild incontinent group, they would suffer from two episodes per day; and in the incontinent group, they would suffer from five episodes per day.

As well as the main effectiveness estimate, there were also adverse events (AEs) and urinary tract infections (UTIs) to consider. AEs were associated with the strategy used to manage incontinence. The UTIs were associated with the continence status of the patient.

Results

Base case 1 results – All interventions compared

The first base case analysis compared the cost-effectiveness of all the interventions outlined in the methods. The analysis revealed that Augmentation Cystoplasty (AC) is the cost-effective option when compared to *botulinum toxin* (BTX) and no treatment (No-Rx) for the treatment of incontinence due to NLUTD using a lifetime horizon. The results of the analysis can be seen in Table 65, below. There is a measure of confidence in this result because, at a threshold of £20,000 per QALY, AC is cost-effective with a probability of 78%.

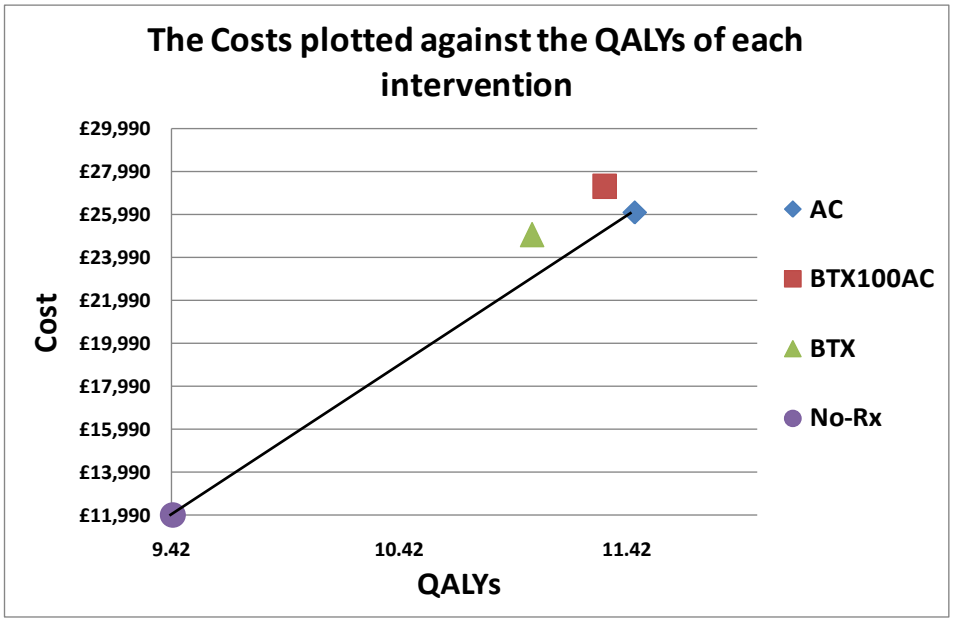
Table 65: Base case results

Intervention	Mean Costs	Mean QALYs	NMB[j] at £20,000 per QALY gained	Rank at £20,000 per QALY gained
AC	£26,084	11.46	£1,119,752	1
BTX100AC	£27,315	11.33	£1,105,610	2
BTX	£25,059	11.01	£1,075,757	3
No-Rx	£11,991	9.43	£930,946	4

Figure 3 demonstrates these cost-effectiveness results graphically. We can see that while BTX and AC are similar in cost-effectiveness, AC is more effective but marginally more expensive than BTX alone. The BTX100AC strategy is more effective than the BTX alone strategy but also more expensive; it is more expensive and less effective than AC. No-Rx is the cheapest strategy but it is also the least effective therefore it will only be cost-effective at a very low threshold.

Figure 6: Cost-effectiveness graph

[j] Net Monetary Benefit (NMB) is a simple rearrangement of the Incremental cost-effectiveness ratio calculation. The equation is as follows: Threshold*Effectiveness-cost>0. The resulting figure gives you the QALY gain expressed in monetary form, with each QALY costed at the threshold, net of cost. Meaning that after taking away cost, the intervention with the highest NMB is the most cost-effective.



When the costs are broken down into the constituent parts, it is possible to pick out the elements that drive the results. This breakdown can be found in Table 66. The increased effectiveness of AC compared with all other interventions is what makes it the most cost-effective option. It is cheaper than BTX100AC over a lifetime and is more effective; it is not, however, cheaper than BTX alone over a lifetime.

Table 66: Breakdown of costs and outcomes

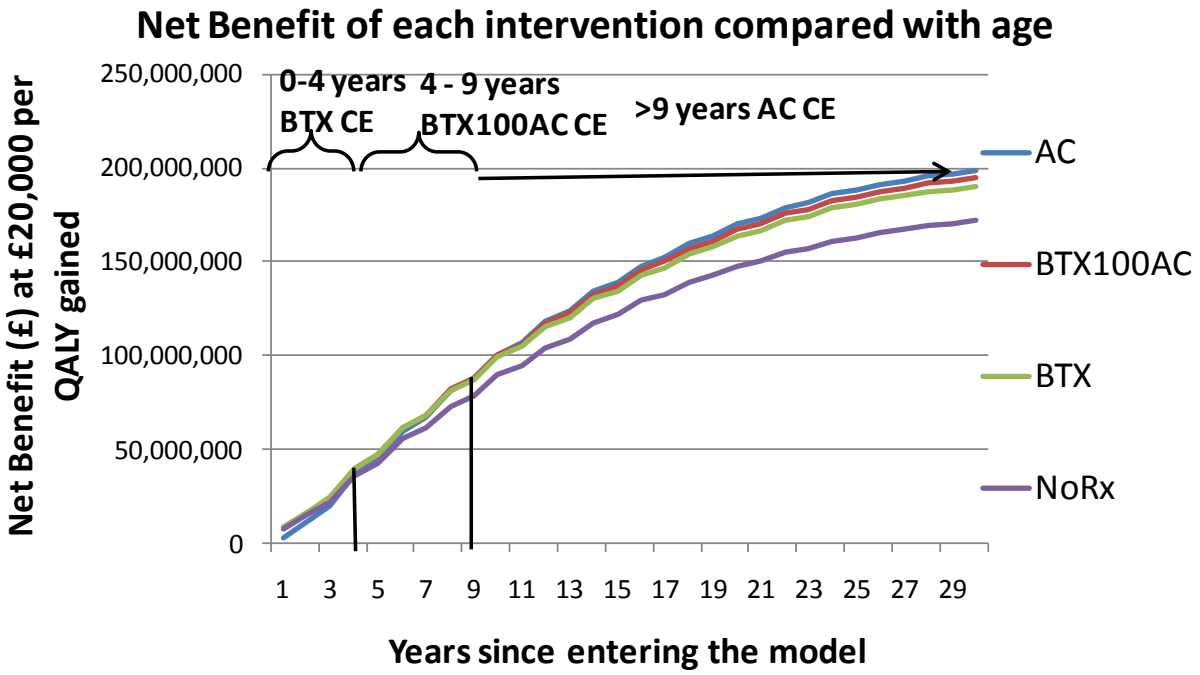
	Input	BTX100AC	BTX	AC arm	NoRx
Mean Costs (Discounted)	BTX costs	£10,328	£10,328	£0	£0
	AC costs	£1,053	£0	£6,433	£0
	AE costs	£600	£15	£3,705	£0
	UTI costs	£181	£233	£169	£497
	Appliance costs	£15,152	£14,483	£15,776	£11,494
	Total costs	£27,315	£25,059	£26,084	£11,991
Mean Outcomes	Years continent	11	8	18	0
	Years mild incontinent	10	9	4	0
	Years incontinent	2	5	1	23
	Life years	22.71	22.71	22.71	22.71
	QALYs (discounted)	11.33	11.01	11.46	9.43

AC is higher cost than the BTX alone strategy, which is a function of the discount rate[k]. However, AC is more effective and only marginally more expensive than BTX, meaning it is cost-effective over a lifetime compared with BTX. A time horizon analysis was also carried out on this comparison in Figure 7: this revealed that for the first 5 cycles, about 3 years, BTX alone is cost effective. Between 5 and 16 cycles, about 10 years, BTX with 100% AC after failed BTX is the cost effective strategy. Beyond 16

[k] The discount rate is applied to all costs and outcomes. The discount rate is applied to future costs and outcomes to establish their present value. The rate of 3.5% reduction in value per year is based on the interest rate. If we invested now for a future expenditure, how much it would cost in present value.

cycles, AC is cost effective. This shows that for patients with a poor prognosis and for older patients, BTX is a more cost effective option.

Figure 7: Net benefit compared with age



Note: CE = Cost Effective

If this is then broken down further into the main comparison, AC-BTX100AC, we can see the key drivers behind AC's cost effectiveness in Table 67. The BTX100AC strategy is analysed against AC because it is more cost effective and is the most relevant comparison for sub analysis. A patient with AC only will spend more time in the continent group than those in the BTX100AC arm, and their cost of treatment will be lower in spite of higher adverse event rates. The 18 years compared to 11 spent in the continent arm counts towards an increased QALY gain compared with BTX100AC.

Table 67: Cost Breakdown AC-BTX100AC

	Input	AC arm	BTX100AC	Difference
Mean Costs	BTX costs	£0	£10,328	-£10,328
	AC costs	£6,433	£1,053	£5,380
	AE costs	£3,705	£600	£3,105
	UTI costs	£169	£181	-£12
	Appliance costs	£15,776	£15,152	£624
	Total costs	£26,084	£27,315	-£1,231
Mean Outcomes	Years continent	18	11	7
	Years mild incontinent	4	10	-6
	Years incontinent	1	2	-1
	Life years	22.71	22.71	0.00
	QALYS undiscounted	17.02	16.84	0.18
	QALYs discounted	11.46	11.33	0.13

Base case 2 results – Botulinum Toxin versus No Treatment

As a second analysis we looked at a comparison of BTX with a no treatment comparator. This was to ensure that we captured the full range of potential patients in the analysis. For some patients, such as multiple sclerosis patients, the AC comparator is not relevant as neurological deterioration is likely to occur and render the management of the augmented bladder problematic. In Table 63 it is possible to see that BTX is cost effective when compared to no treatment with a cost per QALY of under £9,000. This is well below the usual cost effectiveness threshold of £20,000 per QALY gained.

Table 68: BTX – No Treatment base case results

	Mean Cost	Mean QALY	Incremental Cost Effectiveness Ratio
BTX	£25,059	11.01	
No Rx	£11,990	9.43	
Diff (BTX - No Rx)	£13,068	1.58	£8,277

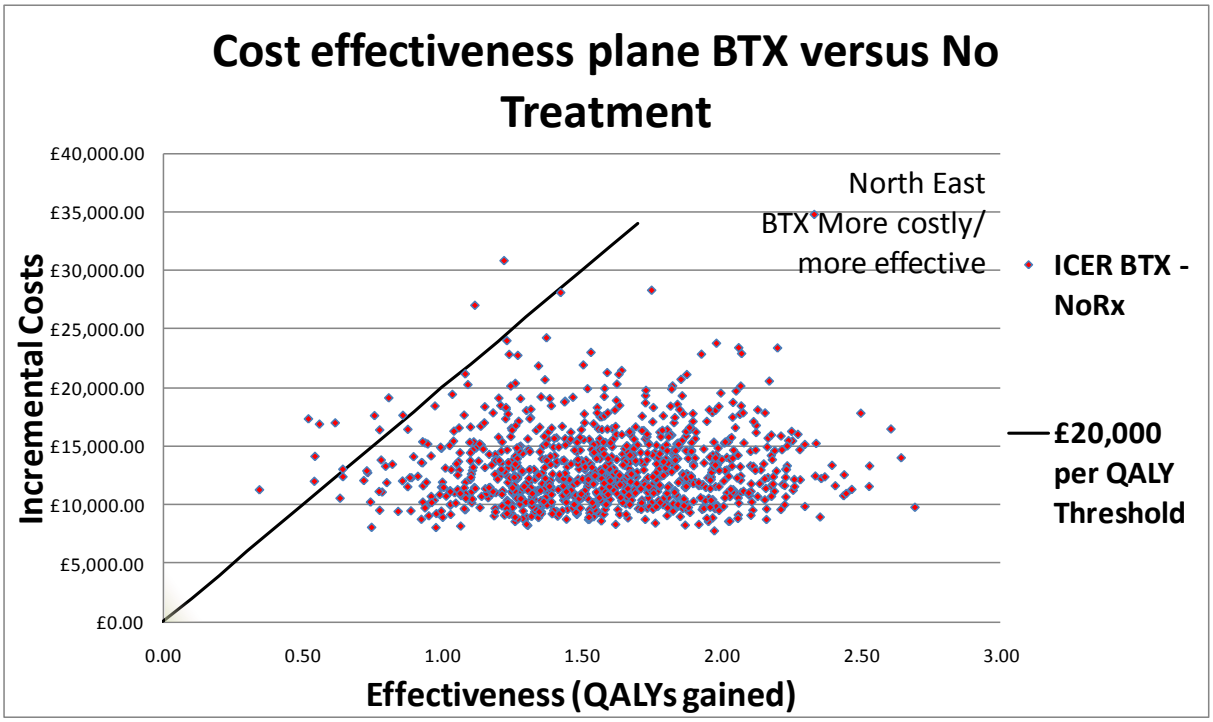
Table 69 shows where the cost and outcome differences lie. The cost of no treatment is lower than BTX but it is not zero. This is due to the cost of incontinence appliances such as pads and catheters. BTX is also more effective with increased time spent in the continence and mild incontinence groups. BTX has higher QALYs but also higher costs, so it is cost effective but not dominant.

Table 69: Breakdown of costs and outcomes (BTX – No Rx)

	Input	BTX	NoRx	Difference
Mean Costs	BTX costs	£10,328	£0	£10,328
	AC costs	£0	£0	£0
	AE costs	£15	£0	£15
	UTI costs	£233	£497	-£263
	Appliance costs	£14,483	£11,494	£2,989
	Total costs	£25,059	£11,991	£13,068
Mean Outcomes	Years continent	8	0	8
	Years mild incontinent	9	0	9
	Years incontinent	5	23	-18
	Life years	22.71	22.71	0.00
	QALYS undiscounted	16.35	14.01	2.35
	QALYs discounted	11.01	9.43	1.58

As a result of these costs and of the increased effectiveness of BTX, BTX is more expensive but also more effective with a high degree of certainty. This is displayed on the cost effectiveness plane in Figure 8. This shows that using the probabilistic analysis, all of the cost effectiveness ratios for BTX versus no treatment are to the North East of zero meaning that for all 1000 iterations of the model, BTX is more costly and more effective. And the vast majority, 988, of these ratios fall under the £20,000 per QALY threshold.

Figure 8: Cost effectiveness plane



Conclusions

The results of the model allow four main conclusions to be drawn:

1. AC is the cost effective intervention over a lifetime horizon in the populations where it is a relevant comparator.
2. BTX is cost effective compared to AC in patients who are unsuitable for surgery.
3. A BTX strategy where AC is used (and relevant) in 100% of patients after failed BTX is cost effective compared to a 0% progression to AC strategy but is higher cost.
4. BTX is cost effective when compared to no treatment.

The results of this model are generally robust to the uncertainty around the assumptions made as shown by the deterministic sensitivity analyses. The probabilistic data shows that at a threshold of £20,000 per QALY gained AC is cost effective with a probability of 78%, again demonstrating the robustness of the model to uncertainty.

The many limitations are almost entirely due to the lack of good quality data to populate the model. Perhaps the most important limitation is the fact that there is no comparative data on AC and BTX. Therefore the comparison between these two interventions is made on the basis of two fairly heterogeneous studies. The BTX vs placebo study was a randomized control trial [63] whereas the study used to provide AC data was based on observational data [91]. This disparity means that the outcomes: continence, mild incontinence and incontinence, are not measured in the same way. It was necessary for the GDG to make assumptions about the definition of what constituted these outcomes, which was not ideal but given the available data was the only solution. The result of this is that it makes the comparison of BTX with no treatment more reliable than the comparison of AC with BTX or no treatment. However, the probabilistic analysis allows us to take this uncertainty into account and deal with it explicitly.

The analysis took place in two parts. The first part being the comparison of all interventions in a population where all comparators were relevant, such as a spinal cord-injured population. The second part was a comparison of just BTX with no treatment. This was therefore in a population where AC was not a relevant comparator such as patients with multiple sclerosis. This analysis is therefore generalisable to any patient that suffers from incontinence due to NLUTD in the UK. The model is also of potential relevance to populations outside of the UK as the model is fairly robust to changes in costs and impact of adverse events.

Only one other cost effectiveness study has been done that analyses AC vs BTX. The study by Padmanabhan et al. 2011[92] showed that BTX would cost about $5,000 less than AC per successful intervention. However this analysis only uses adverse events as outcomes and is a five year study from a US payer perspective. This is in keeping with what our model shows as BTX only is shown to be cost effective when compared with AC for the first six years of the model. However as the Padmanabhan study is from a US payer perspective and does not consider outcomes beyond adverse events, its relevance to the UK perspective is limited.

8.3.1.3 Evidence Statements

Clinical Evidence Statements

Shorter-term safety and efficacy

Adults, Botox 200 U

Evidence statements could not be produced for the following outcomes of the study by Cruz [63] and Schurch [67] as results were presented in a way that meant we could not estimate the size of the intervention effect :

- I-QoL (mean change score (no SD) (6 weeks) (high quality).
- I-QoL (final median score)(6 weeks, 24 weeks) (moderate quality).

One study of 184 participants found a statistically significant reduction for participants receiving botulinum toxin type A compared to placebo for:

- Incontinence episodes/week (mean change score) (6 weeks) (moderate quality).

One study of 40 participants found no statistically significant difference for participants receiving botulinum toxin type A compared to placebo for:

- Incontinence episodes/day (mean change score) (6 weeks) (low quality).

One study of 40 participants found a statistically significant reduction for participants receiving botulinum toxin type A compared to placebo for:

- Incontinence episodes/day (mean change score) (24 weeks) (low quality).

One study of 184 participants found a statistically significant improvement for participants receiving botulinum toxin type A compared to placebo for:

- Maximum bladder capacity (mean change score) (6 weeks) (high quality).

Evidence statements could not be produced for the following outcomes of the study by Schurch [66] as results were presented in a way that meant we could not estimate the size of the intervention effect :

- Maximum bladder capacity (mean change score (no SD)) (6 weeks, 24 weeks) (moderate quality).

One study of 181 participants found a statistically significant increase for participants receiving botulinum toxin type A compared to placebo for:

- All adverse events (end of scheduled follow-up) (moderate quality)

One study of 181 participants found no statistically significant difference for participants receiving botulinum toxin type A compared to placebo for:

- Muscle weakness (end of scheduled follow-up) (moderate quality).

One study of 181 participants found a statistically significant increase for participants receiving botulinum toxin type A compared to placebo for:

- Urinary tract infections (end of scheduled follow-up) (moderate quality).

Adults, Botox 300 U

One study of 57 participants found a statistically significant improvement for participants receiving botulinum toxin type A compared to placebo for:

- I-Qol (mean change scores) (6 weeks, 24 weeks) (moderate to high quality).

Evidence statements could not be produced for the following outcomes of the study by Cruz [63] and Schurch [67] as results were presented in a way that meant we could not estimate the size of the intervention effect:

- I-QoL (mean change score (no SD)) (6 weeks) (high quality).
- I-Qol (final median score) (6 weeks, 24 weeks) (moderate quality).

One study of 183 participants found no statistically significant difference for participants receiving botulinum toxin type A compared to placebo for:

- Incontinence episodes/week (mean change score) (6 weeks) (moderate quality).

One study of 57 participants found a statistically significant reduction for participants receiving botulinum toxin type A compared to placebo for:

- Incontinence episodes/day (mean final score) (6 weeks, 24 weeks) (high quality).

One study of 40 participants found a statistically significant reduction for participants receiving botulinum toxin type A compared to placebo for:

- Incontinence episodes/day (mean change score) (6 weeks, 24 weeks) (low quality).

One study of 183 participants found a statistically significant improvement for participants receiving botulinum toxin type A compared to placebo for:

- Maximum bladder capacity (6 weeks) (high quality).

Evidence statements could not be produced for the following outcomes of the study by Herschorn [65] and Schurch [66] as results were presented in a way that meant we could not of the intervention effect in a way that meant we could not estimate the size of the intervention effect :

- Maximum bladder capacity (final median score) (6 weeks, 24 weeks) (high quality).
- Maximum bladder capacity (mean change score (no SD)) (6 weeks, 24 weeks) (moderate quality).

One study of 179 participants found a statistically significant increase for participants receiving botulinum toxin type A compared to placebo for:

- All adverse events (end of scheduled follow-up) (moderate quality).

Two studies of 145 participants found no statistically significant difference for participants receiving botulinum toxin type A compared to placebo for:

- Muscle weakness (end of scheduled follow-up) (moderate quality).

Three studies of 285 participants found a statistically significant increase for participants receiving botulinum toxin type A compared to placebo for:

- Urinary tract infection (end of schedules follow up) (moderate quality).

Adults, Dysport

Evidence statements could not be produced for the following outcomes of the study by Ehren [62] as results were presented in a way that meant we could not estimate the size of the intervention effect:

- Quality of life
- Continence
- Maximum cystometric capacity

Both/unclear preparations

No studies were identified.

Longer-term follow-up data

Adults, Botox

4 studies of 261 participants suggested that botulinum toxin type A was associated with an:

- Improvement in quality of life

4 studies of 246 participants suggested that botulinum toxin type A was associated with an:

- Improvement in continence

5 studies of 161 participants suggested that botulinum toxin type A was associated with an:

- Improvement in maximum cystometric capacity

1 study of 17 participants suggested that botulinum toxin type A was associated with a:

- Decrease in urinary tract infections

Adults, Dysport

1 study of 199 participants suggested that botulinum toxin type A was associated with an:

- Improvement in maximum cystometric capacity
- Improvement in patient satisfaction

Adults, both/unclear

1 study of 66 participants suggested that botulinum toxin type A was associated with an:

- Improvement in continence

1 study of 27 participants reported

- Muscle weakness

Children

Botulinum toxin type A plus oxybutynin compared with botulinum toxin type A oxybutynin discontinued

(both/unclear preparation)

Evidence statements could not be produced for the following outcomes of the study by Neel [76] as results were presented in a way that meant we could not of the intervention effect in a way that meant we could not estimate the size of the intervention effect

- Continence
- Maximum cystometric capacity
- Side effects

Botulinum toxin A pre vs post treatment

Children, Botox

4 studies of 77 participants suggested that botulinum toxin type A was associated with an:

- Improvement in continence

6 studies of 108 participants suggested botulinum toxin type A was associated with an:

- Increase in maximum cystometric capacity

1 study of 27 participants suggested botulinum toxin type A was associated with an:

- Improvement in kidney function

4 studies of 74 participants suggested botulinum toxin type A was associated with an:

- Increase in urinary tract infections

Children, Dysport

1 study of 19 participants suggested botulinum toxin type A was associated with an:

- Increase in maximum cystometric capacity

Children, both/unclear preparation

1 study of 15 participants suggested botulinum toxin type A was associated with an:

- Improvement in continence

2 studies of 35 participants suggested botulinum toxin type A was associated with an:

- Increase in maximum cystometric capacity

Economic Evidence Statements

- Augmentation cystoplasty is cost effective compared to botulinum toxin type A in patients where it is suitable.
- Botulinum toxin type A is cost effective compared to augmentation cystoplasty in patients who are unsuitable for surgery.
- A Botulinum toxin type A strategy where augmentation cystoplasty is used (and relevant) in 100% of patients after failed Botulinum toxin type A is cost effective compared to a 0% progression to augmentation cystoplasty strategy but is higher cost.
- Botulinum toxin type A is cost effective when compared to no treatment.

8.3.2 Recommendations and links to evidence

Recommendations:	**BOTULINUM TOXIN TYPE A** **30. Offer bladder wall injection with botulinum toxin type A[I] to adults:** • **with spinal cord disease (for example, spinal cord injury or multiple sclerosis) *and*** • **with symptoms of an overactive bladder *and*** • **in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.** **31. Consider bladder wall injection with botulinum toxin type A[I] for children and young people:** • **with spinal cord disease *and*** • **with symptoms of an overactive bladder *and*** • **in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.** **32. Offer bladder wall injection with botulinum toxin type A[I] to adults:** • **with spinal cord disease *and*** • **with urodynamic investigations showing impaired bladder storage *and*** • **in whom antimuscarinic drugs have proved to be ineffective or poorly**

[I] At the time of publication (August 2012), botulinum toxin type A did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's 'Good practice in prescribing medicines – guidance for doctors' for further information.

	tolerated. **33. Consider bladder wall injection with botulinum toxin type A[m] for children and young people:** • **with spinal cord disease *and*** • **with urodynamic investigations showing impaired bladder storage *and*** • **in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.** **34. Before offering bladder wall injection with botulinum toxin type A:** • **explain to the person and/or their family members and carers that a catheterisation regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, *and*** • **ensure that they are able and willing to manage such a regimen should urinary retention develop after the treatment.** **35. Monitor residual urine volume in people who are not using a catheterisation regimen during treatment with botulinum toxin type A.** **36. Monitor the upper urinary tract in people who are judged to be at risk of renal complications (for example, those with high intravesical pressures on filling cystometry) during treatment with botulinum toxin type A.** **37. Ensure that people who have been offered continuing treatment with repeated botulinum toxin type A injections have prompt access to repeat injections when symptoms return.**
Relative value placed on the outcomes considered	The GDG considered quality of life, improved continence and renal preservation to be high value outcomes.
Quality of evidence	The evidence was found to be very low quality for children and young people and very low to high quality for adults. The populations that had been included in the studies were almost exclusively spinal cord injury, spinal dysraphism and multiple sclerosis. The shorter term (one cycle of treatment) efficacy data for adults was provided by RCTs. For children and longer term efficacy in adults most of the studies were observational studies with small patient numbers. The shorter term efficacy data for adults showed consistent and clinically significant benefits associated with botulinum toxin type A for quality of life, continence and maximum cystometric capacity. The longer-term efficacy data was from observational studies and of very low quality. The evidence suggested that the clinical improvements associated with botulinum toxin were maintained over time with repeat injections. The economic evidence is based on an original model with potentially serious limitations and direct applicability.
Trade-off between clinical benefits and	The magnitude of the improvements in quality of life and continence were clinically significant and objective urodynamic data supported the contention that the

[m] At the time of publication (August 2012), botulinum toxin type A did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's 'Good practice in prescribing medicines – guidance for doctors' for further information.

harms	intervention could produce an improvement in the ability of the bladder to store urine. In general clinical benefit was achieved with minor adverse events. Transient muscle weakness was noted to occur in a small number of patients. However, most recent RCTs showed an excess of urinary tract infections in patients treated with botulinum toxin type A. The GDG considered that this was likely to occur in patients who started intermittent catheterisation as a result of increased residual urine volumes after treatment.
Economic considerations	Two limited studies complemented each other to provide some evidence showing the cost effectiveness of Botulinum Toxin type A in adults. No evidence was found for children and young people and conclusions from the adults cannot be extrapolated in children especially because of the additional cost of general anaesthetic. The economic model demonstrated that Botulinum toxin treatment was cost effective when compared to standard care for containment of incontinence with a cost effectiveness ratio of under £10,000 per QALY gained. This was demonstrated with a high degree of certainty. The GDG recognised that it is extremely unusual for augmentation cystoplasty to be offered to patients with progressive neurological conditions due to potential long term difficulties with managing intermittent catheterisation. The GDG also noted that serious adverse events can arise in association with augmentation cystoplasty. In patients where both augmentation cystoplasty and botulinum toxin therapy are viable options, the economic model shows that augmentation cystoplasty is cost effective in those patients who are likely to benefit from incontinence treatment for more than 10 years. The cost effectiveness of AC is chiefly due to its increased effectiveness at preventing incontinence rather than the cost. The absolute difference in costs and effects between the interventions is small and all interventions are more cost effective than simply containing the incontinence. Simple containment is the lowest cost but the least effective. The GDG recognised that the model has certain limitations, such as lack of long term data, lack of directly comparable data and lack of randomised studies in AC. There were also many assumptions made in the model. However all of these limitations and assumptions were tested in various sensitivity analyses. This led to the conclusion that the model is robust, and the conclusion that the recommendations are founded on good economic grounds.
Other Considerations:	The GDG noted that the evidence that is available relates to spinal cord injury, spinal dysraphism and multiple sclerosis. There is a lack of data on the use of botulinum toxin type A in patients with NLUTD due to brain dysfunction. Urodynamic data presented in the studies in the evidence review provides information about the effect of botulinum toxin type A on neurogenic detrusor overactivity. There is a lack of information relating to patients with impaired urine storage due to reduced bladder compliance. Raised bladder pressures during bladder filling can threaten renal function, such as the development of hydronephrosis in some patients with NLUTD. The GDG agreed that there is currently a lack of information regarding the question as to whether botulinum toxin type A can be used reliably to protect renal integrity in the patient where bladder function might be hostile to the kidneys. Urodynamic evidence would suggest that the drug might be protective but the GDG felt that it was vital that close renal surveillance is maintained in patients who are judged to be at risk of upper tract complications. The GDG noted that in current clinical practice there is no age cut off for treatment. However, it would generally not be offered in infancy as they have high pressure overactive bladder physiologically. The GDG agreed that further research was required to determine the duration and adequacy of response to the treatment in different groups of patients. The GDG noted that effective long-term botulinum toxin type A use depends on there being a supportive clinical service which can offer prompt re-treatment as and when

	symptoms recur as the effect of the drug wears off. The duration of response varies from patient to patient so that treatment has to be organised on an individual basis. It is recognised that there may be differences in the efficacy of different brands of botulinum toxin type A given that different forms of the toxin are manufactured. However, the evidence review did not provide the GDG with any studies that directly compared these different products. No studies were found that provided data on the use of botulinum type B and the GDG members understand that this variant of BTX has been found to have a relatively short duration of action in a limited number of pilot studies. It is therefore not being used for treating neurogenic LUT dysfunction at the present time.

8.3.3 Research recommendations

Botulinum toxin A

2. What is the safety and efficacy of botulinum toxin compared with (a) usual care, (b) antimuscarinics and (c) augmentation cystoplasty in people with neurogenic lower urinary tract dysfunction?

- **Why this is important**

  Further research is needed to determine whether repeated intradetrusor injections of botulinum toxin type A have long-term efficacy. The efficacy in terms of continence and upper urinary tract preservation should be studied.

  Botulinum toxin injection into the detrusor is an effective means of managing incontinence, and improves urodynamic measures of bladder storage with the potential to protect the kidneys from the effects of high intravesical pressures. It is well tolerated in a spectrum of conditions and ages. However, the longer term efficacy over many injections has not been established.

  A clinical trial is needed to study the outcome in terms of continence and renal preservation over many cycles of repeated injection. Quality of life is an important outcome. A trial should enrol children and adults. The indications for botulinum toxin need not be modified for inclusion, but entrants into a trial must have anatomically normal kidneys (on imaging) and normal renal function.

3. What is the safety and efficacy of botulinum toxin compared with (a) usual care, (b) antimuscarinics and (c) augmentation cystoplasty in people with primary cerebral conditions with lower urinary tract dysfunction?

- **Why this is important**

  The effects of intradetrusor botulinum toxin type A injection should be investigated in groups of people with underlying cerebral conditions that are associated with lower urinary tract dysfunction, as well as those with spinal cord injury, spina bifida and multiple sclerosis. Reports of its use in other conditions are limited to small numbers of patients within case series studies that include heterogeneous groups of patients. Potential benefits of successful treatment in cerebral disease may include the avoidance of cognitive impairment, which can

be seen as a side effect of antimuscarinic medication.

A trial should include people with primary cerebral conditions including (but not restricted to) stroke, head injury and cerebral palsy, but excluding multiple sclerosis. Children and adults should be recruited. Tolerability and acceptability are important outcomes, as well as the primary outcomes of continence, preservation of the upper urinary tracts and quality of life. Measurement of carer burden and quality of life is also important.

8.4 Augmentation cystoplasty

8.4.1 What is the safety and efficacy of augmentation cystoplasty compared with a) botulinum toxin b) usual care in neurological disease c) urinary diversion?

Clinical Methodological Introduction	
Population:	Patients with incontinence due to NLUTD
Intervention:	• Augmentation cystoplasty
Comparison:	• Botulinum toxin • Urinary diversion • Usual care
Outcomes:	• Incontinence level • The need for intermittent catheterisation • Quality of life / patient or carer perception of symptoms • Adverse events, including UTIs, renal complications, bladder stones, metabolic complications, cancer and unscheduled hospital admissions. • Bladder capacity and detrusor pressures

8.4.1.1 Clinical evidence Review

We searched for observational studies comparing the effectiveness of augmentation cystoplasty as an intervention for improving incontinence in people with neurogenic lower urinary tract dysfunction (NLUTD). We searched for any observational studies that compared the effectiveness of augmentation cystoplasty with one or more of botulinum toxin, urinary diversion and usual care; however no studies made these comparisons, and all compared findings before surgery with those after surgery.

33 observational studies were identified, evaluating the effects of augmentation cystoplasty on incontinence associated with NLUTD [93 94 95 96 97 98 99 100 101 102 103 104 25 105 106 107 108 109 110 111 112 113 114 115 116 91 117 118 119 120 121 122 123]. The augmentation procedures were fairly homogenous across 27 of the studies, varying only by the section of intestine used for the augmentation. However, 4 studies reported auto-augmentation [106 107 120 121], and one used dural tissue [93], and findings from these potentially distinct studies will be highlighted in the following report. There were 11 studies in children (<19 years), 9 in adults (≥19 years) and 13 in mixed age-group samples. The results are reported by outcome. Table 1 summarises the population, age range, follow-up periods and type of surgical material for each of the studies.

Table 70: Summary of studies included in the clinical evidence review

Study	Underlying pathology	Age range (yrs)	Follow up range (months)	Augmentation material
Arikan 1995 (n=10) [93]	Spinal cord injury (SCI), spina bifida	9-51	28	Dura mater
Arikan 2000 (n=18) [94]	SCI, spina bifida, myelitis sequele.	5-17	16-70	sigmoid
Beseghi 1994 (n=15) [95]	Mostly spina bifida	3-18	12-48	sigmoid
Chancellor 1993 (n=2) [124]	SCI	Adults	12-18	stomach
Chen 2009 (n=40) [97]	SCI	20-56	12- 168	Ileum
DeLong 2011 (n=7) [98]	Secondary progressive Multiple Sclerosis	unclear	unclear	unclear
Fiorca 1987 (n=12) [99]	Spina bifida	6-16	6-66	ileum, caecum, sigmoid
Herschorn 1998 (n=59) [100]	Mainly spina bifida and SCI	19-56	2-175	Sigmoid, colon, ileocecum
Kass 1983 (n=14) [101]	Not stated, but neurogenic	4-17	12-60	colon
Khastgir 2003 (n=34) [102]	SCI	11-52	29- 115	Ileum
Linder 1983 (n=18) [103]	Mainly spina bifida, sacral agenesis, SCI	10-68	12-120	Ileum, cecum
Lockhart 1986 (n=15) [104]	Mostly spina bifida	4-48 (only 1 adult)	Not stated	Ileum, cecum, sigmoid
Lopez Pereira 2008 (n=29) [105]	Mostly spina bifida	3-18	96 - 180	Ileum, sigmoid
Lopez Pereira 2009 (n=32) [25]	Mostly spina bifida	2.5 -18	120- 174	Ileum, sigmoid, ureter

Study	Underlying pathology	Age range (yrs)	Follow up range (months)	Augmentation material
MacNeily 2003 (n=17) [106]	Spinal spina bifida	2.2-13.2	4-126	Auto augmentation
Marte 2002 (n=11) [107]	Spina bifida	Mean 12.8	Mean 79	Auto augmentation
McInferney 1995 (n=50) [108]	Spina bifida, SCI, MS, Transverse myelitis, other spastic paraplegia.	15-50	24	ileum
Medel 2002 (n=26) [109]	Spina bifida	5-19	12-120	Ileum
Metcalfe 2006 (n=500) [110]	Spina bifida, sacral agenesis, SCI, SC tumour. 107 non neuropathic	Mean age 11.8	Median 160	Ileum, sigmoid, ileal-sigmoid, gastric, ileal-gastric, sigmo-gastric, cecal, ureter.
Mitsui 2008 (n=15) [111]	Spina bifida	Mean 14.4	13.2 - 210	ileum
Nasrallah 1991 (n=14) [112]	Mostly spina bifida	3-20	3-72	sigmoid
Nomura 2002 (n=21) [113]	SCI, spina bifida	Mean 29	8-135	Ileum
Pereira 2001 (n=16) [114]	Spina bifida	Children	35-90	sigmoid
Quek 2003 (n=26) [115]	SCI, spina bifida, transverse myelitis.	11-53	48-158	Ileum
Radomski 1995 (n=26) [116]	Mostly spina bifida, SCI, SC tumours.	8-43	6-108	Ileum, sigmoid
Reyblat 2009 (n=73) [91]	Mostly SCI	17-66	0.8-67	Ileum, colon
Sidi 1987 (n=18) [117]	Mostly spina bifida and SCI	5-31	7-42	sigmoid
Sidi 1990 (n=12) [118]	SCI	22-53	4-34	sigmoid
Simforoosh 2002 (n=130) [119]	Mostly SCI and neuro-spinal spina bifida	1.5 - 57	21-108	Ileum, ileocecal, sigmoid, stomach

Study	Underlying pathology	Age range (yrs)	Follow up range (months)	Augmentation material
Stohrer 1997 (n=36) [120]	Mainly SCI	Adults	Up to 80	Auto augmentation
Stothers 1994 (n=12) [121]	Spina bifida, SCI and 2 non-neurological	4-14	4-6	Auto augmentation
Sutton 1998 (n=19) [122]	SCI and MS, but also 3 non-neurogenic	27-64	3-67	colon
Zachoval 2003 (n=9) [123]	MS	23-57	6-19	Ileum

Quality of studies

The quality of all evidence was classified as very low. The studies were retrospective observational studies and therefore graded low by default (see Chapter 4). The further downgrade was due to a lack of attempts to eliminate threats to internal validity through the use of a matched comparison group. However it should also be noted that in most studies patients had failed to respond to a period of antimuscarinic medication and intermittent self catheterisation, and so it is unlikely that confounding time effects could wholly explain the changes seen from before to after surgery. Definitions of incontinence were almost always lacking, and so it is unclear what level of severity was used as the threshold measure of "incontinence". Several studies also failed to clarify the number of patients suffering from incontinence pre-operatively, although in most cases it was implicit that the majority were suffering from incontinence at baseline.

Incontinence outcome

All studies suggested that augmentation cystoplasty would reduce the likelihood of incontinence. Auto-augmentation appeared to show less benefit than intestinal augmentation, but this impression was based on only one study. Tables 2-4 show results for children, adults and mixed-age studies respectively.

Table 71: Effects of augmentation on incontinence in children

Study	Pre-op incontinence (count)	Post-op incontinence (count)	Other incontinence findings
Arikan 2000 (n=18) [94]	Unclear, but probably most 18/18	3/18	
Mitsui 2008 (n=15) [111]	20/22	3/15	1 episode/wk: 1/15 2-3 episodes/wk: 1/15 Several episodes/day: 1/15 Small amount: 2/15 Moderate amount: 1/15

Study	Pre-op incontinence (count)	Post-op incontinence (count)	Other incontinence findings
Kass 1983 (n=14) [101]	Unclear, but probably most 14/14	0/14	
Lopez Pereira 2009 (n=32) [25]	Unclear, but probably most 32/32	0/32	
Lopez Pereira 2008 (n=29) [105]	Unclear, but probably most 29/29	0/29	
Beseghi 1994 (n=15) [95]	Not clear but stated that "urinary incontinence improved in all patients" 15/15	3/15	
Fiorica 1987 (n=12) [99]	6/12	2/12	Of the 2 incontinent post-op, 1 needed pads and oxybutynin and the other described as not "satisfactory".
MacNeily 2003 (n=17)* [106]	13/17	8/17	
TOTAL	141/147 (96%)	17/147 (12%)	

(a) **auto augmentation*

Table 72: Effects of augmentation on incontinence in adults

Study	Pre-op incontinence (count)	Post-op incontinence (count)	Other incontinence findings
Nomura 2002 (n=21) [113]	21/21	1/21	
Sidi 1990 (n=12) [118]	10/12	1/12 at 4 months post op	A further 2/12 were continent after artificial sphincter op.
Herschorn 1998 (n=59) [100]	42/59 (unclear)	20/59	Mild incontinence 17/59 Mod-severe incontinence 3/59
Zachoval 2003 (n=9) [123]	Unclear, but probably most 9/9	0/9	Incontinence scores pre/post (0=no problems to 5=great problems) Pollakisuria 4.8/1 Nycturia 3.9/0.7 Urgency 4.0/0.6 Urge incontinence (pads/day) 2.3/0 Need for abdominal straining 2.3/3.9
Chen 2009 (n=40) [97]	38/40	4/40	
Sutton 1998 (n=19) [122]	Unclear, but probably most 19/19	1/18	
DeLong 2011 (n=7) [98]	4/7	0/7	
TOTAL	143/167 (86%)	27/166 (16%)	

Table 73: Effects of augmentation on incontinence in mixed age groups

Study	Pre-op incontinence (count)	Post-op incontinence (count)	Other incontinence findings

Study	Pre-op incontinence (count)	Post-op incontinence (count)	Other incontinence findings
Lockhart 1986 (n=15) [104]	15/15	2/15	
Quek 2003 (n=26) [115]	26/26 (unclear)	8/26	Leak continuously 1/26 Leak 1x /week 4/26 Leak 1x /month 3/26
Nasrallah 1991 (n=14) [112]	11/14	2/14	All dry by day
Simforoosh 2002 (n=130) [119]	86/130	9/130	
Radomski 1995 (n=26) [116]	Unclear, but probably most 26/26	8/26	A further 5 later became continent with anticholinergics
Linder 1983 (n=18) [103]	18/18	3/17 (1 lost to follow up)	
Sidi 1987 (n=18) [117]	17/17 (unclear)	1/17	
Reblat 2009 (n=73) [91]	64/70	15/70	Mild incontinence 12/70 Severe incontinence 3/70
Khastgir 2003 (n=34) [102]	32/32 (unclear)	0/32	2/27 required pads 5/7 reported a reduction in UTIs
Medel 2002 (n=26) [109]	19/26	4/26	
TOTAL	314/374 (84%)	52/373 (14%)	

Need for intermittent catheterisation outcome

This outcome was weakly reported, with many studies failing to clearly specify the number of patients using intermittent catheterisation pre-operatively or post operatively. Overall, the effects of augmentation cystoplasty on the need for intermittent catheterisation are unclear, but there is a possibility that the need for intermittent catheterisation may increase. [Note: Expert evidence advises that intermittent classification is usually required following augmentation cystoplasty in patients with a neuropathic bladder]. Table 5 summarises the results.

Table 74: Effects of augmentation on the need for intermittent catheterisation

Study	Age group	Pre-operation intermittent catheterisation (count)	Post-operation intermittent catheterisation (count)
Arikan 2000 (n=18) [94]	children	18/18	unclear
Lopez Pereira 2009 (n=32) [25]	children	unclear	29/32
Lopez Pereira 2008 (n=29) [105]	children	unclear	26/29

Study	Age group	Pre-operation intermittent catheterisation (count)	Post-operation intermittent catheterisation (count)
Nomura 2002 (n=21) [113]	Adult	11/21	21/21
Herschorn 1998 (n=59) [100]	Adult	59/59	56/59
Zachoval 2003 (n=9) [123]	Adult	2/9	6/9
Chen 2009 (n=40) [97]	Adult	40/40 (unclear)	31/40
Lockhart 1986 (n=15) [104]	mixed	15/15	14/15
Quek 2003 (n=26) [115]	mixed	13/26 (unclear)	26/26
Nasrallah 1991 (n=14) [112]	mixed	14/14	14/14
Linder 1983 (n=18) [103]	mixed	unclear	6/17 (unclear)
Sidi 1987 (n=18) [117]	mixed	unclear	17/17
Khastgir 2003 (n=34) [102]	mixed	21/32	27/32
Medel 2002 (n=26) [109]	mixed	26/26	26/26
McInferney 1995 (n=100) [108]	mixed	6/50	23/50

Quality of life / Patient satisfaction (post surgery) outcomes

Five studies collected data on patient satisfaction or quality of life, and all suggested that the procedure led to patient satisfaction and had a positive impact on quality of life. However, non-validated questionnaires were used for all studies except Mitsui 2008 [111], and there were no reports of methods to reduce bias during collection of these data. The quality of these data is therefore very low.

Children

Mitsui 2008 (n=15) [111]: 14/15 were 'satisfied with surgery' post operatively.

Adults

Herschorn 1998 (n=59) [100]: 41/59 patients delighted, 12/59 pleased, 6/59 mostly satisfied. On a scale of 0-2, with 0 representing the highest satisfaction, mean response was 0.42. All but one would go through the surgery again.

Zachoval 2003 (n=9) [123]: Quality of life score was 0.7/6 post-operatively (with 6=unbearable quality of life), compared to 5/6 pre-operatively.

Mixed age-group

Quek 2003 (n=26) [115]: 'Nearly all patients expressed extreme satisfaction' and all but one would recommend the procedure to others. Mean satisfaction score out of 10 was 8.7.

Khastgir 2003 (n=32) [102]: 26/27 reported excellent quality of life post surgery, and improvement in the management of the urinary tract. 27/27 would recommend the surgery to others. 0/27 reported deterioration in sexual function, and 5/7 reported a reduction in UTIs.

Adverse events (post surgery)

A variety of adverse effects of the surgery were reported, and the most important ones are documented in the tables below, with the data below concerning patients affected at least once. The most commonly reported adverse events were symptomatic UTIs [children aggregate: 13/117; adult aggregate: 34/61; mixed age aggregate: 8/90; all groups 55/268], bladder stones [children aggregate: 7/101; adult aggregate: 13/40; mixed age aggregate: 82/605; all groups 102/746], and bowel obstruction [children aggregate: 7/101; mixed age aggregate: 29/752; all groups: 36/853]. Auto augmentation appeared to show a greater numerical frequency of renal adverse effects than intestinal augmentation in children, but this evidence was from one study only. Note that the lack of reporting of an adverse event does not necessarily imply the adverse event was absent, as some events may only be detected if actively sought (e.g. vesicoureteral reflux [VUR]). Table 6 summarises these results.

Table 75: Adverse effects

	Age group	Symptomatic UTIs/pyuria	Renal dysfunction	Bladder stones requiring surgery	Bowel obstruction	Diarrhoea / other bowel urgency problems	Ileus	cancer	Metabolic complications	Perforation of augmented bladder	VUR
Arikan 2000 [94]	Children	2/18	0/18	0/18				0/18	1/18		
Mitsui 2008 [111]	Children	0/22		1/22	2/22	15/22			0/22	0/22	
Kass 1983 [101]	Children		1/14		1/14				2/14		
Lopez-Pereira 2009 [25]	Children	1/32		3/32	1/32				3/32		
Lopez-Pereira 2008 [105]	Children	1/29		3/29	1/29			0/29	1/29		

	Age group	Symptomatic UTIs/pyuria	Renal dysfunction	Bladder stones requiring surgery	Bowel obstruction	Diarrhoea / other bowel urgency problems	Ileus	cancer	Metabolic complications	Perforation of augmented bladder	VUR
Beseghi 1994 [95]	Children									0/15	
Pereira2001 [114]	Children	1/16	0/16								
MacNeily 2003* [106]	Children		5/17								
Nomura 2002 [113]	Adults						4/21				4/21
Sidi 1990 [118]	Adults	4/12									
Hershorn 1998 [100]	Adults					11/59					
Zachoval 2003[123]	Adults	4/9							0/9		
Chen 2009 [97]	Adults	26/40		13/40		3/40					
Lockhart 1986 [104]	Mixed	2/15									1/15
Quek 2003 [115]	Mixed	2/26				3/26		0/26	0/26	0/26	
Nasrallah 1991 [112]	Mixed		0/14								
Simforoosh 2002 [119]	Mixed		8/130		1/130						
Linder 1983 [103]	Mixed										
Sidi 1987 [117]	Mixed	2/17			3/17						
Metcalfe 2006 [110]	Mixed			75/500	16/500			4/500		44/500	
Reblat 2009 [91]	Mixed			5/73	2/73		12/73				

	Age group	Symptomatic UTIs/pyuria	Renal dysfunction	Bladder stones requiring surgery	Bowel obstruction	Diarrhoea / other bowel urgency problems	Ileus	cancer	Metabolic complications	Perforation of augmented bladder	VUR
Khastgir 2003 [102]	Mixed	2/32		2/32	7/32					1/32	1/5
Medel 2002 [109]	Mixed		2/26					0/18	1/18		3/26
Overall incidence	-	47/268 (18%)	16/235 (7%)	102/746 (14%)	34/849 (4%)	32/147 (22%)	16/94 (17%)	4/591 (0.7%)	8/168 (5%)	45/595 (8%)	9/67 (13%)

*(b) *auto augmentation*

Bladder capacity and detrusor pressure outcome

All studies showed some evidence of benefit. Many studies failed to report useful measures of variance, instead reporting ranges or no measure at all. In general, auto augmentation led to more modest effects than intestinal augmentation. Table 7 summarises these results.

Table 76: Effects of augmentation on bladder capacity and detrusor pressures

	Age group	Pre-operation bladder capacity (ml) Mean (sd) unless stated	Post-operation bladder capacity (ml) Mean (sd) unless stated	Pre-operation detrusor pressure at capacity (cm H20) Mean (sd) unless stated	Post-operation detrusor pressure at capacity (cm H20) Mean (sd) unless stated
Arikan 2000 (n=18) [94]	Children	86 (7)	370 (52)		
Fiorica 1987 (n=12) [99]	Children	Bladder volume increased from 55% to >1000% over baseline, and compliance also “markedly improved”. No other data provided.			
Mitsui 2008 (n=15) [111]	Children	186 921)	380 (25)		
Lopez Pereira 2009 (n=32) [25]	Children	106 (52)	507.8 (165)	50 (32)	10 (4)
Lopez Pereira 2008 (n=29) [105]	Children	89.8 (range 58-252)	521 (range 300-1000)	44.8 (range 22-150)	10 (range 5-15)

	Age group	Pre-operation bladder capacity (ml) Mean (sd) unless stated	Post-operation bladder capacity (ml) Mean (sd) unless stated	Pre-operation detrusor pressure at capacity (cm H20) Mean (sd) unless stated	Post-operation detrusor pressure at capacity (cm H20) Mean (sd) unless stated
Beseghi 1994 (n=15) [95]	Children	126	372		
Pereira 2001 (n=16) [114]	Children	83 (range 50-110)	429		
Marte 2002 (n=11)* [107]	Children	94	297		
Stothers 1994 (n=12) * [121]	Children	"mean increase in capacity of 40%" [no numeric data provided].			
MacNeily 2003 (n=17)* [106]	Children	198 (range 55-575)	291 (range 102-500)	51 (range 24-100)	54.4 (25-100)
Nomura 2002 (n=21) [113]	Adults	148.5 (52)	315 (36)		
Sidi 1990 (n=12) [118]	Adults	134 (range 70-220)	562 (range 300-900)		
Herschorn 1998 (n=59) [100]	Adults	220 (range 20-550)	531.2 (350-1000)	48.9 (20-113)	15.8 (10-50)
Zachoval 2003 (n=9) [123]	Adults	105	797	53	30
Chancellor 1993 (n=2) [124]	Adults	97.5 (range 75-120)	540 (range 500-580)		
Sutton 1998 (n=19)	Adults	179.2	495.1		
Stohrer 1997 (n=15)* [120]	Adults	121	406	86.4	50.9
Lockhart 1986 (n=15) [104]	Mixed	<150	480	>40 for 86% of patients	18
Quek 2003 (n=26) [115]	Mixed	201 (106)	615 (204)	81 (43)	20 (12)
Nasrallah 1991 (n=14) [112]	Mixed	Range 40-120	"improved by an average of 286ml"		
Khastgir 2003 (n=34) [102]	Mixed	143 (range 62-224)	589 (range 401-777)	108 (range 65-151)	19 (4-34)
McInerney 1995 (n=50) [108]	Mixed	196	496		

	Age group	Pre-operation bladder capacity (ml) Mean (sd) unless stated	Post-operation bladder capacity (ml) Mean (sd) unless stated	Pre-operation detrusor pressure at capacity (cm H20) Mean (sd) unless stated	Post-operation detrusor pressure at capacity (cm H20) Mean (sd) unless stated
Arikan 1995 (n=10)** [93]	Mixed	88.7 (19.1)	227.2 (83.8) [sig]	72.5 (15.9)	35.3 (6.9) [sig]

**auto augmentation, ** dura mater*

8.4.1.2 Economic evidence

This area was identified as important for economic evaluation given the uncertainty over the trade-off between cost and effectiveness. Therefore an original cost-effectiveness analysis was conducted to answer this question.

Please see cost- effectiveness analysis in Appendix I for the full model write-up including methods, results and discussion.

8.4.1.3 Evidence Statements

Clinical Evidence Statements

23 Observational studies comprising 680 participants suggested that augmentation might improve incontinence (2 - 210 months)(very low quality).

15 Observational studies comprising 459 participants suggested that augmentation might increase the need for intermittent catheterisation (2 – 175 months)(very low quality).

5 Observational studies comprising 141 participants suggested that augmentation might improve patient satisfaction and quality of life (2 – 175 months)(very low quality).

23 Observational studies comprising 1155 participants suggested that the main adverse effects of augmentation are UTIs, bladder stones and bowel obstruction (2 – 210 months)(very low quality).

23 Observational studies comprising 451 participants suggested that augmentation might improve bladder capacity and reduce detrusor pressures (2 – 210 months)(very low quality).

Health economics evidence statements

- Augmentation cystoplasty is cost effective compared to botulinum toxin type A in patients where it is suitable.
- Botulinum toxin type A is cost effective compared to augmentation cystoplasty in patients who are unsuitable for surgery.
- A Botulinum toxin type A strategy where augmentation cystoplasty is used (and relevant) in 100% of patients after failed Botulinum toxin type A is cost effective compared to a 0% progression to augmentation cystoplasty strategy but is higher cost.
- Botulinum toxin type A is cost effective when compared to no treatment.

8.4.2 Recommendations and links to evidence

Recommendations:	**AUGMENTATION CYSTOPLASTY** **38. Consider augmentation cystoplasty using an intestinal segment for people:** • **with non-progressive neurological disorders *and*** • **complications of impaired bladder storage (for example, hydronephrosis or incontinence) *and*** • **only after a thorough clinical and urodynamic assessment and discussion with the patient and/or their family members and carers about**

	complications, risks and alternative treatments. **39. Offer patients life-long follow-up after augmentation cystoplasty because of the risk of long-term complications. Potential complications include metabolic effects, such as the development of vitamin B_{12} deficiency and the development of bladder cancer.**
Relative value placed on the outcomes considered	The GDG regarded continence and renal protection as being of high health value and noted that there was objective urodynamic data that supported the contention that the intervention could markedly improve the ability of the bladder to store urine. However, it was also noted that serious adverse events can arise in association with augmentation cystoplasty.
Quality of evidence	No studies were found comparing the intervention with botulinum toxin, urinary diversion or usual care. All the studies included compared before and after augmentation cystoplasty surgery. The evidence that emerged from the literature review was in the form of low quality, retrospective case-series. Very limited data were available in relation to quality of life. 33 observational studies were identified, evaluating the effects of augmentation cystoplasty on incontinence in adults, young people and children with a range of neurological disease (including spina bifida and spinal cord injury). Surgery was associated with a decrease in incontinence (96% to 12% children; 86% to 16% adults; and 84% to 14% mixed population). The studies also indicated an improvement in bladder capacity and reduction in detruser pressure The most commonly reported adverse events were symptomatic UTIs, bladder stones and bowel obstruction. Auto augmentation appeared to show a greater numerical frequency of renal adverse effects than intestinal augmentation in children, but this evidence was from one study only. There was insufficient evidence to support the use of auto-augmentation cystoplasty in the same population. The GDG noted that the case series were largely published in the era before the introduction of Botulinum toxin A The economic evidence was based on an original model with potentially serious limitations and direct applicability.
Trade-off between clinical benefits and harms	Significant benefits are obtained at the cost of important side-effects of treatment, including the possible need for future surgery. There is continuing concern regarding the possible increased long-term risk of bladder cancer in patients who have undergone augmentation cystoplasty, therefore the GDG agreed it was important that patients and carers were informed of possible complications and should be offered lifelong follow-up following this intervention. The GDG noted that there are possible differences in the effectiveness and safety profile of augmentation cystoplasty in adults as opposed to children. Specific concerns relate to an increased risk of bladder perforation and a possible reduced long-term effectiveness in children.
Economic considerations	The economic model showed that when compared to no treatment (containment) augmentation cystoplasty is a cost effective treatment for incontinence. In patients where both augmentation cystoplasty and Botulinum toxin therapy are viable options, the economic model shows that augmentation cystoplasty is cost effective in those patients who are likely to benefit from incontinence treatment for more than 10 years. The GDG recognised that it is extremely unusual for augmentation cystoplasty to be used in patients with progressive neurological conditions because of potential long term difficulties with managing intermittent catheterisation.
Other considerations	The GDG agreed that the lack of evidence of the long-term outcome of auto-augmentation meant that the group could only recommend the use of augmentation of the bladder using a segment of intestine.
Economic	Although the initial cost of ileal conduit diversion is high, the follow-on annual costs of

considerations	stoma care and drainage bags are likely to be equivalent to the costs associated with the use of containment products and catheters. It is likely that the costs of urinary diversion will be offset by quality of life gains and the costs of unsatisfactory incontinence care in the long term.
Other considerations	Despite the paucity of high-quality, supportive published data, the GDG felt able to make a recommendation on the basis of their combined clinical experience. They recognised that there is a small population of patients with NLUTD who have devastating LUTS which cannot be controlled by less aggressive interventions. There was a consensus view that to offer such patients the option of an ileal conduit diversion is appropriate. This recommendation was made with a clear understanding that ileal conduit urinary diversion can itself be associated with a number of serious complications. The GDG considered that the patient undergoing ileal conduit diversion should receive preoperative and long-term postoperative support from stoma care specialists. Long-term upper urinary tract surveillance was also felt to be appropriate in patients with a good general prognosis.

9 Treatment for stress incontinence

Stress urinary incontinence arises where the function of the urethral sphincters and or pelvic floor muscles are compromised; leakage of urine can occur if intra-abdominal pressure is raised, even in the absence of a contraction of the detrusor muscle of the bladder wall. Sphincteric or pelvic floor muscle deficiency is seen in patients who have sustained damage to the sacral segments of the spinal cord, the cauda equina or peripheral nerves within the pelvis. The use of indwelling urethral catheters in patients with neurologenic lower urinary tract dysfunction (NLUTD) is a well-recognised risk factor; tension on a urethral catheter can cause pressure necrosis of the urethral sphincters. Patients who lack urethral sensation or who are cognitively-impaired are at particular risk of sustaining catheter-related urethral damage. Stress incontinence in patients who have neurological disease can, of course, have a non-neurological aetiology such as pelvic floor hypermobility that has resulted from previous pregnancies and childbirth.

Many patients with neurogenic stress incontinence who request treatment of the condition are already using intermittent self-catheterisation to empty their bladders. However, for patients who empty the bladder without using a catheter, for example by using abdominal straining, it is important to recognise that effective treatment of stress incontinence will, almost inevitably, precipitate urinary retention which will necessitate the introduction of intermittent catheterisation or the use of an indwelling suprapubic catheter.

Pelvic floor muscle training is widely used in the neurologically intact population with stress incontinence of urine and is supported by evidence of efficacy in the NICE Female Urinary Incontinence Guideline [125] However, the use of pelvic floor muscle training in patients with NLUTD has received relatively little attention. Patients who retain the ability to voluntarily contract their pelvic floor muscles, despite their neurological deficit, are candidates for pelvic floor muscle training programmes as they have the potential to improve the strength and responsiveness of their pelvic floor musculature. A variety of techniques that might improve the outcomes of pelvic floor muscle training have been described; these include electrical stimulation of the pelvic floor and biofeedback systems. However, there is limited information about the treatment regimes that should be used in patients with NLUTD as well as uncertainty about the effectiveness of the treatment.

A wide range of surgical procedures have been used to treat stress incontinence in patients with NLUTD. The most commonly used approaches involve either providing passive support or compression of the urethra using urethral slings or providing active compression using the artificial urinary sphincter. Slings can be made either from the patient's own tissues (for example autologous rectus sheath) or from synthetic materials.

Sling surgery is well-established in the management of stress incontinence in the non-neuropathic female population [125] but it is not possible to extrapolate from the neurologically intact population to patients with NLUTD as the pathophysiology of stress incontinence differs between the two groups. In the neuropathic population it is usually the case that there is damage to the function of the muscle of the urethral sphincter (intrinsic sphincter deficiency) while in neurologically intact patients, excessive mobility of the urethra is the commonest cause of stress incontinence. This is an important distinction as it is generally believed that successful treatment of neuropathic stress incontinence is dependent on a sling compressing the urethra rather than simply preventing descent of the urethra from its normal anatomical position.

To date, autologous tissue has been regarded as the standard sling material to use when managing neuropathic stress incontinence. The perceived need for some tensioning of the sling raises the question as to whether synthetic material should be used in view of there being a theoretical increased risk of a synthetic sling or tape eroding through the wall of the urethra. Despite the fact that sling surgery has been widely used to manage neuropathic stress incontinence, there is relatively little published data on the benefits and risks of this therapeutic option.

For thirty years, the artificial urinary sphincter has been used to manage stress incontinence in neuropathic patients both alone and in combination with other reconstructive procedures [126]. The AMS 800 (American Medical Solutions) is the only device that has been in widespread use. It works on a hydraulic principle. A pressure-generating reservoir supplies fluid to a cuff-mounted balloon which is fitted around the urethra. As the pressures in the two components equalises, the urethral lumen is occluded and continence aided. The patient uses a pump to empty the cuff balloon and transfer fluid back to the reservoir which then allows voiding to take place or a catheter to be passed. Although high continence rates are reported for patients undergoing artificial urinary sphincter implantation, surgical complication rates and the cost of the device have to be taken into consideration when evaluating the implant's role.

9.1 Pelvic floor treatments

9.1.1 Does pelvic floor muscle training with or without electrical stimulation or biofeedback compared with treatment as usual, improve outcomes?

Clinical Methodological Introduction	
Population:	Multiple sclerosis Stroke
Intervention:	Pelvic floor muscle training with or without electrical stimulation or biofeedback
Comparison:	Treatment as usual
Outcomes:	Frequency of voiding by day and night No. of incontinence episodes per week Quality of life Maximum cystometric capacity Residual urine Treatment adherence

9.1.1.1 Clinical Evidence

We searched for RCTs comparing the effectiveness of pelvic floor muscle training with or without electrical stimulation or biofeedback as interventions for improving outcomes for incontinence due to multiple sclerosis or stroke. These conditions were selected as they represented the main diagnostic groups in which pelvic floor muscle training is used in neurogenic LUT dysfunction in clinical practice. We looked for any RCT studies that compared the effectiveness of pelvic floor muscle training with or without electrical stimulation or biofeedback with treatment as usual.

Five RCTs were identified comparing pelvic muscle training for improving incontinence due to neurological disease/injury. All of the RCTs were in the adult population. Table 1 summarises the population, intervention, comparison and length of follow up for each of the studies.

Table 77: Summary of studies included in the clinical evidence review

Study	Population	Intervention	Comparison	Length of follow-up
Lucio 2010[127]	Women with multiple sclerosis (MS) that had been stable for the previous 4 months; relapsing remitting form of MS; >18 years; Expanded Disability Status Score (EDSS) < 6.5; cognitive capacity to complete assessment and treatment	Pelvic floor muscle training 2x 30 minute sessions per week over 12 weeks	Sham procedure N=14	12 weeks

Study	Population	Intervention	Comparison	Length of follow-up
	protocol, ability to contract the pelvic floor muscles, and at least 3 of the following urinary tract symptoms: urgency, urge incontinence, daytime frequency, nocturia, and nocturnal enuresis	N=13		
Vahtera 1997[128]	MS patients admitted for a 21 day comprehensive rehabilitation period. Stable phase of the disease; EDSS < 6.5; symptoms of lower urinary tract disorder; post-void residual volume of <100ml.	Pelvic floor muscle training + Electrical stimulation 6 sessions over 2 weeks. N=40	Untreated group N=40	6 months
McClurg 2008[129]	Patients with MS Inclusion criteria: diagnosed with clinically definite or laboratory supported diagnosis of MS with disease stabilised for the previous 3 mths, over 18 yrs old, an EDSS ≤ 7.5 and sufficient dexterity enabling completion of assessment and treatment protocol. Lower urinary tract dysfunction was confirmed after a clinical assessment. Inclusion criteria: presented with at least one of the following: any involuntary leakage of urine, voiding frequency > 8 per 24 hr, nocturia, and/or reported voiding dysfunction such as hesitancy, straining, poor stream and incomplete emptying demonstrated during uroflowmetry with measurement of post-void residual.	Pelvic floor muscle exercises Plus electromyography (EMG) feedback Plus neuromuscular electrical stimulation (NMES) One session a week for nine weeks N=37	Pelvic floor muscle exercises Plus EMG Plus placebo NMES N=37	24 weeks
McClurg 2006[130]	Female patients with MS Inclusion criteria: Patients were included if they presented with at least one of the following: an involuntary leakage of urine, voiding frequency >8 per 24 hr, nocturia, and/or voiding dysfunction Exclusion criteria included: MS relapse requiring hospitalisation 3 months prior to or during the study, symptomatic prolapse, severe cognitive impairment	Pelvic floor training and advice (PFTA) Plus Electomyography (EMG) Plus Neuromusclar electrical stimulation (NMES) 9 wks duration N=10	PFTA N=10 PFTA plus EMG N=10	24 weeks

Study	Population	Intervention	Comparison	Length of follow-up
Tibaek 2005[131] Tibaek 2004[132]	Inclusion criteria: 1) women, diagnosed with first ever ischemic stroke according to the definition and verified by CT scan. Stroke was defined as focal neurological deficits of acute onset, lasting >24 hr, due to brain ischemia as shown by CT scan or of presumed ischemic nature after appropriate clinical and neuroradiological work up 2) stroke symptoms in at least one month 3) normal cognitive function 4) Urinary incontinence according to the definition of International Continence Society (ICS) with start in close relation to the stroke 5) independent walking abilities indoors >100 m with/without aids 6) independence in toilet visits 7) age between 40 and 85 yrs	Pelvic floor muscle training One per week for 12 weeks N=10	Untreated group N=8	4 weeks

Comparison of pelvic floor muscle training versus sham in patients with multiple sclerosis

Table 78: GRADE profile - Pelvic floor muscle training versus sham in patients with multiple sclerosis - Clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Pelvic floor muscle training Frequency (proportion) / Mean (SD)	Control Frequency (proportion) / Mean (SD)	Relative (95% CI)	Absolute	
Frequency of voiding(No. with) (follow-up 12 weeks)										
Lucio 2010[1]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	4/13 (30.8%)	14/14 (100%)	RR 0.33 (0.15 to 0.72)	670 fewer per 1000 (from 280 fewer to 850 fewer)	MODERATE
Urgency of voiding(No. with) (follow-up 12 weeks)										
Lucio 2010[1]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	4/13 (30.8%)	14/14 (100%)	RR 0.33 (0.14 to 0.76)	670 fewer per 1000 (from 240 fewer to 860 fewer)	LOW
Nocturnal enuresis (No. with) (follow-up 12 weeks)										
Lucio 2010[1]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	12/13 (92.3%)	11/14 (78.6%)	RR 1.17 (0.86 to 1.61)	134 more per 1000 (from 110 fewer to 479 more)	LOW
Incomplete emptying (No. with) (follow-up 12 weeks)										

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Pelvic floor muscle training Frequency (proportion) / Mean (SD)	Control Frequency (proportion) / Mean (SD)	Relative (95% CI)	Absolute	
Lucio 2010[1]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	3/13 (23.1%)	7/14 (50%)	RR 0.46 (0.15 to 1.42)	270 fewer per 1000 (from 425 fewer to 210 more)	LOW
Sessions attended (follow-up 12 weeks; Better indicated by higher values)										
Lucio 2010[1]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	Mean 21.5 SD (1.8)	21.5 (1.8)	MD 0.00 (-1.36 to 1.36)	MD 0.00 higher (1.36 lower to 1.36 higher)	LOW

[a] No details or randomisation or allocation concealment. Single blind (patient blind - patient reported outcomes), no drop-outs reported
[b] 95%CI crosses the minimally important difference (MID) for either benefit or harm

Comparison of pelvic floor muscle training plus electrical stimulation versus control in patients with multiple sclerosis.

Table 79: GRADE profile - Pelvic floor muscle training plus electrical stimulation compared with control in patients with multiple sclerosis

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PFMT + ES Mean (SD)	Control Mean (SD)	Relative (95% CI)	Absolute	
Leakage urine on minimal effort (follow-up 3 weeks; Better indicated by lower values) (0=never, 1=occasionally, 2=often)										

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PFMT + ES Mean (SD)	Control Mean (SD)	Relative (95% CI)	Absolute	
Vahtera 1997[6]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	0.23 (0.5)	0.75 (0.6)	MD -0.52 (-0.76 to -0.28)	MD 0.52 lower (0.76 to 0.28 lower)	VERY LOW
Leakage urine on minimal effort (follow-up 6 months; Better indicated by lower values) (0=never, 1=occasionally, 2=often)										
Vahtera 1997[6]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	0.08 (0.3)	0.55 (0.6)	MD -0.47 (-0.68 to -0.26)	MD 0.47 lower (0.68 to 0.26 lower)	VERY LOW
Nocturia (follow-up 3 weeks; Better indicated by lower values) (0-none, 1=0-1 times, 2=2-3 times, 3= > 3 times)										
Vahtera 1997[6]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	0.98 (0.6)	1.35 (0.7)	MD -0.37 (-0.66 to -0.08)	MD 0.37 lower (0.66 to 0.08 lower)	VERY LOW
Nocturia (follow-up 6 months; Better indicated by lower values) (0-none, 1=0-1 times, 2=2-3 times, 3= > 3 times)										
Vahtera 1997[6]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	0.7 (0.7)	1.43 (0.8)	MD -0.73 (-1.06 to -0.40)	MD 0.73 lower (1.06 to 0.40 lower)	VERY LOW

[a] No details of randomisation or allocation concealment. Open trial. No drop-outs.

[b] The 95%CI crosses the minimally important difference (MID) for either benefit or harm

Comparison of pelvic floor muscle training (PFMT) plus electromyography feedback (EMG) plus active neuromuscular electrical stimulation (NMES) versus PFMT plus EMG plus placebo NMES in patients with multiple sclerosis.

Table 80: GRADE profile - PFMT plus EMG plus active NMES compared with PFMT plus EMG plus placebo NMES in patients with multiple sclerosis - Clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PFMT + EMG + NMES Mean (SD)/Frequency (proportion)	PFMT + EMG Mean (SD)/ Frequency (proportion)	Relative (95% CI)	Absolute	
Urogenital Distress Inventory										
McClurg 2008[2]	Randomised trial	Very serious[a]	no serious inconsistency	no serious inconsistency	No serious imprecision[b]	-	-	Week 24 Irritative sub-scale In favour of PFMT + EMG + NMES vs PFMT + EMG		
Leakage episodes per 24 hr										
McClurg 2008[2]	Randomised trial	Very serious[a]	no serious inconsistency	no serious inconsistency	No serious imprecision[b]	-	-	Week 9 In favour of PFMT + EMG + NMES vs PFMT + EMG Week 24 ns		LOW
Post-void residual urine ml (follow-up 9 weeks; Better indicated by lower values)										
McClurg 2008[2]	randomised trial	Serious[c]	no serious inconsistency	no serious indirectness	Serious[d]	38 (18)	56 (55)	MD -18.00 (-36.65 to 0.65)	MD 18.00 lower (36.65 lower to 0.65 higher)	LOW
Post-void residual urine ml (follow-up 24 weeks; Better indicated by lower values)										

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PFMT + EMG + NMES Mean (SD)/Frequency (proportion)	PFMT + EMG Mean (SD)/ Frequency (proportion)	Relative (95% CI)	Absolute	
McClurg 2008[2]	randomised trial	Serious[c]	no serious inconsistency	no serious indirectness	Serious[d]	38 (23)	49 (32)	MD -11.00 (-23.7 to 1.7)	MD 11.00 lower (23.7 lower to 1.7 higher)	LOW
Withdrawals (follow-up 9 weeks)										
McClurg 2008[2]	randomised trial	Serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	1/37 (2.7%)	1/37 (2.7%)	RR 1.00 (0.06 to 15.4)	0 fewer per 1000 (from 25 fewer to 389 more)	MODERATE

[a] No details of randomisation, unclear allocation concealment, double blind, ITT analysis, incomplete outcome reporting

[b] Imprecision could not be assessed due to incomplete outcome reporting

[c] No details of randomisation, unclear allocation concealment, double blind, ITT analysis

[d] 95%CI crosses the minimally important difference (MID) for either benefit or harm

Comparison of pelvic floor training and advice (PFTA) versus PFTA plus electromyography (EMG) versus PFTA plus EMG plus neuromuscular electrical stimulation (NMES)

Table 81: GRADE profile - PFTA versus PFTA plus EMG versus PFTA plus EMG plus NMES

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Incontinence Impact Questionnaire (IIQ) total score (higher score indicates worse outcomes)										
1 McClurg 2006[3]	RCT	PFTA + EMG +NMES N=10	PFTA N=10 PFTA + EMG N=10	Total score mean (SD) Weeks 0 vs 9 PFTA vs PFTA + EMG + NMES (P=0.027) PFTA vs PFTA + EMG (p=0.036) Week 24 PFTA vs PFTA + EMG + NMES (p=0.040) PFTA vs PFTA + EMG (ns)	S (i)	N	N	S (ii)	N	Low
Outcome: Leakage episodes per 24 hr										
1 McClurg 2006[3]	RCT	PFTA + EMG +NMES N=10	PFTA N=10 PFTA + EMG	Week 0 vs 9 PFTA reduction 12 % (week 0 vs 9; p=0.687) PFTA + EMG 45% (p=0.074) PFTA + EMG + NMES	S (i)	N	N	S (ii)	N	Low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
			N=10	68% (p=0.002) PFTA vs PFTA + EMG + NMES (p=0.014) Week 0 vs 24 PFTA reduction minimal PFTA + EMG 58% (p=0.028) PFTA + EMG + NMES 75% (p=0.003) PFTA vs PFTA + EMG (p=0.007); PFTA vs PFTA + EMG + NMES (p=0.001)						
Outcome: No. incontinent										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 McClurg 2006[3]	RCT	PFTA + EMG +NMES N=10	PFTA N=10 PFTA + EMG N=10	Week 0 vs 9 vs 24 PFTA 6/10 vs 9/10 (RR0.67 (95%CI0.39 to 1.15) vs 8/10 (RR0.75 (0.41 to 1.36) PFTA + EMG 8/10 vs 7/10 (RR1.14 (0.69 to 1.90) vs 5/10 (RR1.60 (0.80 to 3.20) PFTA + EMG + NMES 9/10 vs 7/10 (RR1.29 (0.82 to 2.03) vs 5/10 (RR1.80 (0.94 to 3.46)	S (i)	N	N	S (iii)	N	Low
Outcome: Nocturia										
1 McClurg 2006[3]	RCT	PFTA + EMG +NMES N=10	PFTA N=10 PFTA + EMG N=10	Nocturia was reduced in all groups by week 9 (p=0.035) maintained, albeit by varying degrees, by week 24	S (i)	N	N	S (ii)	N	Low
Outcome: Post-void residual urine ml										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 McClurg 2006[3]	RCT	PFTA + EMG +NMES N=10	PFTA N=10 PFTA + EMG N=10	Week 0 vs 9 vs 24 PFTA 90 vs 60 vs 80 PFTA + EMG 160 vs 60 vs 60 PFTA + EMG + NMES 84 vs 60 vs 30 No significant between groups	S (i)	N	N	S (ii)	N	Low
(i) Allocation concealment unclear, blinding unclear (ii) Imprecision could not be assessed because p values/no standard deviations presented (iii) 95%CI crosses the MID for either benefit or harm										

Narrative summary (for outcomes that are not appropriate for GRADE due to incomplete outcome reporting)

Kings Health Questionnaire (KHQ)

Throughout the duration of the study, results for the KHQ were variable both within and between groups, however significant improvements were demonstrated in the Symptom Severity Scale in the PFTA + EMG and PFTA + EMG + NMES groups at all time points ($p \leq 0.034$)[130]

Multiple sclerosis quality of life (MSQoL-54)

Throughout the duration of the study, results for the MSQoL-54 were variable both within and between groups, however significant improvements were demonstrated in the cognitive function sub-scale at all time points in PFTA + EMG + NMES ($p \leq 0.016$). In addition, statistically significant improvements were also observed in the emotional well-being sub-scale in PFTA + EMG and PFTA + EMG + NMES (week 24; $p \leq 0.027$)[130]

Adherence

Attendance at the weekly clinic sessions averaged 78% in all groups. Home use of the EMG unit was 75% recommended. No major effects or problems with usage were indicated [130].

Comparison of pelvic floor muscle training versus control in patients with stroke.

Table 82: GRADE profile - Pelvic floor muscle training compared with control for stroke

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PFMT Median (quartile range)/ Frequency (proportion	Control Median (quartile range)/ Frequency (proportion)	Relative (95% CI)	Absolute	
SF36 total score (median, quartile range) (follow-up 6 months; Better indicated by lower values)										
Tibaek 2004[4]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	563 (430-682)	623 (494-676)	[c]	ns	VERY LOW
Incontinence Impact Questionnaire total score (Better indicated by lower values)										
Tibaek 2004[4]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	20 (1-50)	27 (6-93)	[c]	ns	VERY LOW
No. of incontinence episodes/24 hr (follow-up 12 weeks; Better indicated by lower values)										
Tibaek 2005[5]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	0 (0-0)	0 (0-1)	[c]	ns	VERY LOW
Withdrawals (follow-up 12 weeks)										
Tibaek 2005[5]	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious imprecision[d]	2/14 (14.3%)	0/12 (0%) 0%	OR 6.92 (0.41 to 118.14)[e]	140 more per 1000 (from 70 fewer to 0	VERY LOW

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	PFMT Median (quartile range)/ Frequency (proportion	Control Median (quartile range)/ Frequency (proportion)	Relative (95% CI)	Absolute	
									360 more)	

[a] Unclear allocation concealment, no blinding, no ITT
[b] Imprecision could not be assessed because median and quartile ranges reported

[c] Relative effect could not be calculated because median and quartile ranges reported

[d] The 95%CI crosses the MID for either benefit or harm

[e] Peto odds ratio

9.1.1.2 Economic evidence

No relevant economic evaluations comparing pelvic floor muscle training, with or without electrical stimulation or biofeedback were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 83: Unit Costs

Item	Cost	Notes
Specialist Nurse [1]	£154 (£77 per hour)	Assuming 1/2 hour visits, 1 a week for 1 month
Specialist Physiotherapist [1]	£68 (£34 per hour)	
Biofeedback module [2]	£1167.43	One-off cost per hospital/department

Source: [1] Unit Costs of Health and Social Care 2010 compiled by Lesley Curtis (PSSRU)[42]

[2] NHS Supply chain catalogue[133]

Economic considerations

No evidence could be found that suggested that pelvic floor training is cost-effective in neuropathic patients with urological incontinence. The cost of pelvic floor training, with or without electrical stimulation or biofeedback is unlikely to be high, as shown in the unit costs above. While the costs of these programmes are not insignificant, the GDG felt that if effective this cost may be offset by the reduced costs associated with a reduction in the use of incontinence aids.

9.1.1.3 Evidence Statements

Clinical Evidence Statements

Pelvic floor muscle training (PFMT) versus sham in patients with multiple sclerosis

One study comprising 27 participants found that a statistically significant lower proportion of patients receiving pelvic floor muscle training compared to sham had:

- Frequency (12 weeks) (moderate quality)
- Urgency (12 weeks) (low quality)

One study comprising 27 participants found no significant difference between pelvic floor muscle training and sham for:

- Nocturnal enuresis (12 weeks) (low quality)
- Incomplete emptying (12 weeks) (low quality)
- No. of sessions attended (12 weeks) (low quality)

PFMT plus electrical stimulation compared with control in patients with multiple sclerosis

One study comprising 80 participants found that a statistically significant lower proportion of patients receiving pelvic floor muscle training compared with control had:

- Leakage of urine on minimal effort (3 weeks, 6 months) (very low quality)
- Nocturia (3 weeks, 6 months) (very low quality)

PFMT plus electromyography feedback (EMG) plus neuromuscular electrical stimulation (NMES) compared with pelvic floor muscle training plus EMG in patients with multiple sclerosis

One study comprising 74 participants found no significant difference in:

- Post-void residual urine (9 weeks, 24 weeks) (low quality)
- Withdrawals (9 weeks) (low quality)

Evidence statements could not be produced for the following outcomes of the studies by McClurg [134] as the results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect :

- Urogenital Distress Inventory – irritative subscale (week 24) (very low quality)
- Leakage episodes per 24 hr (week 9) (very low quality)

Comparison of pelvic floor training and advice (PFTA) versus PFTA plus electromyography (EMG) versus PFTA plus EMG plus neuromuscular electrical stimulation (NMES)

One study of 30 participants found no significant difference for each group (PFTA, PFTA + EMG, PFTA + EMG + NMES) when comparing pre vs post treatment values for:

- No. of patients incontinent (week 9, 24) (low quality)

Evidence statements could not be produced for the following outcomes of the study by McClurg [130] as the results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect :

- Incontinence Impact Questionnaire total score
- Leakage episodes per 24 hr
- Nocturia
- Post-void residual urine
- Kings Health Questionnaire
- Multiple Sclerosis quality of life

Pelvic floor muscle training plus electrical stimulation compared with control in patients with stroke

One study comprising 18 participants found no significant difference for PFMT compared with control for:

- Withdrawals (12 weeks) (low quality).

Evidence statements could not be produced for the following outcomes of the study by Tibaek [132]; [131] as the results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect :

- SF36 total score (6 months) (very low quality).
- Incontinence Impact Questionnaire (6 months) (very low quality).

- No. of incontinence episodes/24 hr (12 weeks) (very low quality)

Economic evidence statements

While the costs of these programmes are not insignificant, the GDG felt that if effective this cost may be offset by the reduced costs associated with a reduction in the use of incontinence aids

9.1.2 Recommendations and links to evidence

Recommendations:	**PELVIC FLOOR MUSCLE TRAINING** **40. Consider pelvic floor muscle training for people with:** • **lower urinary tract dysfunction due to multiple sclerosis or stroke *or*** • **other neurological conditions where the potential to voluntarily contract the pelvic floor is preserved.** **Select patients for this training after specialist pelvic floor assessment and consider combining treatment with biofeedback and/or electrical stimulation of the pelvic floor.**
Relative value placed on the outcomes considered	The GDG considered the outcomes of urinary continence, nocturia and quality of life to be important.
Quality of evidence	Overall, the evidence showed that pelvic floor muscle training with or without electrical stimulation or feedback improved continence outcomes. Although some quality of life data was available, it was not presented in a format that could be analysed using the GRADE methodology. The GDG recognised that the evidence presented is graded as being of generally low or very low quality. The sample sizes were small and follow up periods were generally short. The GDG noted that the evidence was limited predominately to patients with multiple sclerosis. The very limited evidence in the stroke population was in women only although there was some uncertainty regarding the clinical effectiveness of the interventions, the GDG agreed that overall there was sufficient evidence to suggest an improvement in continence outcomes. These improvements had the potential to improve quality of life. No economic evidence was found on pelvic floor muscle training. The GDG made their considerations on the basis of unit costs of staff time.
Trade-off between clinical benefits and harms	The GDG agreed that the interventions had the potential to deliver clinical benefit, improve patient/carer quality of life with very limited risk of harm. The GDG noted that the two studies (Lucio 2010; Vahtera) that compared pelvic floor muscle training interventions with sham or no treatment indicated there was some benefit in offering treatment, although the limitations of the studies were acknowledged. The group noted the significant improvement in the symptom severity scale and quality of life outcomes shown in the McClurg (2006) study. The group agreed that stress incontinence can cause distress to the patient and for some people these interventions may help alleviate this.
Economic considerations	While the costs of pelvic floor muscle training programmes are not negligible, particularly with respect to staff time, if effective, their cost may be offset by the cost-savings associated with a reduction in the use of incontinence aids.
Other considerations	Pelvic floor muscle exercises are often advised to be undertaken for patients with neurological conditions such as MS to prevent urinary incontinence and control urgency. These exercises are often advocated for use in the earlier stages of disease. Basic instruction can be provided by one of the patient's usual treating clinicians, such as an MS nurse but, it is important that the patient is undertaking the exercises correctly and if they express uncertainty then referral to a specialist continence advisor

	or physiotherapist is required. The use of adjuncts such as electrical stimulation or biofeedback can then be offered by these specialists. The GDG considered that the evidence review did not fully capture the complexity of treating NLUTD patients using pelvic floor training and that it would be wrong to exclude the possibility of using electrical stimulation and biofeedback as there may be particular circumstances where a therapist will find such techniques valuable. The GDG noted that patients with very weak pelvic floor muscle contraction or poor sensation, such as patients with MS, can benefit from biofeedback or electrical stimulation as it can aid motivation to continue the pelvic floor exercises.

9.2 Urethral tape and sling surgery

9.2.1 What is the safety and efficacy of urethral tape and sling surgery compared with a) bladder neck closure b) usual care in neurological disease?

Clinical Methodological Introduction	
Population:	Patients with incontinence due to neurogenic lower urinary tract dysfunction (NLUTD)
Intervention:	Urethral tape and sling surgery
Comparison:	Bladder neck closure Usual care
Outcomes:	Number of incontinence episodes per week. Severity of incontinence. Symptoms relating to bladder emptying, for example poor urinary stream, need for intermittent catheterisation. Quality of life. Patients and carers' perception of symptoms. Adverse events, including urinary tract infections, renal complications, bladder stones and unscheduled hospital admissions. Damage caused by catheterisation

9.2.1.1 Clinical review

We searched for RCTs and observational studies comparing the effectiveness of urethral tape and sling surgery as interventions for improving outcomes in patients with incontinence due to NLUTD. We looked for any RCT or observational studies that compared the effectiveness of urethral tape and sling surgery with bladder neck closure or with treatment as usual.

24 observational studies were identified. Four observational studies were on tape or synthetic sling surgery [135 136 137 138] and 20 were on sling surgery [139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158]. No studies were identified comparing urethral tape or sling surgery with bladder neck closure. The evidence is presented according to whether the population was adults or adults and children (mixed) or children. The evidence is also presented according to whether augmentation cystoplasty was performed (either before or at the same time as the tape or sling surgery) or not.

Quality of included studies

Overall, the studies were observational studies of very low quality. The vast majority of studies were before and after studies. Most importantly, there were no attempts to eliminate threats to internal validity through the use of a matched comparison group, although in most studies patients had failed

to respond to a period of antimuscarinic medication and intermittent self catheterisation, and so it is unlikely that confounding time effects could wholly explain the changes seen from before to after surgery.

Tables 1 and 2 summarises the population, intervention, comparison and length of follow up for each of the studies.

Table 84: Synthetic Tapes and Slings - Summary of studies included in the clinical evidence review

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
Dean[135]	Patients aged 14 to 20 yrs. History of myelomeningocele. Urodynamics showed normal compliance, adequate capacity and sphincter incompetence. Previous surgery: 5/6 (1 appendicovesicostomy and augmentation cystoplasty, 4 bladder neck bulking) 6/6 male	Suburethral polypropylene sling was placed on an outpatient basis through a small perineal incision N=6	Pre surgery	Median 33 mths (range 27 to 39 mths)
Godbole [136]	Children with a neuropathic bladder who underwent a Gore-tex bladder neck sling procedure. All patients had a poorly compliant bladder, neurogenic sphincteric weakness with low leak-point pressure. Management consisted of clean intermittent catheterisation, pharmacotherapy and cystoplasty (4/19)	Gore-tex bladder neck sling 7/19 concomitant augmentation cystoplasty	Pre-surgery	Median 7 yrs

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
	7/19 concomitant augmentation cystoplasty			
Hamid[137]	Women with neuropathic bladder dysfunction and stress urinary incontinence	Tension-free vaginal tape N=12	Pre-surgery	Mean 27.1 mths (range 17 to 54 mths)
Abdul-Rahman [138]	Follow up of Hamid			10 yrs

Table 85: Autologous and Biological Slings – Summary of studies included in the evidence review

(N.B. Hershorn[128] includes two patients with synthetic slings)

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
Adults				
<u>With augmentation cystoplasty (rectus fascia)</u>				
Herschorn[139]	Male patients with neurogenic incontinence Patient population: Spina bifida n=10, spinal cord injury n=3, mean age 27 yrs (range 17 to 40 yrs)	Urethral sling plus augmentation cystoplasty 2/13 Marlex mesh 11/13 rectus fascial sheath 12/13 underwent bladder neck tapering N=13	Pre-surgery	34.3 mths (range 5.5 to 49 mths)
Daneshmand[140]	Males with neurogenic bladder due to spinal cord injury (n=9) and spina bifida (n=3)	Autologous fascial sling (rectus fascia) 10/12 underwent simultaneous augmentation cystoplasty N=12	Pre-surgery	Mean 14.25 (1 to 39 mths)
Children				
<u>With augmentation cystoplasty (rectus fascial)</u>				
Barthold[141]	Children with neurogenic sphincter incontinence Myelomeningoce	Rectus fascia sling (N=10 procedures) and wrap (N=18 procedures) (one patient underwent both procedures)	Pre-surgery	Minimum 1 yr

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
	le 21/27 7 boys and 20 females	22/27 augmentation cystoplasty N=27		
Bugg[142]	Children with neurogenic intrinsic sphincter deficiency and a poorly compliant and/or small capacity bladder 14/15 female 1/15 male	Sling (rectus fascia) applying circumferential pressure All patients underwent ileal augmentation N=15	Pre-surgery	10 to 36 mths
Dik 1999[143]	Male patients with neurogenic sphincter incontinence and spina bifida mean age 11.7 yrs (range 6.5 to 15.2 yrs)	Puboprostatic sling suspension (rectus fascia) Simultaneous auto augmentation of the bladder 8/14 2/14 simultaneous ileocystoplasty N=14	Pre-surgery	Not reported
<u>With augmentation cystoplasty (other)</u>				
Misseri[144]	Patients treated with small intestinal submucosa (SIS) bladder neck sling procedure for neuropathic urinary incontinence (all with myelodysplasia) with a leak point pressure less than 25 cm H2O and a minimum of 6 mths follow up 21 females and 15 males, mean age 9 yrs (range 3 to 10 yrs)	Small intestinal submucosa (SIS) bladder neck sling N=27 Bladder neck repair with SIS sling N=9 All patients underwent Augmentation cystoplasty N=36	Pre surgery	Mean 15 mths

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
	All had failed on clean intermittent catheterisation and anticholinergic treatment			
Snodgrass 2009[145]	Children with spina bifida with neurogenic urinary incontinence Bladder neck sling with augmentation: male:female 10:8, ambulatory 7/18, mean age at operation 8.6 (range 3.2 to 13.6) yrs Bladder neck sling without augmentation: male:female 11:12, ambulatory 12/23, ambulatory 12/23, mean age at operation 8.0 (range 4.1 to 14.0) yrs	The type of sling varied according to surgeon preference. N=18	Pre-surgery	Not reported
<u>Without augmentation cystoplasty/unknown (rectus fascia)</u>				
Austin[146]	Children with neuropathic bladder secondary to myelodysplasia or traumatic spinal cord injury mean age 14 yrs (range 8 to 18 yrs), myelodysplasia n=16 8 males and10 females	Rectus fascia sling surgery	Pre-surgery	Mean 21.2 mths
Dik 2003[147]	Female patients	Transvaginal sling	Pre-surgery	Mean 3 yrs (range 0.6

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
	with spina bifida and neurogenic sphincter paralysis mean age 9 yrs (range 1 to 17 yrs)	suspension (rectus fascia) Adjunct augmentation cystoplasty in a few patients N=24		to 11 yrs)
McGuire[148]	Female children with myelodysplasia	Pubovaginal sling (rectus fascia) Simultaneous augmentation cystoplasty 1/8 N=8	Pre-surgery	Not reported
Nguyen[149]	Male children with neurogenic sphincteric incontinence myelodysplasia 5/7	Fascial sling (rectus fascia) Simultaneous continent stoma (N=4) N=7	Pre-surgery	1 to 9 yrs
Snodgrass 2010[150]	360-degree tight bladder neck sling for incontinence due to neurogenic bladder outlet incompetence mean age 8.1 yrs, 32 male 3/35 female	360-degree tight bladder neck sling (rectus fascia) N=35	Pre-surgery	Mean 28 mths (6 to 94 mths)
<u>Without bladder augmentation/unknown (other)</u>				
Snodgrass 2009[145]	Children with spina bifida with neurogenic urinary incontinence Bladder neck sling with augmentation: male:female 10:8, ambulatory 7/18, mean age at operation 8.6 (range 3.2 to 13.6) yrs	The type of sling varied according to patient preference N=23	Pre-surgery	Not reported

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
	Bladder neck sling without augmentation: male:female 11:12, ambulatory 12/23, ambulatory 12/23, mean age at operation 8.0 (range 4.1 to 14.0) yrs			
Mixed/unknown				
<u>With augmentation cystoplasty (rectus fascia)</u>				
Bauer[152]	All female. Age range 6-22 yrs (mean 14 yrs). All had urinary incontinence. Underlying cause of incontinence was myelodysplasia (8), sacral agenesis (1) and non-neurogenic etiology (2). 3 had undergone prior bladder neck reconstruction, and 2 had previous augmentations.	Rectus fascia sling 4/11 underwent augmentation (plus n=2 had previous augmentation) N=11	Pre-surgery	mean 12 months
Castellan[153]	Patients with neurogenic bladder. 43 females, 15 males, median age 11.4 yrs (range 4 to 40 yrs). Spina bifida 52/58	Rectus fascial sling neck procedure All patients underwent augmentation cystoplasty N=58	Pre-surgery	Mean 4.16 (range 1 to 10 yrs)
Decter[154]	Patients with neurogenic incontinence 8 patients with meningomyelocele, 2 sacral anomalies. Age range 6 to 26 yrs	Fascial sling (n=5 rectus abdominus fasica, n=5 fascia lata) 6/10 underwent augmentation cystoplasty N=10	Pre surgery	Mean 2.2 yrs

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
Elder[155]	Patients with myelodysplasia undergoing periurethral and puboprostatic sling repair mean age 12.6 yrs (range 7 to 25 yrs) None had undergone previous bladder neck surgery or augmentation cystoplasty. All patients had failed pharmacological therapy	Female – periurethral sling using rectus fascia N=10 Male – puboprostatic sling N=4 13/14 underwent augmentation cystoplasty N=14	Pre-surgery	Mean 12 months (2 to 27 months)
Fontaine[156]	Patients with neurogenic incontinence unresponsive to conservative treatment in whom postoperative volitional voiding was not expected 13 patients with congential lesions, 8 with acquired cord lesions. 21/21 female	Rectus fascial sling procedure and augmentation ileocystoplasty N=21	Pre-surgery	28.6 mths (range 6 mths to 5 yrs)
Wa lker[157]	Patients with spina bifida who underwent rectus fascial wrap procedure 7 males and 8 females	Rectus fascial wrap Augmentation cystoplasty 14/15 N=15	Pre-surgery	Mean 58 mths (Minimum 36 mths)
<u>With augmentation cystoplasty (other)</u>				
Albouy[151]	Patients with neurogenic bladder resulting from spinal	Bladder wall wraparound sling procedure	Pre surgery	Mean 5 yrs (range 2 to 8 yrs)

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW-UP
	dysraphism mean age 14 yrs (range 8 to 22 yrs) Incontinent despite anticholinergic therapy and clean intermittent catheterisation 7 females and 7 males	Plus augmentation cystoplasty N=14		
<u>Without augmentation cystoplasty/unknown (other)</u>				
Snodgrass 2010A[158]	Patients with neurogenic incontinence Inclusion criteria: urodynamics within one yr postoperatively and additional testing at least 18 mths postoperatively 21/26 myelomeningocele. 15 male and 11 female	360-dregree tight fascial wrap around the bladder neck with appendicovesicostomy but no augmentation N=26	Pre-surgery	Mean 39 mths (19 to 94 mths)

Quality of studies

Tapes and slings

Definitions of incontinence were almost always lacking, and so it is unclear what level of severity was used as the threshold measure of "incontinence". Several studies also failed to clarify the number of patients suffering from incontinence pre-operatively, although in most cases it was implicit that the majority were suffering from incontinence at baseline.

Tapes

Continence outcome

Table 86: Synthetic Tapes and Slings – No. continent

Study	Pre-surgery (frequency)	Post-surgery (frequency)

Study	Pre-surgery (frequency)	Post-surgery (frequency)
Dean[135]	0/6	5/6 (completely dry)
Godbole 2003 [136]	0/17 implied	15/17 (initially dry) 4/17 (dry long-term)
Hamid 2003[137]	0/12	10/12
Abdul-Rahman[a138] 5 yr follow up 10 yr follow up	 0/12 0/9	 10/12 7/9

[a]Same patients as in Hamid 2003

Quality of life outcome

The study reported the 'no. of patients' satisfied and did not use a validated measure of quality of life.

Table 87: Synthetic Tapes and Slings – Health related quality of life (no. of patients 'satisfied')

Study	Pre-surgery (frequency)	Post-surgery (frequency)
Abdul-Rahman [138] 5 yr follow up 10 yr follow up	 Not applicable	 11/12 9/9

Adverse events

Table 88: Synthetic Tapes and Slings – No. with adverse events

Study	Any adverse event (frequency)	Urinary tract infections(frequency)	Reoperation (frequency)
Dean[135]	Not reported	Not reported	3/6
Godbole 2003 [136]	0/17		14/17 sling removal due to erosion

Table 89: Synthetic Tapes and Slings – Damage caused by catheterisation

Study	Damage caused by catheterisation (frequency)	Difficulties caused by catheterisation (frequency)
Dean[135]	0/5 urethral erosion	Not reported
Godbole 2003 [136]		17/17 (unable to catheterise urethrally)

Table 90: Synthetic Tapes and Slings –No. with urinary tract infection

Study	Pre-surgery (frequency)	Post-surgery (frequency)
Hamid 2003 [137]	Not applicable	3/12

Slings

Continence outcome

The results are presented in the table below:

Table 91: Autologous and Biological Slings - No. continent

Study	Pre-surgery (frequency)	Post-surgery (frequency)
Adults		
<u>With augmentation</u>		

Study	Pre-surgery (frequency)	Post-surgery (frequency)
Daneshmand[140]	0/12	8/12 (completely dry)
Herschorn[139]	0/13	9/13 (completely dry)
OVERALL INCIDENCE	0/25	17/25 (68%)
Children		
With augmentation		
Barthold[141]	0/10 sling 0/18 wrap implied	5/10 (sling) 5/18 (wrap) (totally dry)
Bugg[142]	0/15	9/15 (completely dry)
Dik 1999[143]	0/14	10/14 (daytime continence)
Misseri[144]	0/36 implied	19/27 sling alone (dry) 8/9 sling plus bladder neck reconstruction (dry)
Snodgrass 2009[145]	0/18 patient reported 0/18 surgeon reported	11/18 patient reported 13/18 surgeon reported
OVERALL INCIDENCE	**0/111**	**75/111 (68%)**
Without augmentation/unknown		
Austin[146]	0/18 implied	14/18
Dik 2003[147]	0/24 implied	19/24
McGuire[148]	0/8	8/8 (dry)
Nguyen[149]	0/7	1/7 (completely dry) 6/7 (occasional wetting)
Snodgrass 2009[145]	0/23 patient reported 0/23 surgeon reported	12/23 patient reported 10/23 surgeon reported
Snodgrass 2010[150]	0/35	16/35 (dry)
OVERALL INCIDENCE	**0/132**	**91/132 (69%)**
Mixed/unknown		
With augmentation		
Albouy[151]	0/14	13/14 (results 'very good or good')
Bauer[152]	0/11	8/11 (completely dry)
Castellan[153]	0/58	51/58 (completely dry)
Decter[154]	0/5 rectus fascia 0/5 fascia lata	2/5 rectus fascia 2/5 fascia lata
Elder[155]	0/14 implied	12/14 (completely dry)
Fontaine[156]	0/21	20/21 daytime 18/21 night time
Walker[157]	0/15 implied	5/15 (completely dry)
OVERALL INCIDENCE	0/143	113/143 daytime (79%) 111/143 night time (78%)
Without augmentation/unknown		
Snodgrass 2010A[158]	0/26	16/26 (dry)
OVERALL INCIDENCE	**0/26**	**16/26 (62%)**

Table 92: Autologous and Biological Slings - Severity of incontinence

Study	Pre-surgery	Post-surgery
Mixed/unknown		
With augmentation		
Walker[157]	5.5 mean no. of pads used	1.1

Adverse events

The majority of studies did not specify what adverse events were actively monitored.

Table 93: Autologous and Biological Slings - Adverse events reported by patients undergoing sling surgery

Study	Any adverse event (frequency)	Urinary tract infections (frequency)	Re-operation (frequency)
Adults			
With augmentation			
Herschorn[139]	2/13 bladder neck narrowing 1/13 wound infection 2/13 Marlex erosions 1/13 bladder stones	7/13	3/13
Daneshmand[140]	0/12		
Overall incidence	**6/25 (24%)**	**7/13 (54%)**	**3/13 (23%)**
Children			
With augmentation			
Dik 1999[143]	1/14 erectile dysfunction		
OVERALL INCIDENCE	**1/14 (7%)**		
Without augmentation/unknown			
Austin[146]			2/18
Dik 2003[147]	1/24 vesicovaginal fistula 0/24 infections		
McGuire[148]	0/8 renal complications	0/36	
Nguyen[149]			1/7 1/7 complications due to surgery
Snodgrass 2010[150]	0/35 hydronephrosis		
OVERALL INCIDENCE	**1/57 (2%)**	**0/36 (0%)**	**3/25 (12%)**
Mixed/unknown			
With augmentation			
Albouy[151]		0/14	
Bauer[152]	0/11		
Castellan[153]	0/58 upper tract deterioration 2/58 bladder neck occlusion		
Fontaine[156]	13/21 asymptomatic bacteriuria 0/21 bladder calculi		
OVERALL INCIDENCE	**15/90 (17%)**	**0/14 (0%)**	
Without augmentation/unknown			
None			

Autologous and Biological Slings - Damage caused by catheterisation

Study	Damage caused by catheterisation (frequency)	Difficulties with catheterisation (frequency)
Adults		

Study	Damage caused by catheterisation (frequency)	Difficulties with catheterisation (frequency)
With augmentation		
Daneshmand[140]		0/12
OVERALL INCIDENCE		**0/12 (0%)**
Children		
With augmentation		
Barthold[141]		0/10 sling 0/18 wrap
Bugg[142]		0/15
Dik 1999[143]		2/14
OVERALL INCIDENCE		**2/39 (5%) sling 0/18 (wrap)**
-Without augmentation/unknown		
Dik 2003[147]		0/24
McGuire[148]		0/8
Nguyen[149]		1/7
Snodgrass 2010[150]		1/35 traumatic catheterisation
OVERALL INCIDENCE		**2/74 (3%)**
Mixed/unknown		
With augmentation		
Albouy[151]		0/14
Decter[154]	1/10 erosion	3/10 transient
Fontaine[156]		0/21
OVERALL INCIDENCE	**1/10 (10%)**	**3/45 (7%)**
Without augmentation/unknown		
NONE		

9.2.1.2 Economic evidence

No relevant economic evaluations comparing urethral tape and sling surgery with bladder neck closure were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 94: Unit Costs

Item	Cost	Notes
LB23Z Bladder Neck Open Procedures - Female	£ 1,419	Vast majority of procedures are open rather than laproscopic (31 against 11,000)
LB24Z Laparoscopic Bladder Neck Procedures – Female	£ 3,194	
LB21Z Bladder Neck Open Procedures - Male	£ 4,617	More open than laproscopic (2,995 vs 1,826)
LB22Z Laparoscopic Bladder Neck Procedures - Male	£ 5,304	
Tape	£632	Min: £568 Max: £700

Source: NHS Reference Costs 2009-10; NHS Supply Chain Catalogue 2011

Economic considerations

These interventions (bladder neck open procedures) are categorized in the same Healthcare Resource Group (HRG) codes, costing £1,419 for females (LB23Z, NHS reference cost 2009-10), and £4,617 for males (LB21Z, NHS reference cost 2009-10). However, the unit cost of a tape is not included in the cost of the operation, therefore an additional cost of £632 should be added to the operation cost.

These interventions are currently performed in selective patients and as the difference in costs is negligible, the recommendation should be based on clinical grounds. The cost of these interventions is fairly high, however if shown to be effective, the costs could be offset by a reduction in the costs of incontinence aids and an increase in quality of life. The sling operation is marginally cheaper than the cost of synthetic tape surgery, as the sling is made of human tissue and therefore no extra cost is incurred. However, with no useful effectiveness data it is difficult to draw conclusions on the cost effectiveness of either intervention. If the effectiveness of the two operations is considered equivalent, then autologous sling surgery is likely to be cost saving.

9.2.1.3 Evidence Statements

Narrative summary

Synthetic Tapes and Slings

Four observational studies (two of the same population) (27.1 mths to 10 yrs) (very low quality) suggested that synthetic tapes and slings were associated with an improvement in continence. Adverse events include reoperation, difficulties caused by catheterisation and urinary tract infections.

Autologous and Biological Slings

Adults with augmentation

Two observational studies (14.25 to 34.3 mths) (very low quality) reported an improvement in continence. Adverse events included Marlex erosions, urinary tract infections and re-operation.

Children with augmentation

Five observational studies (10.3 to 15 mths) (very low quality) reported an improvement in continence. Adverse events included erectile dysfunction and difficulties with catheterisation.

Children without augmentation/unknown

Six observational studies (10 to 36 mths) (very low quality) reported an improvement in continence. Adverse events included vesicovaginal fistula, re-operation and difficulties with catheterisation

Mixed/unknown with augmentation cystoplasty

Seven observational studies reported an improvement with continence (12 mths to 5 yrs) (very low quality). Adverse events included bladder neck occlusion, asymptomatic bacteriuria and difficulties with catheterisation.

Mixed/unknown without augmentation/unknown

One observational study (39 mths) (very low quality) reported an improvement in continence.

Economic evidence statements

- Autologous and biological sling surgery is marginally cheaper than synthetic tape and sling surgery, however as the two operations are already done on highly selected populations, the direct comparison is not necessarily relevant.
- If the effectiveness of the two operations are considered equivalent, then autologous sling surgery is likely to be cost saving compared to synthetic taping.

9.2.2 Recommendations and links to evidence

Recommendations:	**URETHRAL TAPE AND SLING SURGERY** **41. Consider autologous fascial sling surgery for people with neurogenic stress incontinence.** **42. Do not routinely use synthetic tapes and slings in people with neurogenic stress incontinence because of the risk of urethral erosion.**
Relative value placed on the outcomes considered	The GDG placed a high value on the outcome of continence however the lack of data on quality of life was noted.
Quality of evidence	Overall, the studies were observational studies of very low quality. The majority of studies compared status before with after surgery. Most importantly, there were no attempts to eliminate threats to internal validity through the use of a matched comparison group, although in most studies patients had failed to respond to a period of antimuscarinic medication and intermittent self catheterisation, and so it is unlikely that confounding time effects could wholly explain the changes seen from before to after surgery. In general, longer-term follow-up data was not reported in the studies. There was a lack of evidence for quality of life. For children, the majority of data was on patients with spinal bifida. The GDG noted that there was variation in the surgical techniques used. The very limited and low quality data on synthetic tapes and slings reported an improvement in continence. However, the surgery was also associated with a need for reoperation and increased incidence on urinary tract infections (UTIs). The data on autologous and biological slings was of very low quality, but the studies demonstrated that surgery was associated with an improvement in continence pre vs post surgery in those with and without augmentation cystoplasty. The overall rate of adverse events ranged from 2 to 24%. The incidence of UTIs ranged from 0 to 54% and the frequency of reoperation ranged from 12 to 23%
Trade-off between clinical benefits and harms	Urethral sling procedures are capable of rendering a proportion of patients with neurogenic stress incontinence continent. There are associated risks which include the possibility of damage to the urethra or bladder during or after surgery. The GDG considered that tapes or slings that are made from synthetic materials are likely to carry an excess risk of tissue erosion and local infection. Furthermore there is extremely limited data available for synthetic tape procedures. Stress incontinence frequently coexists with abnormal bladder storage due to detrusor overactivity or impaired compliance in patients with NLUTD. Therefore it is common for a patient to undergo a combined operation that is designed to treat the abnormality of sphincter and bladder function. The case series that have been reviewed illustrate this as many include patients who have undergone sling surgery and

	augmentation cystoplasty. The GDG felt that It is important to recognise that upper tract deterioration can be associated with the treatment of stress incontinence in patients with NLUTD if bladder storage pressures are high. Bladder storage requires thorough pre-operative assessment. Post-operative upper urinary tract surveillance should be maintained. A subsequent augmentation cystoplasty may be required if bladder storage is unsafe.
Economic considerations	The GDG considered the costs of slings and tapes and the surgeries required to install them. The surgeries are high cost but the GDG considered that the costs are likely to be offset by the long term reduction in the use of continence aids. In addition, the GDG thought they would improve the quality of life of the patient due to the reduced incontinence. These interventions are currently performed in selective patients and as the difference in costs is negligible, the recommendation should be based on clinical grounds. The cost of these interventions is fairly high, however if shown to be effective, the costs could be offset by a reduction in the costs of incontinence aids and an increase in quality of life. The sling operation is marginally cheaper than the cost of synthetic tape surgery, as the sling is made of human tissue and therefore no extra cost is incurred. However, with no useful effectiveness data it is difficult to draw conclusions on the cost effectiveness of either intervention. If the effectiveness of the two operations is considered equivalent, then autologous sling surgery is likely to be cost saving.
Other considerations	The GDG noted that whilst there is a risk of damage to the urethra or bladder for any patient having this procedure it is particularly high in the neuropathic population due to the anatomical changes that can be present and the effects of chronic inflammation in the tissues.

9.3 Artificial urinary sphincter

9.3.1 What is the safety and efficacy of artificial urinary sphincters compared with other treatments in neurological disease?

Clinical Methodological Introduction	
Population:	Children and adults with stress urinary incontinence resulting from neurological disease
Intervention:	Implantation of an artificial urinary sphincter
Comparison:	Other treatments; however no studies made such comparisons, and all compared findings before and after implantation.
Outcomes:	• Incontinence – frequency and severity • Symptoms relating to bladder emptying • Quality of life / patient or carer perception of symptoms • Adverse events, including UTIs, renal complications, bladder stones, infection of prosthesis, device failure and unscheduled hospital admissions.

9.3.1.1 Clinical evidence

We searched for observational studies that examined the effectiveness of implantation of an artificial urinary sphincter in improving incontinence in people with NLUTD. We looked for any observational studies that compared the effectiveness of implantation of an artificial urinary sphincter with other treatments, but only one study [159] used a comparison group. All studies compared findings before implantation with those after implantation, and these results form the main body of this report.

25 observational studies were identified which evaluated the effects of artificial sphincter implantation on incontinence in neurological disease. The implantation procedures and prostheses used were fairly homogenous across the studies. The only outcomes addressed by these studies were incontinence and adverse events. Table 1 summarises the population characteristics in each study.

Table 95: Summary of studies included in the clinical evidence review

Study	Underlying pathology	Age range (yrs)	Follow up range (months)	Prosthesis type (if stated)
Aaronson 1986[160] (n=10)	Myelodysplasia	6-16	12-14	AS800
Aprikian 1992[161] (n=27)	Myelomeningocele or sacral agenesis	9-19	6-31	AS800
Barrett 1982[162] (n=24)	Myelodysplasia	7-56	Up to 40	
Belloli 1992[163] (n=37)	Not stated	13-19	unclear, but possibly 12-108	AS792, AS800
Bersch 2009[164] (n=51)	SCI, myelomeningocele, spinal stenosis, spinal infarction	Mean (sd): 38.7 (14)	60-174	
Bitsch 1990[165] (n20)	Myelodysplasia	15-47	12-156	
Brantley Scott 1973[166] (n=3)	Spina bifida	16-26	unclear	
Brantley Scott 1986[167]	Myelomeningocele, SCI,	3-68	3-130	AS791, AS792,

Study	Underlying pathology	Age range (yrs)	Follow up range (months)	Prosthesis type (if stated)
(n=120)	congenital sacral dysgenesis			AS800
Chartier-Kastler 2010[168]	Myelomeningocele, SCI	18-58	6-208	AS800
De Badiola 1992[169] (n=23)	Myelomeningocele, SC tumours or sacral agenesis		12-160	AS791, AS800
Gonzalez 1995[170] (n=19)	Myelodysplasia	4-17	Mean 96	AS791, AS792, AS800
Gonzalez 1982[171] (n=15)	Myelomeningocele, SC tumours, sacral agenesis	5-17	Up to 88	AS791, AS792
Gonzalez 1979[172] (n=12)	Myelomeningocele, SC tumours, sacral agenesis	7-45	Mean 25	AS721
Jakobsen 1986[173] (n=33)	Myelodysplasia, neural tumours, SCI.	9-75	Up to 96	AS721, AS 761, AS742, AS791, AS792, AS800
Light 1983[174] (n=50)	SCI	8-69	3-60	
Lopez Pereira 2005[175] (n=17)	Myelomeningocele	12-21	18-117	
Lopez Pereira 2006[176] (n=35)	Myelomeningocele, sacral agenesis, spinal cord lipoma, sacral teratoma	11.5-18	5-132	
Murphy 2003[177] (n=13)	Spina bifida, SCI, severe pelvic trauma		Mean 72	
Murray 1988[178] (n=19)	Spina bifida, sacral agenesis.	5-42	7-39	AS792, AS800
O'Flynn 1991[179] (n=44)	Meningocele, lipoma of cauda equine, sacral agenesis	11-43	Not stated	AS792, AS800
Patki 2006[180] (n=9)	SCI	27-47	3-133	AS800
Sidi 1987[159] (n=27)	Not stated	5-44	12-144	AS800
Simeoni 1996[181] (n=107)	Meningocele, sacral agenesis, medullary lipoma.	8-18	Mean 60	AS800
Singh 1996[126] (n=90)	Mostly meningocele	13-62	12-120	AS792, AS800
Spiess[182] 2002 (n=30)	Spina Bifida	9-19	36-177	AS800

Quality of studies

The confidence in the findings reported below is undermined by the lack of attempts to eliminate threats to internal validity through the use of a matched group. Definitions of incontinence were often lacking, and so it is unclear what was the threshold measure. Several studies also failed to clarify the number of patients suffering from incontinence pre-operatively, although in most cases it was implicit that the large majority were suffering from incontinence at baseline.

Incontinence outcome

Pre-test to post-test comparisons

All studies suggested that artificial sphincters would reduce the likelihood of incontinence, through a comparison of incontinence before and after the sphincter implantation, and this did not appear to vary by age group. Table 2 shows results for these studies.

Table 96: Effects of artificial sphincters on incontinence

Study	Age group	Pre-implantation incontinence (count)	Post-implantation incontinence (count)	Other post-implantation incontinence findings
Aaronson 1986[160] (n=10)	Children	10/10 ("severe")	2/10	These 2 were improved but still incontinent
Aprikian 1992[161] (n=27)	Children	27/27 (unclear)	3/25	
Belloli 1992[163] (n=37)	Children	37/37 (day and night) (unclear)	4/37 (day) 15/37 (night)	
Gonzalez 1995[170] (n=19)	Children	19/19 (Unclear)	3/19	1/19 stress incontinence and 2/19 complete incontinence. Incontinence defined as inability to stay dry for at least 4 hours without pads
Gonzalez 1982[171] (n=15)	Children	15/15 (unclear)	5/15	Girls responded less well – 4/5 girls still incontinent
Lopez Pereira 2006[176] (n=35)	Children	35/35 (unclear)	2/35	
Simeoni 1996[181] (n=107)	Children	107/107	63/107 (all patients) 16/84 (3 yrs) 5/38 (6 yrs)	All patients includes those that had to undergo surgery for revisions etc
Spiess[182] 2002 (n=30)	Children	30/30 (unclear)	11/30	6/30 slightly wet (some leaking but socially continent), 5/30 incontinence leading to social embarrassment or physical discomfort.
Bersch 2009[164] (n=51)	Adult	51/51 [4/51 – moderate but bothersome; 24/51 – severe; 23/51 - permanent urine loss]	15/51	10 had minimal leakage on video-urodynamics but no need for continence aids; 4 needed 1 pad/day; 1 needed >1 pad per day.
Patki 2006[180] (n=9)	Adult	9/9 (unclear)	0/9	But at 3 months post implantation 2/9, and at time of publication 3/9.
Barrett 1982[162] (n=24)	Mixed	24/24	2/24	1 additional patient had to wear pads for mild stress incontinence, and 1 more developed insidious incontinence at 12 months
Brantley Scott 1986[167] (n=120)	Mixed	3/3 (one unclear)	0/3	
Chartier Kastler 2010[168]	Mixed	unclear	20/50	Of those with the AS800 still in place at the final follow up, 12/40 were incontinent.
Gonzalez 1979[172]	Mixed	12/12 (unclear)	4/12	Incontinence defined as not dry for 2 hours
Jakobsen 1986[173] (n=33)	Mixed	33/33	7/33	6 had slight but not socially significant incontinence and 1 severe.
Light 1983[174] (n=50)	Mixed	50/50 (unclear)	24/42	
Lopez Pereira 2005[175] (n=17)	Mixed	17/17 (unclear)	0/16	
O'Flynn 1991[179] (n=44)	Mixed	44/44 (unclear)	4/44	2 "damp" but leaked only on maximal exertion or when excited, 2 were "wet".
Sidi 1987[159] (n=27)	Mixed	No data	Mean (sd) incontinence	Scored from 1 to 5, with 1=total incontinence (or dry < 2 hours), 2=

Study	Age group	Pre-implantation incontinence (count)	Post-implantation incontinence (count)	Other post-implantation incontinence findings
			score of 3.62 (0.7)	stress and/or night incontinence, dry 2-4 hours, 3= stress and/or night incontinence, dry >4hrs, 4= minor stress incontinence and/or night dampness, dry >4 hrs, 5= continent day and night, dry > 4 hours) [mean(sd)].
Singh 1996[126] (n=90)	Mixed	90/90	7/90	7/90 at last follow up, but some had needed repeat surgery
De Badiola 1992[169] (n=23)	Unclear	23/23 (unclear)	7/23	
Murphy 2003[177] (n=13)	Unclear	13/13 (unclear)	10/13	1/13 rare dribble, 4/13 need for CISC, 3/13 convene catheter, 2/13 need for pads
TOTAL		**649/649 (unclear)**	**173/649 (including *daytime* data from** Belloli 1992[163]**)** **184/649 (including *night time* data from** Belloli 1992[163]**)**	

Comparison to other treatments

Sidi 1987[159] compared a group of 16 young people of mean age 17.2 years (range 5-44) who had undergone an artificial sphincter implantation to a group of 9 young people of mean age 16.3 years (range 4-27) who had undergone a Young-Dees-Leadbetter bladder neck reconstruction. The mean (sd) postoperative continence score (0-5 range, and a higher score is better) in the artificial sphincter group was 3.62 (0.7) and in the bladder neck reconstruction group was 3.72 (0.9). This difference was not statistically significant (see Appendix B). This was not a randomised trial, and these results are therefore prone to bias from factors such as varying diagnoses.

Adverse events (post implantation)

A variety of adverse effects of the implantation were reported, and the most important ones are documented in the tables below, with the following data concerning patients affected at least once. The most prominent risks are the need for revision (34%), device failure (26%), the need for complete removal (22%), bladder neck erosion or device infection (11%), UTIs (9%) and upper tract complications (8%). There appears to be no risk for mortality. Note that the lack of reporting of an adverse event does not necessarily imply the adverse event was absent, as some events may only be detected if actively sought. It was not possible to make a meaningful comparison of the incidence in adults and children, as only two studies had exclusively adult patients, most data being from studies with mixed-age groups. Table 3 outlines these results, with a summary for each age group and overall. The only study Sidi 1987[159] to compare artificial sphincter implantation to another treatment did not report adverse events.

Table 97: **Adverse effects**

	Age group	Follow up range (months)	Bladder neck erosion or device infection	Device failure	Need for revision	Need for complete removal	UTI	Upper tract complications
Aaronson 1986[160] (n=10)	Children	12-14			4/10		3/10	2/10
Aprikian 1992[161] (n=27)	Children	6-31	4/27	7/27	7/27	4/27		
Belloli 1992[163] (n=37)	Children	possibly 12-108	1/37					2/37
Gonzalez 1995[170] (n=19)	Children	mean 96	0/19		19/19			4/19
Gonzalez 1982[171] (n=15)	Children	up to 88	3/15	11/15				
Lopez Pereira 2006[176] (n=35)	Children	5-132	3/35	7/35				
Simeoni 1996[181] (n=107)	Children	mean 60			29/107	26/107		
Spiess[182] (n=30)	Children	36-177		5/30	17/30			6/30
Overall incidence	**Children**	**5-177**	**11/133 (8%)**	**30/107 (28%)**	**76/193 (39%)**	**30/134(22%)**	**3/10 (30%)**	**14/96 (15%)**
Bersch 2009[164] (n=51)	Adults	60-174	4/51		16/51	4/51		
Patki 2006[180] (n=9)	Adults	3-133	1/9					
Overall incidence	**Adults**	**3-174**	**5/60 (8%)**		**16/51 (32%)**	**4/51 (8%)**		
Barrett 1982[162] (n=24)	Mixed	up to 40	2/24	3/24			0/24	0/24
Bitsch 1990[165] (n20)	Mixed	12-156						4/20
Brantley Scott 1973[166] (n=3)	Mixed	unclear						
Brantley Scott 1986[167] (n=120)	Mixed	3-130						12/120
Chartier-Kastler 2010[168] (n=51)	Mixed	6-208	3/51	13/51				
Gonzalez 1979[172] (n=12)	Mixed	mean 25	3/12	4/12	1/12	4/12	1/12	1/12
Jakobsen 1986[173] (n=33)	Mixed	up to 96	9/33		7/34			
Light 1983[174] (n=50)	Mixed	3-60				12/50		0/50
Lopez Pereira 2005[175] (n=17)	Mixed	18-117	1/17					1/17
Murray 1988[178] (n=19)	Mixed	7-39						2/19

	Age group	Follow up range (months)	Bladder neck erosion or device infection	Device failure	Need for revision	Need for complete removal	UTI	Upper tract complications
O'Flynn 1991[179] (n=44)	Mixed	Not stated	3/44					1/44
Sidi 1987 [159] (n=16)	Mixed	12-144						
Singh 1996[126] (n=90)	Mixed	12-120	7/90					
Overall incidence	**Mixed**	**3-144**	**28/261 (11%)**	**20/87 (23%)**	**8/46 (17%)**	**16/62 (26%)**	**1/36 (3%)**	**21/306 (7%)**
De Badiola 1992 [169] (n=23)	Unclear	12-160						1/23
Murphy 2003[177] (n=13)	Unclear	mean 72	9/13			7/13		
Overall incidence	**Unclear**	**12-160**	**9/13 (7%)**			**7/13 (54%)**		**1/23 (4%)**
Overall incidence	**All**	**3-177**	**53/467 (11%)**	**50/194 (26%)**	**100/290 (34%)**	**57/260 (22%)**	**4/46 (9%)**	**36/425 (8%)**

9.3.1.2 Economic evidence

No relevant economic evaluations comparing the use of the artificial urinary sphincter with sling surgery or other treatments were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 98: Unit Costs

Item	Cost
Artificial Sphincter costs	
Balloon	£797*
Control Pump	£2,449*
Cuff	£701*
Accessory Kit	£172*
Total cost	**£4,119***
Operation costs	
Bladder Neck Open Procedures (female)	£1,419†
Bladder Neck Open Procedures (male)	£4,617†
Total Costs	
Females	**£5,538**
Males	**£8,736**

*Source: * Personal Communications (Mid Yorkshire Hospitals NHS Trust) †NHS Reference Costs 2009-10*

Economic considerations

The comparison relevant for this question is artificial urinary sphincter versus sling surgery. These interventions are categorized in the same HRG code, costing £4,617 for men and £1,419 for women (LB23Z and LB21Z, NHS reference cost 2009-10). There is however the additional cost to consider of the artificial sphincter itself, which costs £4,119 (Personal communication Mid Yorkshire Hospitals NHS Trust). In current practice, the choice of procedure is made on the basis of surgeon preference.

The clinical review has not shown any significant clinical advantage over other interventions with similar aims. Added to which the clinical review has shown that the **rate of re-operation** and adverse effects associated with artificial sphincter implantation is quite high, adding to the long term costs and reductions in quality of life. It is estimated by the GDG and on the basis of data from several studies that the re-operation rate on artificial sphincters is one re-operation/replacement of the device **every ten years** [183,183]. This means that there are additional life-time costs for many patients who have artificial urinary sphincters implanted as a result of the need to manage complications and undertake revisional surgery.

Therefore the cost of alternative surgical options, such as sling surgery, are likely to be considerably lower as a result of there being a requirement for fewer re-operations. This will also be likely to have a quality of life advantage. On this basis, the artificial sphincter is not considered to be cost-effective

when compared to sling surgery in circumstances where the procedures would be expected to have similar success rates in treating stress incontinence.

9.3.1.3 Evidence Statements

Clinical evidence statements

22 Observational studies comprising 695 participants suggested that artificial sphincter implantation might improve incontinence (3 – 208 months) (very low quality)

24 Observational studies comprising 835 participants suggested that the main adverse effects of artificial sphincter implantation are device failure (26%), device infection/bladder neck erosion (12%), the need for revision (34%), the need for complete removal (22%), 11UTIs (9%), and upper tract complications (8%). There appears to be no risk for mortality (3-208 months) (very low quality).

Economic evidence statements

The cost of artificial urinary sphincter is considerably high when the cost of the sphincter, surgery and revisional surgery is considered. This does not support the use of artificial sphincters where another option is available that is judged to be of equal efficacy such as autologous sling surgery. However where no other option is available, the gains in quality of life combined with a partially offset cost of incontinence aids may make this intervention cost effective compared to other treatments.

9.3.2 Recommendations and links to evidence

Recommendations:	**<u>ARTIFICIAL URINARY SPHINCTER</u>** **43. Consider surgery to insert an artificial urinary sphincter for people with neurogenic stress incontinence only if an alternative procedure, such as insertion of an autologous fascial sling, is less likely to control incontinence.** **44. When considering inserting an artificial urinary sphincter:** • **discuss with the person and/or their family members and carers the risks associated with the device, the possible need for repeat operations and alternative procedures** • **ensure that the bladder has adequate low-pressure storage capacity.** **45. Monitor the upper urinary tract after artificial urinary sphincter surgery (for example, using annual ultrasound scans) as bladder storage function can deteriorate in some people after treatment of their neurogenic stress incontinence.**
Relative value placed on the outcomes considered	The GDG recognised that a high value is placed on continence and quality of life.
Quality of evidence	The evidence consisted of observational studies with no comparison groups being assessed therefore the data are at high risk of bias. There is low confidence in the estimate of effect. The populations studied were largely restricted to congenital spinal disorders. There was little evidence on quality of life. Although the studies were very low quality, all studies reported that surgery was associated with improvements in

	continence. The economic evidence was based on unit costs of interventions.
Trade-off between clinical benefits and harms	The most prominent risks found in the studies were device failure (26%), bladder neck erosion or device infection (11%), the need for revision (34%), the need for complete removal (22%), UTIs (9%) and upper tract complications (8%). It is accepted that sphincter devices have a finite lifespan of around 10 years and therefore will require replacement at some point as a matter of routine. However, the device is capable of curing or markedly improving incontinence in the majority of patients who receive implants for neurogenic stress urinary incontinence. Significant harm can arise if device infection or erosion occurs as revision surgery will then be essential. It is also accepted that upper tract deterioration will be seen in some patients if appropriate assessment and treatment of bladder dysfunction is not undertaken preoperatively and patient follow up is neglected. The GDG were aware of the experience of clinicians who first introduced the artificial urinary sphincter into clinical practice; the importance of the preoperative urodynamic assessment of bladder function was not appreciated at that time and upper tract deterioration was seen in some patients in whom low pressure storage capacity was lacking. The GDG agreed that preoperative assessment of the bladder to ensure low pressure storage capacity was necessary.
Economic considerations	The cost of artificial urinary sphincter is considerably high when the cost of the sphincter, surgery and revisional surgery is considered. This does not support the use of artificial sphincters where another option, such as autologous sling surgery, is available and is judged to be of equal efficacy. However where no other option is available, the gains in quality of life combined with partially offset costs of incontinence aids may make this intervention a cost effective compared to other treatments.
Other considerations	The AUS is currently established as a standard treatment for uro-dynamically-proven stress urinary incontinence in adult males with NLUTD. Its role in children and in women is less well established. Despite the limited evidence base that was obtained from the literature review, the GDG was able to make the above recommendation on the basis of the consistent effect on continence improvement that the studies reported. This was supported by the clinical experience of GDG members. It was also noted that alternative treatment options are not necessarily available (especially in men) or reliable in reducing incontinence levels. The GDG made the recommendation while acknowledging the significant complication rates and associated need for re-operation in some patients that are associated with artificial urinary sphincter implantation.

10 Treatment to improve bladder emptying

The efficiency of bladder emptying is dependent on the ability of the bladder to contract and the urethral sphincters to relax. Unfortunately, there has been only limited success when attempts have been made to improve bladder emptying in patients with NLUTD so that many patients are dependent on the use of either intermittent catheterisation or an indwelling catheter.

Distal urethral sphincterotomy has been used in the management of spinal cord injured men[184]. Division of the distal urethral sphincter of patients with detrusor sphincter dyssynergia can improve bladder emptying, although the patient is then reliant on a penile sheath system to contain the resulting incontinence. Electrical stimulation of spinal nerve roots has also been developed but is only applicable to patients with complete spinal cord lesions[185]. These surgical procedures are only used in specialist centres and their evaluation falls outside the scope of this guideline.

Alpha-blockers have an established role in managing bladder outflow obstruction in men with a normally innervated urinary tract [186]. Relaxation of the smooth muscle of the bladder neck and prostate is believed to be the primary mode of action of such drugs. However, in men with NLUTD, there is a different pathophysiological basis for bladder outflow obstruction. In patients with suprasacral spinal cord lesions, detrusor sphincter dyssynergia is commonly seen to impair bladder emptying. In such cases, it is the striated muscle of the distal urethral sphincter and pelvic floor which is obstructing the bladder outflow tract.

10.1 Alpha-blockers

10.1.1 What is the safety and efficacy of alpha-blockers compared with a) other alpha-blockers b) placebo/usual care for the treatment of incontinence due to neurological disease?

Clinical Methodological Introduction	
Population:	Patients with incontinence due to NLUTD
Intervention:	Alpha-blockers
Comparison:	• Other alpha-blockers • Placebo/Usual care
Outcomes:	• Quality of life • Frequency of voiding by day and night • Urgency • Symptoms relating to bladder emptying, for example poor urinary stream • Q-max (maximum flow rate) • Residual urine volume • Adverse events, including postural hypotension and unscheduled hospital admissions. • Treatment adherence

10.1.1.1 Clinical evidence

We searched for RCTs in adults and RCTs and observational studies in children comparing the effectiveness of alpha–blockers as an intervention compared with other alpha-blockers or placebo/usual care for improving incontinence in patients with neurological disease/injury .

For the adult population, three RCTs were included in the review [187]; [188]; [189]. For children and young people one observational study was included [190]. All of the studies were comparing alpha-blockers with usual care/placebo for improving urinary symptoms in neurological disease. The following table summarises the population, intervention, comparison and outcomes for each of the studies.

Table 99: Summary of studies included in the clinical evidence review

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
ABRAMS 2003[187]	Adults with neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury	Tamsulosin 0.4 N=88 0.8 mg N=83	Placebo (N=92)	4 weeks
O'RIORDAN 1995[188]	Men < 50 yrs with multiple sclerosis and symptoms of urinary tract dysfunction	Indoramin 20 mg twice daily N=9	Placebo (N=9)	4 weeks
PETERSEN 1989[189]	Adults with neurological conditions < 70 yrs with difficulty voiding and detrusor hyperreflexia	Prazosin 3 mg three times daily N=19	Placebo N=19	6 weeks
SCHULTE-BAUKLOH 2002[190]	Children with upper motor neurone lesions with detrusor hyperreflexia	Alfuzosin > 2 yrs 2.5 mg three times daily < 2 yrs 0.625 mg two or three times daily N=17	Before vs after treatment	3 weeks

Comparison of tamsulosin versus placebo

Adults – spinal cord injury

Table 100: Tamsulosin versus placebo - Clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Tamsulosin 0.4	placebo	Relative (95% CI)	Absolute	
Mean frequency of incontinence episodes/24 hrs (follow-up 4 weeks; Better indicated by lower values)										
Abrams[187]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	62 -0.3 (0.8)	60 -0.2 (0.8)	-	MD 0.1 lower (0.38 lower to 0.18 higher)	MODERATE
Mean frequency of urgency episodes/24 hrs (follow-up 4 weeks; Better indicated by lower values)										
Abrams[187]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	69 -0.2 (0.8)	65 -0.1 (1.6)	-	MD 0.1 lower (0.53 lower to 0.33 higher)	MODERATE
Urinary symptoms questionnaire - total subscale score (Better indicated by lower values)										
Abrams[187]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	82 -0.3 (4.5)	82 -0.8 (6.3)	-	MD 0.5 lower (1.18 lower to 2.18 higher)	MODERATE
Residual urine (follow-up 4 weeks; Better indicated by lower values)										
Abrams[187]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	41 -5.6 (124.9)	46 23.7 (92.9)	-	MD 29.3 lower (76.02 lower to 17.42 higher)	LOW

Any adverse events (follow-up 4 weeks)										
Abrams[187]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	31/86 (36%)	38/90 (42.2%)	RR 0.85 (0.59 to 1.24)	63 fewer per 1000 (from 173 fewer to 101 more)	LOW
Dizziness										
Abrams[187]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	1/86 (1.2%)	5/90 (5.6%)	RR 0.21 (0.02 to 1.76)	44 fewer per 1000 (from 54 fewer to 42 more)	VERY LOW
Discontinuations due to adverse events (follow-up 4 weeks)										
Abrams[187]	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	2/86 (2.3%)	4/90 (4.4%)	RR 0.52 (0.1 to 2.78)	21 fewer per 1000 (from 40 fewer to 79 more)	VERY LOW

[a] No details of randomisation or allocation concealment
[b] 95%CI crossed the minimally important difference (MID) for either benefit or harm
[c] 95%CI crosses the MID for benefit and harm

Comparison of indoramin versus placebo

Adults – multiple sclerosis

Table 101: Indoramin versus placebo - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Overall improvement										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	RCT	Indoramin N=9	Placebo N=8	No. of patients reporting improvement indoramin vs placebo 7/9 vs 3/8 RR 2.07 (95%CI0.79 to 5.42) Total symptom score (max 21 points) baseline vs follow-up indoramin 9.4 vs 7.8 (18% improvement) placebo 8.75 vs 7.75 (12% improvement)	S (i)	N	N	S (ii)	N	Low
Outcome: Maximum flow rates										
1 [A]	RCT	Indoramin N=9	Placebo N=8	No. of patients with improvement indoramin vs placebo 6/9 vs 2/8.RR 2.67 (0.74 to 9.65) 41% improvement vs 7.4% worsening; p<0.05	S (i)	N	N	S (iii)	N	Very Low
Outcome: Residual urine										
1 [A]	RCT	Indoramin N=9	Placebo N=8	Baseline vs follow-up ml indoramin 223 vs 166 (change 26%) placebo 162 vs 124 (change 24%)	S (i)	N	N	N (iv)	N	Moderate
Adverse events										
1 [A]	RCT	Indoramin N=9	Placebo N=8	Indoramin vs placebo 3/9 vs 1/8 RR 2.67 (95%CI 0.34 to 20.78)	S (i)	N	N	S (iii)	N	Very Low
Adverse events leading to withdrawal										
1 [A]	RCT	Indoramin N=9	Placebo N=9	Indoramin vs placebo 0/9 vs 1/9 RR 0.33 (95%CI 0.02 to 7.24)	S (i)	N	N	S (iii)	N	Very Low

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
S serious N none RR relative risk CI confidence interval (i) No details of randomisation or allocation concealment, assessor not blinded (ii) The 95%CI crossed the minimally important difference for benefit or harm (iii) The 95%CI crossed the MID for benefit and harm – downgraded two levels (iv) Imprecision could not be assessed [A] O'Riordan et al. (1995)[188]										

Comparison of prazosin versus placebo

Adults – detrusor hyperreflexia

Table 102: Prazosin versus placebo - Clinical study characteristics and clinical summary of findings

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Incontinence episodes										
1 [A]	RCT (Crossover)	Prazosin N=18	Placebo N=18	9 patients experienced an event Mean no. Prazosin vs placebo 2.6 vs 2.1	S (i)	N	N	N (ii)	N	Moderate
Outcome: Subjective assessment frequency of voiding and incontinence										

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 [A]	RCT (Crossover)	Prazosin N=18	Placebo N=18	No. preferring active treatment, Prazosin n=5 placebo n=1 and 12 reported no change	S (i)	N	N	N (ii)	N	Moderate
Outcome: Maximum flow										
1 [A]	RCT (Crossover)	Prazosin N=18	Placebo N=18	Treatment mean (SD) ml/sec prazosin vs placebo 8 (6.8) vs 7 (3.8); MD 1 (95%CI -1.21 to 3.21)	S (i)	N	N	S (iii)	N	Very Low
Outcome: Residual urine										
1 [A]	RCT (Crossover)	Prazosin N=18	Placebo N=18	Treatment mean (SD) ml/sec prazosin vs placebo 250 (219) vs 248 (168); MD 2 (95CI -77.05 to 81.05)	S (i)	N	N	S (iii)	N	Very Low
Adverse events (dizziness)										
1 [A]	RCT (Crossover)	Prazosin N=18	Placebo N=18	Prazosin vs placebo 7/18 vs 3/18 RR 2.33 (0.71 to 7.63)	S (i)	N	N	S (iii)	N	Very Low

S serious N none RR relative risk CI confidence interval

(i) Crossover trial, no details of randomisation, allocation concealment or blinding
(ii) Imprecision could not be assessed
(iii) The 95%CI crossed the minimally important difference for benefit and harm
[A] Petersen et al. (1989)[189]

Alfuzosin (before vs after treatment)

Children – upper motor neurone lesion

Table 103: Clinical study characteristics and clinical summary of findings – Alfuzosin before vs after treatment

No. of studies	Design	Treatment (n)	Control (n)	Results	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Incontinence episodes										
1 [A]	Non-comparative case series	Alfuzosin N=17	-	"There was no measurable change in continence"	S (i)	N	N	N (ii)	N	Very low
Outcome: Adverse events (side effects)										
1 [A]	Non-comparative case series	Alfuzosin N=17	-	3/17 "side effects were rare and not severe"	S (i)	N	N	N (ii)	N	Very low

S serious N none
(i) No comparator, before vs after study
(ii) Imprecision could not be assessed
[A] Schulte-Baukloh et al. (2002)[190]

10.1.1.2 Economic Evidence

No relevant economic evaluations comparing alpha-blockers with usual care were identified.

Unit costs are provided to give an indication of the cost of treatment.

Table 104: Unit costs of alpha-blockers included in the clinical review

Alpha-blockers	Dose	Pack size	Pack cost (£)	Pill cost (£)
Tamsulosin Hydrochloride	400mg	30	4.42	0.15
Indoramin	20mg	60	25.85	0.43
Prazosin	500ug	56	2.51	0.04
	1mg	56	3.23	0.06
	5mg	56	8.75	0.16
Alfuzosin Hydrochloride	2.5mg	60	10.39	0.17

10.1.1.3 Evidence Statements

Clinical Evidence Statements

Tamsulosin vs placebo

Adults – spinal cord injury

One study comprising 263 participants found there was no significant difference for tamsulosin compared with placebo for:

- Mean frequency of incontinence episodes/24 hrs (4 weeks)(moderate quality)
- Mean frequency of urgency episodes/ 24 hrs (4 weeks) (moderate quality)
- Urinary symptoms questionnaire (total subscale score) (4 weeks) (moderate quality)
- Residual urine (4 weeks) (low quality)
- Any adverse event (4 weeks) (low quality)
- Dizziness (4 weeks) (very low quality)
- Discontinuations due to an adverse event (4 weeks) (very low quality)

Indoramin vs placebo

Adults – multiple sclerosis

One study comprising 17 participants found there was no significant difference for indoramin compared with placebo for:

- Overall improvement (4 weeks) (low quality)
- maximum flow (4 weeks) (very low quality)
- adverse events (4 weeks) (very low quality)
- adverse events leading to withdrawal (4 weeks) (very low quality)

Evidence statements could not be produced for the following outcome of the study by O'Riordan

[188] as results were presented in a way that we could not estimate the size of the intervention effect:

- residual urine (very low quality)

Prazosin vs placebo

Adults – detrusor hyperreflexia

One study comprising 18 participants found there was no significant difference for prazosin compared with placebo for:

- maximum flow (6 weeks)(very low quality)
- residual urine [one study] (6 weeks) (very low quality)
- dizziness [one study](6 weeks) (very low quality)

Evidence statements could not be produced for the following outcome of the study by Petersen [189] as results were presented in a way that we could not estimate the size of the intervention effect

- Incontinence episodes
- Subjective assessment frequency of voiding and incontinence

Alfuzosin (before vs after treatment)

Children – upper motor neurone lesion

Evidence statements could not be produced for the following outcome of the study by as results were presented of the intervention effect in a way that meant we could not estimate the size of the intervention effect Schulte-Baukloh et al. [190]

- Incontinence episodes
- Adverse events

Economic evidence Statements

Due to the lack of efficacy of alpha-blockers in reducing incontinence and altering other outcomes, they are judged to be not cost effective compared to usual care.

10.1.2 Recommendations and links to evidence

Recommendations:	**ALPHA-BLOCKERS** **46. Do not offer alpha-blockers to people as a treatment for bladder emptying problems caused by neurological disease.**
Relative value placed on the outcomes considered	The GDG recognised that improvements in bladder emptying have the potential to improve quality of life by reducing problems such as increased urinary frequency; this would represent an important potential benefit. On the other hand, a patient is unlikely to consider an improved flow rate, in itself, as being of huge significance in terms of improvement in quality of life.
Quality of evidence	The GDG noted that there was limited data available for this question and that the quality of evidence was rated between moderate and very low. The studies emerging from the literature search had short term follow-up and lacked data on quality of life. The GDG discounted the improvement in flow rate reported by

	one paper as there was low confidence in the estimate of effect due to a small sample size.
Trade-off between clinical benefits and harms	There was no significant evidence of benefit associated with the drug interventions. Similarly the limited data available did not raise any safety concerns when alpha-blockers were used in patients with NLUTD.
Economic considerations	Due to the lack of efficacy of alpha-blockers in reducing lower urinary tract symptoms in patients with neurological disease, they are judged not to be cost-effective compared to usual care.
Other considerations	The GDG's view was that these drugs were only rarely prescribed for patients with NLUTD. The effect of these drugs is to relax the smooth muscle of the bladder neck and prostate. However, as noted by the GDG, there is a different pathophysiological basis for bladder outflow obstruction in men with NLUTD. The potential to cause postural hypotension in frailer patients should be considered.

11 Management with catheter valves

11.1 Catheter valves

11.1.1 What is the safety and efficacy of the catheter valve compared with urinary drainage bags in neurological disease?

Clinical Methodological Introduction	
Population:	Incontinence due to neurogenic lower urinary tract dysfunction (NLUTD)
Intervention:	Catheter valve
Comparison:	Urinary drainage bags
Outcomes:	No. of incontinence episodes per week Patient and carer perception of symptoms Quality of life Kidney function (hydronephrosis) Treatment adherence Adverse events (UTI, catheter blockage) Successful trial without a catheter

We searched for RCTs and observational studies comparing the effectiveness of catheter valves as interventions for improving outcomes for patients with neurological disease or injury. We looked for any RCTs or observational studies that compared the effectiveness of one or more of catheter valves with urinary drainage bags.

11.1.1.1 Clinical Evidence Review

No RCTs or observational studies were identified comparing catheter valves with urinary drainage bags for improving outcomes in patients with incontinence due to NLUTD.

11.1.1.2 Economic evidence

No relevant economic evaluations comparing catheter valves with urinary drainage bags were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 105: Unit Cost of catheter valves and urinary drainage bags

Item	Cost†	Source
Catheter valve	£2.23	NHS Drug Tariff 2011 [191]
Drainable Night Bag	£1.31	NHS Drug Tariff 2011 [191]

Non-Drainable Night Bag	£0.32	NHS Drug Tariff 2011 [191]
Leg bag (drainable)	£2.41	NHS Drug Tariff 2011 [191]
Valves		
Weekly cost with drainable night bag	£5.95	GDG assumption:
Annual cost with drainable night bag	**£309**	1x leg bag, 1 x valve + 1x drainable night bag
Weekly cost with non-drainable night bag	£6.88	GDG assumption:
Annual cost with non-drainable night bag	**£358**	1x leg bag, 1 x valve + 7x non drainable night bag
Drainage Bags		
Weekly cost with drainable night bag	3.73	GDG assumption:
Annual cost with drainable night bag	**193**	1x leg bag + 1x drainable night bag
Weekly cost with non-drainable night bag	£4.65	GDG assumption:
Annual cost with non-drainable night bag	£242	1x leg bag + 7x non drainable night bag

Economic considerations

Catheter valves and day use urinary drainage bags (**Table 105**) are similar in cost and both are used in current practice. However, when considered at the cost per annum, urinary drainage bags, used on their own, are the marginally cheaper intervention; this is due to the slight increase in cost associated with catheter valves. Extra costs for fitting the valves will have to be considered also, however this is not considered to be high and can be done by the patient or carer readily with minimal training.

11.1.1.3 Evidence statements

Clinical Evidence statement

No clinical evidence

Economic evidence statements

The costs of the interventions are similar. However there is no evidence of benefit of one intervention over the other in terms of reducing incontinence. However, taken as a whole it is very likely that the costs associated with the interventions will easily be offset by the benefits of incontinence reduction and the reduction in cost of incontinence aids.

If one intervention is shown to be associated with fewer infections, then it is likely that this intervention will be cost effective compared with the other.

11.1.2 Recommendations and links to evidence

Recommendations:	**MANAGEMENT WITH CATHETER VALVES** **47. In people for whom it is appropriate a catheter valve may be used as an alternative to a drainage bag.** **[This recommendation is from 'Infection: prevention and control of healthcare-associated infections in primary and community care' (NICE clinical guideline 139).]** **48. To ensure that a catheter valve is appropriate, take into consideration the person's preference, family member and carer support, manual dexterity, cognitive ability, and lower urinary tract function when offering a catheter valve as an alternative to continuous drainage into a bag.** **49. Consider the need for continuing upper urinary tract surveillance in people who have impaired bladder storage (for example, due to reduced bladder compliance).**
Relative value placed on the outcomes considered	The GDG recognised the high value placed on quality of life.
Economic considerations	The clinical review will inform which one should be used in which group of patients, and this is likely to lead to cost savings as clinicians will avoid recommending the wrong equipment for use and later switching to the other option. Using both options at the same time will also be avoided. Based on a simple cost analysis based on unit costs and GDG assumptions on the quantity of resources needed, catheter valves and urinary drainage bags have similar costs. As the clinical review has revealed that there is no difference in incontinence, the main issue to consider in terms of cost effectiveness is the risk of urinary tract infections and adherence (patient comfort). If one intervention is shown to be associated with fewer infections, then this will probably be cost effective, due to a reduction in longer term costs. The greater the comfort of the patient also will lead to better adherence and greater effectiveness of the treatment A fairly simple analysis of cost allows us to see that while there is very little difference between catheter valve and bag usage, using drainage bags rather than non drainable bags is cheaper. Whether they are more cost effective is dependent on the prevalence of infection and patient comfort.
Quality of evidence	There was no evidence of harm or benefit available to the GDG as no relevant studies were identified in the literature review. Recommendations on the use of catheter valves were made on the basis of the clinical experience of the GDG members.
Trade-off between clinical benefits and harms	In selected patients there may be significant quality of life benefits from the use of intermittent bladder drainage using a catheter valve rather than continuous drainage of urine into a bag but there is a risk of harm (in the

	form of incontinence, infection and renal damage) if catheter valves are used in patients whose bladders are not capable of storing urine at safe pressures. The GDG agreed that the recommendation from the Infection control guideline be incorporated.
Other considerations	The GDG noted that the use of catheter valves was dependent on the patient's cognitive ability, dexterity, or the availability of a carer to assist and these factors need to be considered when drawing up an individuals support plan. A valve may not be suitable for all patients, however the group agreed that a valve was often the option preferred by patients, because of convenience, the feeling of increased control over their bladder management and the relatively discreet nature of a valve as opposed to a leg bag.

12 Management with ileal conduit diversion

12.1 Ileal conduit diversion

The construction of an ileal conduit urinary diversion involves a major intra-abdominal surgical procedure. A segment of ileum is isolated, along with its blood supply, and intestinal continuity is restored by means of an ileo-ileal anastomosis. The ureters are divided in the region of the pelvic brim and the distal ends ligated. The proximal ends, carrying urine from the kidneys, are anastomosed to the proximal end of the ileal segment (which forms the ileal conduit) and the distal end of the conduit is brought through the abdominal wall, creating a stoma (urostomy).

An ileal conduit leaves the bladder defunctioned. Infection can develop within the bladder and lead to the formation of pus (pyocystis) which can cause an offensive urethral discharge and infection-related symptoms.

12.1.1 What is the efficacy of the ileal conduit diversion compared with usual care in neurological disease?

Clinical Methodological Introduction	
Population:	Children and adults with lower urinary tract symptoms (LUTS) resulting from neurological disease
Intervention:	Ileal conduit diversion surgery
Comparison:	Usual care; however no studies made these comparisons, and all compared findings before diversion with those after diversion
Outcomes:	The outcomes as per the protocol were: • Quality of life • Patient or carers' perception of symptoms • Adverse events, including urinary tract infections, renal complications, pyocystis, complications with the stoma (e.g. parastomal hernia) and unscheduled hospital admissions.

12.1.1.1 Clinical evidence review

We searched for observational studies evaluating the effectiveness of Ileal conduit diversion surgery for improving quality of life in people with neurogenic bladder problems. We looked for any observational studies that compared the effectiveness of Ileal conduit diversion surgery with usual care. However, no studies made this comparison, and all compared findings before surgery with those after surgery.

Eight observational studies (Chartier-Kastler 2002[192]; deLong 2011[193]; Flanigan 1975[194 195]; Kato 2002[196 197]; Moeller 1977[198]; Smith 1979[199]) were identified, evaluating the effects of Ileal conduit diversion surgery for improving quality of life in people with neurogenic bladder problems. The surgical procedures used were fairly homogenous across the studies. The outcomes addressed by these studies were quality of life and adverse events. The quality of the studies was uniformly low, as none of the studies used a comparison group, and therefore there were no means to reduce threats to internal validity. Table 1 summarises the population characteristics in each of the studies.

Table 106: Summary of studies included in the clinical evidence review

Study	Underlying pathology	Age range (yrs)	Follow up range (months)	Surgery details	Outcomes reported

Study	Underlying pathology	Age range (yrs)	Follow up range (months)	Surgery details	Outcomes reported
Chartier-Kastler 2002[192] (n=33)	Mostly spinal cord injury (SCI), with some multiple sclerosis and myelitis	Mean 40.6	12-240	Bricker's approach. 14 also had cystectomy	Quality of life/ patient satisfaction; adverse events.
Delong 2011[193]	Secondary progressive multiple sclerosis	not given	unclear, but possibly to 16 months	Ileal conduit	Adverse events
Flanigan[194] 1975 (n=58)	Myelodysplasia	0.4 - 13	12-156	Standard Bricker's used in earlier patients, and then an Albert-Persky method in later patients.	Adverse events
Guillotreau 2011 [195]	Majority multiple sclerosis	Mean 50.6 yrs	At least 6 mths after surgery	Ileal conduit and cystectomy	Quality of life
Kato 2002[196] (n=16)	SCI patients (all cervical)	19-70	24 - 204	Ileal conduit	Patient satisfaction; Adverse events
Legrand 2011 [197]	Multiple sclerosis	23-74	Follow-up performed at 6 mths then yearly	Bricker's approach	Quality of life
Moeller 1977[198] (n=31)	SCI	20-60	58	Bricker's approach.	Adverse events
Smith 1979[199] (n=46)	Myelomeningocele	1.5 – 19	12 - >180	Ileal conduit used for most but colonic conduits in three patients (sigmoid colon in 2 and transverse colon in one).	Adverse events

Quality of life and patient satisfaction

Two studies used validated quality of life measures to reported on mean score changes pre versus post surgery [195]; [197].

Guillotreau 2011 [195] reported on the Qualiveen and the SF-36. On the Qualiveen significant improvements pre versus post surgery were reported for 'limitations (related to urinary incontinence)' (before mean 1.55 (SD1.35) vs after 0.57 (0.64); p<0.001); 'constraints (related to urinary incontinence)' (2.64 (1.12) vs 2.12 (0.83); p=0.046) and the 'specific impact of urinary symptoms (1.79 (0.95) vs 1.29 (0.65); p=0.015). No significant differences were reported on the SF-36.

Legrand 2011 [197] reported on the Qualiveen. Significant improvements were reported for 'discomfort' (before mean 1.2 (SD 0.71) vs after 0.48 (0.48); p=0.01; 'feeling' (2.45 (1) vs 1.31 (0.98);

'overall quality of life' (2.1 (1.18) vs 1.16 (0.63); p=0.02 and 'health-related quality of life' (1.1 (0.31) vs 0.06 (0.61); p=0.03.

Quality of life outcomes were only partially reported by two studies (Chartier Kastler 2002[192]; Kato 2002[196]).

Chartier Kastler 2002[192] reported that 100% of patients were satisfied with their stomal appliances and cutaneous diversion after surgery. The mean (sd) satisfaction score given by patients was 9.1 (2.8)/10. This was on a visual analogue scale defined by a score of 0 denoting a worse situation than before, and 10 denoting a high level of satisfaction in terms of quality of life. However, this scale was not adequately described and there were no indications that it had been either validated or piloted.

Kato 2002[196] reported that "most patients were more satisfied with ... ileal conduit formation than with their previous management". No details of the methods by which these opinions were collected were given, other than that the patients' views were "canvassed a few months post-surgery". In addition, no details of the data collected were available.

Adverse events (post surgery)

A variety of adverse effects of the surgery were reported in the five studies (Chartier-Kastler 2002[192]; deLong 2011[193]; Flanigan 1975[194]; Kato 2002[196]; Moeller 1977[198]; Smith 1979[199]), and the most important ones are documented in the tables below, with the data below concerning patients affected at least once.

Of participants in studies where these adverse events were measured, death affected 5/84 (6%) adults and 0/104 (0%) children. Stomal stenosis or obstruction was observed in 38/104 (37%) children but was not measured in adults. Bladder stone formation was seen in 6/46 (13%) children and 9/42 (21%) adults. Stomal haemorrhage was seen in 8/58 (14%) children, but not measured in adults. Pyocystis was observed in 5/104 (5%) children and 12/46 (26%) adults. Pyelonephritis or UTIs affected 5/58 (9%) children and 6/64 (9%) adults. Table 2 outlines these results.

In addition, Flanighan 1975[194] noted that non-stomal complications were more frequent with the Bricker uretero-ileal anastomosis, compared to the Albert Persky method.

Table 2:Adverse effects

	Age group	Follow up (months)	Mortality related to surgery	Stomal stenosis/ obstructions	Uretero-ileal stenosis/ obstruction/leak	Stomal haemorrhage	Bladder Stone formation	Renal stones	Pyocysitis	Pyelonephritis or UTIs	Bowel obstruction	Renal insufficiency or hydronephrosis	Metabolic complications
Smith 1979[199] (n=46)	Children	12 - >180	0/46	2/46	2/46		6/46		1/46			1/46	2/46
Flanigan 1975[194] (n=58)	Children	12-156	0/58	36/58	6/58	8/58		3/58	4/58	5/58	1/58		
De Long 2011[193] (n=4)	Adults	unclear	1/4										
Kato 2002[196](n=16)	Adults	24 - 204	2/16				5/11		8/13	3/16			
Moeller 1977[198] (n=31)	Adults	58	2/31				4/31			2/31		2/31	
Chartier-Kastler 2002[192] (n=33)	Adults	12-240	0/33		1/33		1/33		4/33	4/33	0/33		

	Age group	Follow up (months)	Mortality related to surgery	Stomal stenosis/ obstructions	Uretero-ileal stenosis/ obstruction/leak	Stomal haemorrhage	Bladder Stone formation	Renal stones	Pyocysitis	Pyelonephritis or UTIs	Bowel obstruction	Renal insufficiency or hydronephrosis	Metabolic complications
Overall	**Children**	**12-180**	**0/104 (0%)**	**38/104 (37%)**	**8/104 (8%)**	**8/58 (14%)**	**6/46 (13%)**	**3/58 (5%)**	**5/104 (5%)**	**5/58 (9%)**	**1/58 (2%)**	**1/46 (2%)**	**2/46 (4%)**
Overall	**Adults**	**12-240**	**5/84 (6%)**	**-**	**1/33 (3%)**	**-**	**9/42 (21%)**	**-**	**12/46 (26%)**	**6/64 (9%)**	**0/33 (0%)**	**2/31 (6%)**	
Overall incidence	**All**	**12-240**	**5/188 (3%)**	**38/104 (37%)**	**9/137 (7%)**	**8/58 (14%)**	**15/88 (17%)**	**3/58 (5%)**	**17/150 (11%)**	**11/122 (9%)**	**1/91 (1%)**	**3/77 (4%)**	**2/46 (4%)**

12.1.1.2 Economic evidence

No relevant economic evaluations comparing ileal conduit diversion with other types of bladder neck procedures such as sling surgery or usual care were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 107: Unit Costs of urinary diversion and usual care

Item	Cost	Assumptions
Cost of ileal conduit diversion		
Ileal conduit diversion without Cystectomy	£6,112*	
Ileal conduit diversion with Cystectomy and Reconstruction with complications	£10,387*	
Ileal conduit diversion with Cystectomy and Reconstruction without complications	£5,015 *	
Initial cost (one-off)	**£7,269**	
Annual Cost of Bags	£492†	3x leg bag + 7x non drainable night bag per week**
Barrier Cream	£66†	Assuming 1 tub every 2 months (£11 per tub)**
District nurse	£372‡	1 hour per month (£31 per hour‡)
Annual cost after first year	**£930**	
Cost of Usual Care		
Annual cost of Pads	£400†	5 per day**
Annual Cost of intermittent catheters	£1,460†	5 per day**
Annual Cost of Usual Care	**£1,860**	

*Source: *NHS Reference Costs 2009-10, †NHS Drug Tariff, ** GDG Assumption, ‡ PSSRU 2010*

Economic considerations

Ileal Conduit Diversion is currently offered to a small percentage of "end-stage" patients where other treatments such as long-term intermittent or indwelling catheterisation have failed.

While the initial cost is high, the follow on costs of stoma care and drainage bags are smaller compared to the annual cost of usual care. It is likely that the costs of urinary diversion will be offset by the costs of incontinence care in the long term. The quality of life gain from being dry will also impact on the cost-effectiveness of this intervention.

12.1.1.3 Evidence statements

Clinical evidence statements

2 Observational studies comprising 49 participants suggested that ileal conduit diversion surgery might improve patient satisfaction (at least six months) (very low quality).

5 Observational studies comprising 184 participants suggested that the main adverse effects of ileal conduit diversion ileal conduit diversion are stomal obstruction or stenosis, bladder stone formation, stomal haemorrhage, pyocystis, and pyelonephritis or UTIs (12 to 204 months) (very low quality).

Economic evidence statements

Although the initial cost of ileal conduit diversion is high, the annual follow-on costs of stoma care and drainage bags are likely to be equivalent to the costs associated with containment products and catheters.

The quality of life gain from being dry will also impact the cost-effectiveness of this intervention.

12.1.2 Recommendations and links to evidence

Recommendation:	**MANAGEMENT WITH ILEAL CONDUIT DIVERSION** **50. For people with neurogenic lower urinary tract dysfunction who have intractable, major problems with urinary tract management, such as incontinence or renal deterioration:** • **consider ileal conduit diversion (urostomy) *and*** • **discuss with the person the option of simultaneous cystectomy as prophylaxis against pyocystis.**
Relative value placed on the outcomes considered	The GDG recognised that a high value is attached by the patient to both continence and quality of life.
Quality of evidence	No studies were found that compared ileal conduit diversion with usual care. All the studies included in the review compared before and after surgery. The evidence consisted of observational studies with no comparison group therefore the data is at high risk of bias. There was low confidence in the estimate of effect. Very low quality data on outcomes from the 8 studies weakly suggest that ileal conduit diversion may improve quality of life and patient satisfaction. Two studies reported using the validated Qualiveen and SF-36 scores. The most prominent adverse events reported were stomal obstruction or stenosis, bladder stone formation, stomal haemorrhage, pyocystitis, and pyelonephritis or urinary tract infections. The study populations were largely restricted to spina bifida and spinal injury.
Trade-off between clinical benefits and harms	The GDG recognised that the risk of serious morbidity and mortality associated with ileal conduit diversion, particularly in patients with advanced neurological disease, is offset by potential gains in general well being, continence and overall quality of life. The intervention would normally be considered when alternative less invasive options had failed or were felt to be likely to be unsuccessful. The evidence review identified that there is a risk of infection and stone formation in the defunctioned bladder that may, in some circumstances, justify a cystectomy being carried out at the time of urinary diversion.
Economic considerations	Although the initial cost of ileal conduit diversion is high, the follow-on annual costs of stoma care and drainage bags are likely to be equivalent to the costs associated with the use of containment products and catheters. It is likely that the costs of urinary diversion will be offset by quality of life gains and the costs of unsatisfactory incontinence care in the long term.
Other considerations	Despite the paucity of high-quality, supportive published data, the GDG felt able to make a recommendation on the basis of their combined clinical experience. They

	recognised that there is a small population of patients with NLUTD who have devastating LUTS which cannot be controlled by less aggressive interventions. There was a consensus view that to offer such patients the option of an ileal conduit diversion is appropriate. This recommendation was made with a clear understanding that ileal conduit urinary diversion can itself be associated with a number of serious complications. The GDG considered that the patient undergoing ileal conduit diversion should receive preoperative and long-term postoperative support from stoma care specialists. Long-term upper urinary tract surveillance was also felt to be appropriate in patients with a good general prognosis.

13 Treatment to prevent urinary tract infection

Damage to the neurological control system of the LUT leads to a breakdown of the normal micturition cycle so that the protective effect of low pressure storage of sterile urine and complete bladder emptying is disrupted. The patient with neurogenic lower urinary tract dysfunction (NLUTD is at increased risk of urinary tract infection (UTI) as a result of a variety of factors which include incomplete bladder emptying, vesico-ureteric reflux and the use of catheters (Esclarin De Ruz et al., 2000, Journal of Urology, 164, 1285-9).

For many patients with NLUTD, a UTI will be associated with a few days of ill health and urinary symptoms that might include pain, increased frequency and worsening incontinence. However, recurrent UTIs are frequently seen in this population of patients and can impact greatly on quality of life and in MS may lead to neurological deterioration. Even more significant is the risk of serious complications from UTI. Renal damage can be a further complication particularly in those with detrusor overactivity, detrusor sphincter dyssynergia and vesico-ureteric reflux. Such renal scarring can be seen in all age groups of patients with neurogenic LUT dysfunction but is a particular concern in infants and children [200]. Renal injury can also be seen in association with infection-related stones.

The goal of reducing both the frequency and severity of UTIs can be achieved in some patients by general measures such as increasing fluid intake and attention to hygiene in relation to urinary tract management. Investigations may demonstrate treatable causes for repeated UTIs such as the presence of urinary tract stones or incomplete bladder emptying.

The use of prophylactic long-term antibiotic administration against UTI in those with neurogenic LUT dysfunction has been widely used in the past. However, questions have now been raised about the efficacy of such regimes and furthermore, the emergence of multi-drug resistant bacteria is becoming a major world-wide health concern; reducing non-essential antibiotic usage is a key strategy in combating this threat. It is therefore important to reassess the place of antibiotic prophylaxis regimes in the management of neurogenic LUT dysfunction.

13.1 Antibiotics

13.1.1 Do prophylactic antibiotics compared with a) no treatment b) other antibiotic reduce the risk of symptomatic urinary tract infections?

Clinical Methodological Introduction	
Population:	Neurological disease
Intervention:	Prophylactic antibiotics
Comparison:	Other antibiotic (strategies) No treatment
Outcomes:	Symptomatic urinary tract infections (UTIs) Adverse events

We searched for RCTs evaluating the effectiveness of prophylactic antibiotics for prevention of symptomatic urinary tract infections (UTI) in patients with neurological disease or injury. We looked for any RCT studies that compared the effectiveness of prophylactic antibiotics with other antibiotics or no treatment.

13.1.1.1 Clinical Evidence Review

Thirteen RCTs were found that dealt with prophylaxis of symptomatic UTIs in neurological patients. Three were cross-over trials (Biering-Sorensen 1994[201], Duffy 1982[202], Schlager, 1998[203]), and the rest were parallel trials.

Three studies compared continuation of prophylaxis to discontinuation (Clarke 2005[204], Sandock 1995[205], Zegers 2011[206]), whilst the rest compared new prophylaxis with placebo or no treatment. No studies made comparisons with other antibiotics.

Studies were primarily stratified into those involving adults or children. There were four studies in children (Johnson 1994[207], Clarke 2005[204], Schlager, 1998[203] Zegers 2011[206]), all of which were clinically homogenous in terms of all addressing prophylaxis of UTIs in congenital neurological conditions. However there was methodological heterogeneity, in that Clarke 2005[204] and Zegers 2011[206] looked at continuation of prophylaxis to discontinuation, whilst the other two studies looked at new prophylaxis versus no prophylaxis. Analysis was therefore carried out according to those categories.

In contrast, the nine adult studies were clinically heterogeneous. Six studies dealt with prophylaxis of UTIs in new spinal cord injury (SCI) cases (Anderson 1980[208], Gribble 1993[209], Lindan 1984[210], Maynard 1984[211], Mohler 1987[212] ,Sandock 1995[205]). Furthermore, within these six studies, there was methodological heterogeneity, as one (Sandock 1995[205]) looked at continuation of prophylaxis to discontinuation, while the rest looked at new prophylaxis compared to no prophylaxis.

The other three adult studies dealt with other clinical categories, although all looked at new prophylaxis compared to no prophylaxis. They were:

- Darouiche 1994 ([213]) which involved prophylaxis before urodynamics,
- Biering-Sorensen 1994[201] which involved prophylaxis for established neurological cases with a history of recurrent UTIs, and
- Duffy 1982[202] which dealt with prophylaxis for neurogenic bladder clinic patients.

Analyses were therefore separated for these main categories. This information is summarised in table 1.

Table 108: Characteristics of the included studies [IC=Intermittent catheterisation. SCI=Spinal Cord Injury]

Study	Patient group	Reason for prophylaxis	Bladder management strategy	Prophylactic antibiotic	Comparator	Follow up	Outcomes
Clarke 2005[204]	Spina bifida; children	Congenital condition	IC	Continuation of un-named prophylactic antibiotic	Discontinuation of un-named prophylactic antibiotic	4 months	Symptomatic UTI
Zegers 2011[206]	Spina bifida; children	Congenital condition	IC	Continuation of un-named prophylactic antibiotic	Discontinuation of un-named prophylactic antibiotic	18 months	Symptomatic UTI
Johnson 1994[207]	Meningocele; children	Congenital condition	IC	Nitrofurantoin 25-50mg/day depending on body mass	Placebo	6 months	Symptomatic UTI
Schlager 1998[203]	Undefined "neurogenic bladder"; children	Congenital condition	IC	Nitrofurantoin 25-50mg/day depending on body mass	Placebo [Cross-over]	11 months	Symptomatic UTI Adverse events
Anderson 1980[208]	SCI; adults	New SCI	IC	Nitrofurantoin 100mg/day	Sterile IC only	Unclear	Symptomatic UTI
Gribble 1993[209]	SCI; adult	New SCI	IC	Trimethoprim-sulphamethoxazole 240mg/day (1:5 Ratio)	Placebo	4 months	Symptomatic UTI Adverse events
Lindan 1984[210]	SCI; adults	New SCI	External catheter with reflex voiding, IC and Foley catheterisation.	Nitrofurantoin 100mg/day	No treatment (no placebo)	3 months	Symptomatic UTI Adverse events
Maynard 1984[211]	SCI; adults	New SCI	IC	Trimethoprim-	No treatment	1.5 months	Symptomatic UTI

Study	Patient group	Reason for prophylaxis	Bladder management strategy	Prophylactic antibiotic	Comparator	Follow up	Outcomes
				sulphamethoxazole 480mg/day	(no placebo)		Adverse events
Mohler 1987[212]	SCI; adults	New SCI	IC	Trimethoprim-sulphamethoxazole 960mg/day	Placebo	2 months	Symptomatic UTI
Sandock 1995[205]	SCI; adults	New SCI	IC, reflex voiding, indwelling catheters	Continuation of Trimethoprim-sulphamethoxazole 480mg/day	Discontinuation of prophylaxis	7 months	Symptomatic UTI Adverse events
Darouiche 1994[213]	SCI; adults	Prior to urodynamic testing	Unclear	Ciprofloxacin 1g/day	Placebo	18 months	Symptomatic UTI Adverse events
Biering-Sorenson 1994[201]	SCI; adults	Recurrent UTIs in mostly long-standing SCI patients.	Mixed – abdominal pressure, suprapubic tapping and/or IC.	Ciprofloxacin 100mg/day	Placebo [Cross-over]	12 months	Symptomatic UTI Adverse events
Duffy 1982[202]	Undefined – “Neurogenic bladder”; adults	Neurogenic bladder clinic patients	IC	Nitrofurantoin 200mg/day	Placebo [Cross-over]	6 months	Adverse events

Comparison of prophylactic antibiotics to no prophylactic antibiotics

Outcomes appropriate for GRADE

Table2. GRADE profile for the comparison of prophylactic antibiotics to no prophylactic antibiotics.

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Antibiotic prophylaxis	control	Relative (95% CI)	Absolute	
Incidence of symptomatic UTIs for children - new prophylaxis vs no prophylaxis										
2 Johnson 1994,Schlager 1998	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	12/71 (16.9%)	13/71 (18.3%)	RR 0.92 (0.52 to 1.62)	15 fewer per 1000 (from 88 fewer to 114 more)	VERY LOW
Incidence of symptomatic UTIs for children - continue prophylaxis vs discontinue prophylaxis										
2 Clarke 2005 Zegers2011	randomised trials	serious[1]	very serious inconsistency[3]	no serious indirectness	very serious[2]	22/119 (18.5%)	7/110 (6.4%)	Random effects RR 1.69 (0.19 to 15.17)	44 more per 1000 (from 52 fewer to 902 more)	VERY LOW
Incidence of symptomatic UTIs for Adults with new SCI (new prophylaxis)										
3 Anderson 1980 ,Lindan 1984 Gribble 1993	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	6/112 (5.4%)	20/105 (19%)	RR 0.3 (0.13 to 0.68)	133 fewer per 1000 (from 61 fewer to 166 fewer)	MODERATE

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Antibiotic prophylaxis	control	Relative (95% CI)	Absolute	
Incidence of symptomatic UTIs for Adults prior to urological investigations										
1 Darouiche 1994	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	0/18 (0%)	3/22 (13.6%)	RR 0.17 (0.01 to 3.14)	113 fewer per 1000 (from 135 fewer to 292 more)	VERY LOW
Adverse events – resistance - for adults with new SCI (new prophylaxis)										
1 Gribble 1993	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	47/66 (71.2%)	45/60 (75%)	RR 0.95 (0.77 to 1.17)	38 fewer per 1000 (from 173 fewer to 127 more)	MODERATE
Adverse events - GI disturbance - for adults with new SCI (new prophylaxis)										
1 Gribble 1993	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	1/66 (1.5%)	0/66 (0%)	Peto OR: 7.39 (0.15 – 372.38)	20 more per 1000 (from 30 fewer to 60 more)	VERY LOW
Adverse events - skin or soft tissue infection - for adults with new SCI (new prophylaxis)										
1 Gribble 1993	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	15/66 (22.7%)	20/60 (33.3%)	RR 0.68 (0.39 to 1.21)	107 fewer per 1000 (from 203 fewer to 70 more)	LOW
Adverse events - Pseudomonas colonisation - for adults with new SCI (new prophylaxis)										
1 Lindan 1984	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	23/31 (74.2%)	17/31 (54.8%)	RR 1.35 (0.92 to 1.98)	192 more per 1000 (from 44 fewer to 537 more)	VERY LOW
Adverse events - skin rash - for adults with new SCI (new prophylaxis)										
1 Gribble 1993	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	2/66 (3%)	1/60 (1.7%)	RR 1.82 (0.17 to 19.54)	14 more per 1000 (from 14 fewer to 309 more)	VERY LOW

[1] The studies were downgraded for a lack of allocation concealment, blinding or intention to treat. A single omission led to a grading of serious limitation, and an omission of two or more led to a grading of very serious limitations.

[2] If the 95% CIs crossed either the 1.25 or 0.75 default MIDs then imprecision was graded as serious. If the 95% CIs crossed both the 1.25 and 0.75 default MIDs then imprecision was graded as very serious.

[3]The I squared was >75%, indicating serious inconsistency. A random effects model was applied. No sub-grouping was attempted as there were only two studies, and so any strategy of sub-grouping would inevitably lead to elimination of heterogeneity, thus failing to indicate the true source of heterogeneity.

Narrative summary (for outcomes that are not appropriate for GRADE due to incomplete outcome reporting)

Incidence of symptomatic UTI

Adults- new SCI cases (new prophylaxis)

Maynard 1984[211] presented data on the episodes of symptomatic UTI in a parallel group study. They reported one episode of symptomatic UTI in the prophylaxis group, and 7 in the control group.

Mohler 1987[212] reported the infection rate of symptomatic UTIs arising in the prophylaxis and placebo groups. The prophylaxis group had 1.11 infections/100 days at risk, while the placebo group had 1.86 infections/100 days at risk.

Adults- new SCI cases (continuation versus discontinuation)

In a continuation versus non-continuation study, Sandock 1995[205] reported the mean number of symptomatic UTIs per week per person, with 0.043 in the group continuing with prophylaxis and 0.035 in the discontinuation group. The difference was reported as non-significant.

Adults – established neurological cases with recurrent UTIs

Biering –Sorensen 1994[201] measured the episodes of symptomatic UTI in their prophylaxis and placebo groups over the 12 months of the study, and reported 5 episodes in the Ciproflaxin prophylaxis group compared to 59 in the placebo group. This difference was reported as highly statistically significant ($p<0.00005$).

Adverse events

Children – new prophylaxis v no prophylaxis

Schlager 1998[203] observed that carriage of klebsiella/pseudomonas lasted significantly longer in the antibiotic group, lasting for a total of 140 subject-weeks out of a possible total of 330 in the antibiotic group and 43 subject-weeks out of a possible total of 330 in the control group.

Adults- new SCI cases (continuation versus discontinuation)

In a continuation versus non continuation study, Sandock 1995[205] reported the percentage of cultures resistant to trimethoprim-sulphamethoxazole as 42.5% in the prophylaxis group and 37.5% in the discontinuation group. This difference was reported as non-significant.

Adults – established neurological cases with recurrent UTIs

Biering –Sorensen 1994[201] measured the number of episodes of both antibiotic-resistant and antibiotic-sensitive infection (>10^5 pathogens/ml) of 22 different types of bacteria in the ciprofloxacin and placebo groups. Overall, the ciprofloxacin group had 19 episodes of resistant infection compared to 17 episodes of sensitive infection, whilst the placebo group had 15 episodes of

resistant infection compared to 94 episodes of sensitive infection. No statistical analysis was performed. Although the ratio of resistant to sensitive episodes was far greater in the ciprofloxacin group, the actual number of resistant episodes was similar across the groups.

Adults - neurogenic bladder clinic patients

Duffy 1982[202] reported on the numbers of episodes of bacterial resistance (in patients who had bacteriuria) to four separate classes of antibiotics. No significant differences between groups were reported. The results, which are expressed as a proportion of those with bacteriuria, are summarised in Table 3.

Table 109: Bacterial resistances as reported by Duffy 1982

	Nitrofurantoin	placebo
Resistant cultures* to nitrofurantoin (resistant/(resistant+sensitive))	2/4	5/21
Resistant cultures* to TMP/SMX (resistant/(resistant+sensitive))	2/4	4/22
Resistant cultures* to carbenicillin (resistant/(resistant+sensitive))	1/4	4/21
Resistant cultures* to aminoglycosides (resistant/resistant+sensitive)	0/4	0/21

13.1.1.2 Economic evidence

Literature review

No relevant economic evaluations comparing prophylactic antibiotics with usual care or no prophylactic antibiotics were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 110: Unit costs

Prophylactic antibiotic	dose	packaged dose	pack cost (BNF)	pack size	unit cost	annual cost (max if range)
Ciprofloxacin	100mg/day	100mg	£1.42	6	£0.24	£86
	1g/day	500mg	£1.22	20	£0.12	£45
Nitrofurantoin	25-50mg/day depending on body mass	50mg	£1.86	28	£0.07	£24
	100mg/day	100mg	£4.43	28	£0.16	£58
	200mg/day	100mg	£4.43	28	£0.16	£58
Trimethoprim-sulphamethoxazole	240mg/day	480 mg	£18.99	28	£0.34	£124
	480mg/day	480 mg	£18.99	28	£0.68	£248
In hospital cost of UTI					£489	
GP appointment					£32	

Source: BNF 61, NHS reference costs 2009-10

13.1.1.3 Evidence Statements

Clinical Evidence Statement

Comparison between prophylactic antibiotics to no prophylactic antibiotics

Incidence of symptomatic UTIs

Children – new prophylaxis v no prophylaxis

2 studies comprising 142 participants (6 to 11 months) found that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the incidence of symptomatic UTIs (very low quality)

Children – continuation v no continuation

2 studies comprising 229 participants (4 to 18 months) found that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the incidence of symptomatic UTIs (very low quality)

Adults - new SCI cases

3 studies comprising 217 participants (3 to 4 months) found that prophylactic antibiotics led to a statistically significant reduction in incidences of symptomatic UTIs compared to no prophylaxis (moderate quality)

Adults - prior to urodynamic testing

1 study comprising 40 participants (18 months) found that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the incidence of symptomatic UTIs (very low quality)

Adverse events- resistance

Adults - new SCI cases

1 study comprising 126 (4 months) participants found that that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the adverse event of greater bacterial resistance (moderate quality).

Adverse events- GI disturbance

Adults - new SCI cases

1 study comprising 132 participants (4 months) found that that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the adverse event of GI disturbance (very low quality).

Adverse events- skin or soft tissue infection

Adults - new SCI cases

1 study comprising 126 participants (4 months) found that that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the adverse event of skin or soft tissue infection, although there was a weak trend (p=0.19) towards a benefit for prophylaxis (low quality).

Adverse events- pseudomonas colonisation

Adults - new SCI cases

1 study comprising 62 participants (3 months) found that that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the adverse event of pseudomonas colonisation(very low quality).

Adverse events- skin rash

Adults - new SCI cases

1 study comprising 126 participants (4 months) found that that there was no statistically significant difference between prophylactic antibiotics and no prophylactic antibiotics for the adverse event of skin rash (very low quality).

i. Other outcomes for which evidence statements could not be produced

Evidence statements could not be produced for the following outcomes of the study by Biering –Sorensen 1994[201] as results were presented in a way that meant we could not estimate the size of the intervention effect :

- Incidence of symptomatic UTIs
- Resistance

Evidence statements could not be produced for the following outcomes of the study by Sandock 1995[205] as results were presented in a way that meant we could not estimate the size of the intervention effect :

- Incidence of symptomatic UTIs
- Pseudomonas colonisation

Evidence statements could not be produced for the following outcomes of the study by Maynard 1984[211] as results were presented in a way that meant we could not estimate the size of the intervention effect :

- Incidence of symptomatic UTIs

Evidence statements could not be produced for the following outcomes of the study by Mohler 1987[212] as results were presented in a way that meant we could not estimate the size of the intervention effect :

- Incidence of symptomatic UTIs

Evidence statements could not be produced for the following outcomes of the study by Duffy 1982[202] as results were presented in a way that meant we could not estimate the size of the intervention effect :

- Resistance

Economic evidence statements

- If effective, prophylactic antibiotics will be either cost saving or close to cost neutral and if they are currently over prescribed, then any reduction in use will be also be cost saving.

13.1.2 Recommendations and links to evidence

Recommendations:	**<u>TREATMENT TO PREVENT URINARY TRACT INFECTION</u>** **51. Do not routinely use antibiotic prophylaxis for urinary tract infections in people with neurogenic lower urinary tract dysfunction.** **52. Consider antibiotic prophylaxis for people who have a recent history of frequent or severe urinary tract infections.** **53. Before prescribing antibiotic prophylaxis for urinary tract infection:** • **investigate the urinary tract for an underlying treatable cause (such as urinary tract stones or incomplete bladder emptying)** • **take into account and discuss with the person the risks and benefits of prophylaxis** • **refer to local protocols approved by a microbiologist or discuss suitable regimens with a microbiologist.** **54. Ensure that the need for ongoing prophylaxis in all people who are receiving antibiotic prophylaxis is regularly reviewed.** **55. When changing catheters in patients with a long-term indwelling urinary catheter:** • **do not offer antibiotic prophylaxis routinely** • **consider antibiotic prophylaxis[n] for patients who:** **-have a history of symptomatic urinary tract infection after catheter change *or*** **-experience trauma[o] during catheterisation.** **[This recommendation is from 'Infection: prevention and control of healthcare-associated infections in primary and community care' (NICE clinical guideline 139).]**
Relative value placed on the outcomes	Symptomatic urinary tract infections are a major clinical problem both in terms of the impact of symptoms on the patient and, in some cases, the risk of progression to

[n] At the time of publication (August 2012), no antibiotics had a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's 'Good practice in prescribing medicines – guidance for doctors' for further information.

[o] The GDG for 'Infection: prevention and control of healthcare-associated infections in primary and community care' defined trauma as frank haematuria after catheterisation or two or more attempts of catheterisation.

considered	severe sepsis The GDG recognised the world-wide concerns that exist in relation to the increasing problem of bacterial antibiotic resistance. This issue necessitates the need for balancing the potential for benefit from antibiotic use in the individual patient with the requirement for adherence with the public health strategy to control the spread of antibiotic-resistant organisms.
Quality of evidence	The evidence was assessed to be moderate, low or very low quality. The studies that addressed the question were carried out before antibiotic resistance became a critical issue. The lack of recent high quality studies on this issue was felt to be a major concern. There was a notable absence of studies looking at the use of prophylaxis in high-risk patient groups, such as those with frequent urinary tract infections. In children, the four studies that were included in the evidence review all involved patients with congenital neurological conditions. Three studies were prone to bias due to limitations in their design but Zegers was of higher quality[206]. The nine studies that were included in the review and looked at an adult population were graded between moderate and very low in quality. They found that, for adults with new spinal cord injuries, prophylactic antibiotics led to a reduction in the incidence of symptomatic UTIs. This conclusion was based on a meta-analysis graded as moderate in quality for these outcomes, but it was noted that some studies which were not included in the meta-analysis did not reach a similar conclusion.
Trade-off between clinical benefits and harms	For individual patients the reduction in the frequency of symptomatic urinary tract infections can be a major benefit. In some cases urinary tract infection can be life threatening and any reduction in such episodes will be of major importance. For the large majority of patients the use of antibiotic prophylaxis is a benign intervention that is not associated with troublesome complications. However, the widespread use of antibiotics is known to be associated with the development of antibiotic resistance which is a risk both to individual patients and to the wider population. It is also recognised that the use of prophylactic antibiotics can be associated with serious complications. For example Nitrofurantoin use can be associated with the development of pulmonary, neurological and hepatic disease. The GDG agreed from the limited evidence presented, and their own clinical experience, prophylactic antibiotics should not be routinely prescribed. They also agreed that frequent urinary tract infections could have a significant impact on the quality of life for a patient, and acknowledged the associated risks of serious complications, such as renal damage, that may warrant the use of this treatment in some circumstances.
Economic considerations	The GDG was of the opinion that there is currently an over use in the frequency of the prescription of antibiotics for the prophylaxis of UTIs in patients with neurogenic LUT dysfunction. The clinical evidence shows that there is no benefit to prescribing prophylactic antibiotics routinely. However, this evidence is highly uncertain. If antibiotics were indeed effective, perhaps in the longer term, then the low cost of prophylactic antibiotics compared with the relatively high cost of a hospital admitted UTI is probably favourable. The cost of a normal course of antibiotics and the cost of a doctor's appointment for the treatment of a UTI is also similar to the price of prophylactic antibiotics. This means that if effective, they will be cost saving or at least cost neutral. If they are currently over prescribed then, any reduction in use will be cost saving.
Other considerations	The GDG recognised that many patients with NLUTD will have permanent urinary tract colonisation with bacteria and that asymptomatic bacteriuria should not, in general, be treated. Furthermore, in some cases, it can be difficult to determine whether an active infection is present because symptoms are not always directly attributable to the urinary tract; a judgement may have to be made as to whether non-specific symptoms are present as a result of UTI.

	The difficulty in diagnosing UTI is compounded by the problems that are associated with the laboratory interpretation of urine samples in some patients with NLUTD. For example, the use of intermittent or indwelling catheters can lead to the presence of bacteruria and pyuria which might be of no clinical significance. These difficulties not only create problems in clinical practice but present challenges to those who are conducting research in this field. The importance of providing the microbiology department with correctly taken samples and appropriate clinical information was emphasised by the GDG. The GDG recognised the importance of avoiding inappropriately prolonged antibiotic prophylaxis. There was low quality evidence in children to suggest that discontinuing treatment may be beneficial rather than harmful. Long term prophylactic antibiotics may promote antibiotic resistance.

13.1.3 Research recommendations

Treatment to prevent urinary infection

4. **In people with neurogenic lower urinary tract dysfunction, which management strategies (including the use of prophylactic antibiotics and various invasive and non-invasive techniques to aid bladder drainage) reduce the risk of symptomatic urinary tract infections?**

- **Why this is important**

  Recurrent urinary tract infections in people with neurogenic bladder dysfunction are a cause of considerable morbidity. Urinary tract infections may exacerbate incontinence, cause symptoms of malaise and may progress to involve the upper urinary tract with possible loss of renal function. In the population with neurological diseases such as multiple sclerosis, Parkinson's disease and dementia, the rise in temperature with urinary tract infections can cause deterioration in neurological function and even a relapse of multiple sclerosis. There are therefore numerous reasons why people with neurogenic lower urinary tract dysfunction should avoid urinary tract infections.

  The causes for the high prevalence of urinary tract infections in such people include loss of physiological bladder function and high intravesical pressures. Intermittent or permanent catheterisation inevitably exacerbate the problem, but incomplete bladder emptying is also a predisposing factor for urinary tract infections.

  Research in this area is faced with methodological difficulties, not least because it may be difficult to distinguish between bladder colonisation (asymptomatic bacteriuria) and true infection.

  In view of the considerable clinical burden of urinary tract infections and the global problem of antibiotic resistance, it is important to establish whether or not any infection prevention strategies, including patient training or the provision of information relating to prophylactic antibiotics are effective in reducing symptomatic urinary tract infections.

14 Monitoring and surveillance protocols

Patients with neurogenic lower urinary tract dysfunction (NLUTD) are known to be at high risk of suffering from urinary tract symptoms and complications. For some conditions, such as spina bifida and spinal cord injury, there is a risk of silent renal deterioration due to the development of hydronephrosis or the formation or renal stones. Furthermore, some patients with NLUTD will have progressive neurological conditions which will be expected to have an increasing adverse impact on LUT function. The effect of ageing on a damaged LUT will often be greater than its effect on the normally innervated LUT.

For all these reasons, there is an argument to be made for offering patients with NLUTD long-term monitoring of their urinary tract. However, as with any surveillance programme, there has to be a balance struck between benefits accrued and the risks, costs and inconvenience that are attached to surveillance. There are inherent difficulties in measuring benefit because it can be multi-faceted; for example, regular follow up has the potential to protect renal function, reduce the frequency and severity of urinary tract infections, reduce troublesome symptoms by providing regular advice and provide psychological support. On the other hand, offering long-term follow up to large groups of patients is expensive in terms of clinical, patient and carer time and investigation costs. Investigations may also have risks from radiation exposure or, in the case of invasive tests, discomfort and infection; some patients will also find follow up processes psychologically stressful.

Life-long renal surveillance is currently in use in some groups of patients with neurological disease such as spinal cord injury and spinal dysraphisms (including spina bifida). There is a need to define whether all such patients will benefit from follow up and whether patients with other neurological conditions might also gain from long-term monitoring.

14.1 Monitoring and surveillance protocols

14.1.1 Does monitoring or do surveillance protocols improve patient outcomes?

Clinical Methodological Introduction	
Population:	• Spinal cord injury • Multiple sclerosis • Spinal dysraphism including Spina bifida • Anorectal malformations
Intervention:	Monitoring and surveillance protocols • Ultrasound • Renography • intravenous urograms • abdominal x-rays • urodynamics • blood tests • blood pressure
Comparison:	na
Outcomes:	• Quality of life • Kidney function • Renal impairment (hydronephrosis, urinary tract stones, urinary tract infection, malignancy (bladder cancer) • Unplanned hospital admissions

14.1.1.1 Clinical evidence review

We searched for observational studies reporting on monitoring and surveillance protocols for the management of incontinence in patients with spinal cord injury, multiple sclerosis, spina bifida or anorectal malformations.

17 observational studies [214]; [215]; [216]; [217]; [218]; [219]; [220]; [221]; [222]; [223]; [224]; [225]; [226]; [227]; [228]; [229]; [230]were identified that reported on monitoring on surveillance protocols for the management incontinence in patients with spinal cord injury, multiple sclerosis, spina bifida or anorectal malformations. Evidence was found for creatinine, ultrasound, cystoscopy and renal scintigraphic scan. All of the studies were in adults except for the study in patients with anorectal malformations [224]. Table 1 summarises the population, intervention, comparison and length of follow up for each of the studies.

Table 1: Summary of studies included in the clinical evidence review

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
Bodner 1990 [214]	Asymptomatic patients with spinal cord injury	Standard routine radiology imaging study (excretory urography, computerised tomography (CT) or radiology performed and interpreted ultrasound)	Office ultrasound (US study)	Mean duration since injury 8.75 yrs
Calenoff 1982 [215]	Patients with spinal cord injury	Ultrasound	Excretory urogram (IVP) and/or voiding cystourethrogram	Not Reported (NR)
Gousse 2003 [216]	Patients with spinal cord injury	Routine renal ultrasound Frequency: Annual routine surveillance scan Average of 2.95 paired study comparisons per patient	Renal nuclear scan Data not reported	mean time elapsed since injury 23.9 yrs
Gupta 1994 [217]	Patients with spinal cord injury	Routine radiological screening	Not applicable (na)	Mean time since injury 2 months to 20 yrs
Lemack 2005 [218]	Patients with multiple sclerosis referred for lower urinary tract symptoms	Renal ultrasound	Na	NR
Macdiarmid 2000m[219]	Patients with spinal cord injury	Serum creatinine level	Na	NR
Morcos 1988 [220]	Patients with spinal cord injury	Routine renal ultrasound	Intravenous urography	Mean duration of paralysis 10.5 yrs

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
Navon 1997[230]	Patients with spinal cord injury	Screening with cystoscopy	No cystoscopy screening	8+ years
Persun 1999 [221]	Adults with a history of lumbar myelomeningocele all of whom performed CIC and were dry between catheterisations	Patients with normal ultrasounds/ creatinine Ultrasound, serum creatinine Cystometry	Na	NR
Sepahpanah 2006 [222]	Patients with spinal cord injury who had annual inpatient evaluations for 5 separate years	Annual evaluation including ultrasound and serum creatinine	Na	Mean interval (SD) between the first and fifth test 5.57 yrs (2.13)
Sliwa 1996 [223]	Patients with multiple sclerosis with symptoms of neurogenic bladder dysfunction	Ultrasound	Na	NR
Tarcan 2001 [224]	Patients with myelodysplasia	Routine ultrasound	Na	(Age) Mean 9.1 yrs (SD 5.5 yrs) (range 1 to 18.6 yrs)
Tins 2005 [225]	Patients with spinal cord injury	Routine kidney, ureter and bladder radiograph	Routine ultrasound	Mean time since injury 11 yrs
Tsai 2001 [226]	Patients with spinal cord injury	Intravenous urography Frequency: routine	Renal ultrasound	NR
Vaidyanathan 2006 [227]	Patients with spinal cord injury	Ultrasound in spinal cord injury patients who had symptoms related to the urinary tract (passing purulent urine, temperature, rigors, passing blood in urine, severe kidney/bladder pain, recurrent urine infections)	Ultrasound in spinal cord injury patients with no urinary symptoms when they underwent ultrasound examination	NR
Waites 1995 [228]	Patients with spinal cord injury	Patients who had missed two or more consecutive annual examinations Patients underwent renal scintigraphic	Patients who were compliant with routine annual examinations for the previous three consecutive years Patients	NR

STUDY	POPULATION	INTERVENTION	COMPARISON	LENGTH OF FOLLOW UP
		scanning	underwent renal scintigraphic scanning	
Yang 1999 [229]	Spinal cord injury patients who were chronically catheterised	Annual health maintenance evaluation to include cystoscopy on patients who were continuously catheterised for 10 more years, or were smokers and catheterised for 5 or more years.	Na	6 year period (1992 to 1997)

Quality of evidence

The majority of studies were retrospective observational studies, predominantly with a before and after design, and without a control group. The studies were therefore graded low by default (see Chapter 4). Further downgrading was due to increased the risk of confounding by uncontrolled factors such as time effects. In addition, a number of the studies reported on interventions that were performed once only and therefore did not form part of an ongoing monitoring and surveillance programme.

MONITORING AND SURVEILLANCE PROTOCOLS:

Creatinine

Spinal cord injury

One study (n=36) assessed the sensitivity of serum creatinine levels in detecting clinically important and early deterioration of renal function in patients with spinal cord injury [219].

Of the 36 patients 11 (31%) had a measured creatinine clearance of <100 mL/min (mean 84.8) and a corresponding normal serum creatinine level. Creatinine clearance calculated by the Cockcroft-Gault formula did not correlate well with that measured by the 24 hr endogenous clearance (r=0.426) and ^{99m}Tc-DTPA clearance (r=0.366), overestimating creatinine clearance in all but three patients. The mean (SD) difference between the creatinine clearance measured by the 24 hr and DTPA clearance technique was 17.7 (16.5%) and the correlation between these techniques was good (r=0.71) [219].

One study (N=70) reported on patients with spinal cord injury who had annual inpatient evaluations for 5 separate years [222].

For individual patients, the results of 24 hr C_{cr} were highly variable from one evaluation to the next; the within-subject standard deviation (SD) for C_{cr} was 25.9 mL/min. The within-subject SD for serum creatinine was 0.12 mg/dL. For all comparisons variability and reliability, serum creatinine was superior to C_{cr}. No medical management decisions were made based on the result of the 24 hr creatinine clearance [222].

58/70 patients had bilateral normal kidneys on 5 consecutive annual evaluation ultrasounds. Four had kidney stones on 1 or more ultrasound studies and 5 patients had at least one renal ultrasound that showed hydronephrosis. For the 3 patients who had normal renal ultrasounds at time one, but developed abnormalities over subsequent studies (hydronephrosis for 2, cortical scarring for 1), the

largest change in C_{cr} was 19.7% which is less than the mean variability between serial C_{cr} measurements. The remaining two patients who developed new renal ultrasound abnormalities had changes in C_{cr} of less than 1% [222].

ULTRASOUND

Spinal cord injury

One study (n=86) investigated the effectiveness of office ultrasonography of the bladder and kidneys to provide routine urological follow-up in the outpatient spinal cord injury clinic [214].

106 scans were performed on 86 asymptomatic spinal cord injury patients. Of the patients, 68 had a blinded excretory urography for comparison, including 20 who underwent additional studies (computerised tomography scans of the abdomen and pelvis, and/or radiologist-performed ultrasound examination of the kidneys and bladder). Office ultrasound detected 5 of 6 kidney stones, 6 of 6 hydronephrotic kidneys, 5 of 7 renal masses (4 of 6 cysts and 1 of 1 renal tumour), 3 of 3 bladder stones and 3 of 3 bladder diverticula. Subtle changes of chronic renal infection noted on excretory urography in 4 patients were not detected on corresponding ultrasound scans but voiding cystourethrograms revealed no reflux, and comparison to prior studies confirmed that these renal units were stable [214].

One study (n=54) compared ultrasound findings with those obtained from excretory urogram (IVP) and/or voiding cystourethrogram in spinal cord injury patients [215]. Kidneys: For 15/54 there were concerns regarding renal abnormalities based on the excretory urogram (IVP). Of these 15 patients ultrasound confirmed the radiographic findings in five (two with renal calculi, one with chronic pyelonephritis, one with peripelvic cyst and one with focal pyelonephrtitis), ruled out questionable radiographic findings in six and revealed abnormalities not present radiographically in four (one with renal cyst, one with hydronephrosis, one with cortical atrophy and one with renal calculi). Ureters: Of the 15 patients in whom the ureters were examined nine had different degrees of vesicoureteric reflux on voiding cystourethrography, which was confirmed by ultrasound in five (56%) and not demonstrated in four. The remaining 6 patients had ureterctasis on an IVP, which was confirmed by ultrasound in two (33%) and not noted successfully in 4. In two patients with a known allergy to the contrast medium ultrasound demonstrated vesicoureteral reflux in one, and hydroureter and hydronephrosis in one. Bladder: The bladder was examined in 32 patients during ultrasound voiding cystourethrography but was imaged adequately in only 30. Ultrasound confirmed the positive radiographic findings in 23 (six with bladder calculi, three with trabeculated bladders and 12 with normal bladders), ruled out questionable radiographic findings in three and yielded additional information in four (one with bladder calculi, two with lithogenic bladder sediment and one with calcific crust on the Foley catheter balloon) [215].

One study (n=162) reported on the results of a comparison between renal ultrasound (RUS) and renal nuclear scans (RNS) as part of upper tract surveillance in spinal cord injury patients [216].

Only the results of the renal ultrasound scan are reported here. A RUS scan was judged to be positive if it demonstrated any degree of caliectasis or pyelocaliectasis; parenchymal disease; or the presence of complex cysts, calculi, solid masses, or other renal and/or peri-renal processes. Simple renal cysts were not considered an abnormality because they did not dictate any change in patient management. RUS abnormalities were found in 57/162 patients (35.2%). Of the 75 positive ultrasound studies, 39 were positive for hydronephrosis, 39 revealed parenchymal disease, 22 revealed renal stones, and 8 revealed solid renal mass (renal malignancy found in 2 of these 8 patients). Many ultrasounds had more than one pathologic finding [216].

One study (n=109) reported on the diagnostic accuracy of ultrasound and radioisotope renography compared to intravenous urography to detect hydronephrosis in patients with spinal cord injury [226].

Of 235 kidneys studied, 43 kidneys in 23 patients showed hydronephrosis on the final findings. The estimated prevalence was 21% (23/109) in the study. The diagnostic accuracy of sonography and renal ultrasound are summarised in the table below.

Table 2: Diagnostic accuracy of ultrasound and radioisotope renography compared to intravenous urography

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Ultrasound	0.96	0.90	0.68	0.99
Radioisotope renography	0.91	0.84	0.56	0.98

One study (n=100) reported on the findings from routine radiological surveillance in patients with spinal cord injury [217]. In paraplegics, 26/47 patients had abnormalities (upper tract changes, calculi, bladder abnormalities, persistent post-voidal residual urine > 100 ml) detected on routine radiological screening. 24/26 abnormalities were detected 0 to 10 years after the injury compared with only 2/26 after 10 yrs of injury. For tetraplegics, 35/50 abnormalities were detected. All of these were detected within 10 yrs after the injury [217].

One study (n=75) reported on patients with spinal paralysis who had undergone intravenous urography (IVU) and renal ultrasonography as part of routine assessment of the upper urinary tract [220].

The results are presented in the table below.

Table 111: Normal IVU and abnormal ultrasound

Ultrasound findings	No. of patients
A simple renal cyst of a left kidney	1
Bilateral multiple renal cysts and simple cysts in the spleen; appearance is consistent with adult polycystic disease	1
A small right kidney (7cm in length)	2
Mild dilatation of the calyces of a left kidney	1
Left kidney not clearly seen	2
Total	7

Table 112: Abnormal IVU and normal ultrasound

Intraveous urogram findings	No. of patients
Mild dilatation of the calyces of a left kidney	1
Scar of the upper pole of left kidney with blunting of the upper calyx	1
Scar of the upper pole of the right kidney with mild dilatation of the right ureter and lower third of the left ureter	1
Dilatation of the lower third of the ureters	1
Dilatation of the left ureter	1
Dilatation of the right ureter	1
Poor visualisation of right kidney	1
Total	7

Table 5: Abnormalities demonstrated by IVU and also indicated or shown by ultrasound

Dilatation of calyces and renal pelvis	5
Cortical scarring and small kidneys	7
A renal calculus and mild hydronephrosis of a kidney	1
Total	13

One study compared Kidney, Ureter, Bladder (KUB) radiography with ultrasound in 100 consecutive patients with spinal cord injury [225]. A total of 199 kidneys and 99 urinary bladders were examined. On average, less than 50% of the renal area and about 70-75% of the urinary bladders were visualised. Five patients had renal stones identified on KUB radiograph, and of these two were seen on ultrasound. There were no stones seen on ultrasound only. Ultrasound identified renal abnormalities in a further 14 patients. There were seven patients with renal scarring in eight kidneys. There were five patients with hydonephrosis in six kidneys; all cases were mild to moderate. There were two patients with a small kidney with thinned cortex. The KUB identified none of these patients. Ultrasound identified a number of other abnormalities. There was one patient with a duplex renal collecting system, one case of nephrectony, one case of adrenal myolipoma, one situs inversus, one case of abnormally high echogenicity of the liver and two cases of gallstones. In one of these an additional gallbladder polyp was seen. One of the cases of gallstones was also identified on the KUB; all other abnormalities were not seen on the radiographs. Abnormalities of the urinary bladder were seen in 20 cases. A total of 19 cases showed evidence of bladder wall hypertrophy, and one case of incomplete bladder emptying. There was one case of previous cystectomy and a neobladder. KUB did not identify any of the abnormalities. Therefore, apart from the renal stones and one patients with gallstones, KUB did not identify any of the other abnormalities seen on ultrasound [225].

One study (n=108) reported on patients who underwent ultrasound who had no urinary symptoms compared with patients who had urinary symptoms [227].

In the asymptomatic group no abnormalities were reported in 63 patients. The following findings were reported in 24 patients

Table 113: Ultrasound findings in asymptomatic patients

Abnormal findings	No. of patients
Simple cyst in the kidney	4
Reduced size of a kidney	3
Some increased echogenicity of the left kidney	1
Primineny extrarenal pelvis and mild calyceal dilation	1
Slightly dilated renal pelvis and calyceal system	1
Right pelvic kidney showing mild hydronephrosis	1
Fetal lobulation of kidney	2
Multicystic kidney (no interval changes since last examination)	1
Small (2 cm diameter) parapelvic cyst	1
Small (4 mm) renal calculus in the lower pole	2
4 mm calculus in the upper pole of kidney	1
5 mm renal calculus in the mid pole	2
A little cortical scarring bilaterally	1
Focal renal scar	2
Generalised renal cortical thinning	3

Abnormal findings	No. of patients
Some increase in renal sinus fat	3
Trabeculated bladder	2
Small bladder diverticulum	1
Mild generalised bladder wall thickening	1
Small residual urine in postvoid scan	2

There were 21 spinal cord injury patients who exhibited urinary symptoms (passing purulent urine, temperature, rigors, passing blood in urine, severe kidney/bladder pain, recurrent urine infections) when they underwent ultrasound examination of the urinary tract. Abnormalities such as hydronephrosis, pyonephrosis, bladder calculi, or bladder polyp were detected in 20 of 21 patients and, subsequently, all 20 patients required therapeutic intervention on the basis of ultrasound findings [227].

MULTIPLE SCLEROSIS

One study (n=66) reported on the incidence of upper tract abnormalities using renal ultrasound in patients with multiple sclerosis referred to the neurourology clinic for evaluation of lower urinary tract symptoms [218].

Table 114: Radiologic findings in patients with abnormal renal ultrasound findings

Radiologic findings	Patients (n)
Unilateral focal caliectasis	6
Bilateral focal caliectasis	1
Unilateral cortical scarring	1
Unilateral mild hydronephrosis	1
Bilateral stones (5 mm) mild hydronephrosis	1
Unilateral stone (<5 mm)	1

One study (n=48) reported on ultrasound findings in patients with multiple sclerosis with symptoms of neurogenic bladder dysfunction (exacerbation-free for 6 months) [223]

Renal ultrasound examination showed significant MS-related upper urinary tract abnormalities in 10 patients (21%). These abnormalities included renal stones in five patients, grade one hydronephrosis in two patients, cortical atrophy in two patients, and a reflecting pattern in the renal pelvis of one patient representing an early stone or vascular calcifications. In addition, 14 ultrasounds identified bladder trabeculation (29%), which was considered a non-significant MS-related change. Only five of these were associated with abnormal upper tract findings. Eight patients had incidental findings [223].

Spina bifida

One study (n=25) reported ultrasound on children with myelodysplasia with normal urodynamics at birth [224]. The mean follow up was 9.1 yrs (range 1 to 18.6 yrs). No child had hydronephrosis or reflux [224].

One study (n=40) reported on ultrasound and serum creatinine in adults with spina bifida who were using clean intermittent catheterisation [221]. In patients with normal ultrasound and normal serum creatinine (1.5 mg/dl), there were no individuals (0/20) whose average catheterised volume corresponded to a bladder pressure of >40 cm H_2O on cystometry. However, in patients with hydronephrosis and/or elevated creatinine, 30% (6/20) had average catheterised volumes corresponding to a bladder pressure of >40 cm H_2O [221].

CYSTOSCOPY

Spinal cord injury

One study (N=59) reported on the results of an annual health maintenance evaluation to include cystoscopy on patients with spinal cord injury who were continuously catheterised for 10 more years, or were smokers and catheterised for 5 or more years [229]Ninety three bladder biopsies and 18 urine cytologies were obtained, none of which demonstrated malignant changes. No bladder cancers were diagnosed through screening. During the same six year period four spinal cord injury patients were diagnosed at the hospital with bladder cancer, all outside of the surveillance protocol [229].

One study [230] reviewed all 14 SCI patients diagnosed with squamous cell bladder cancer during a 16 year period and divided them into those who had 1) been given annual cytoscopy for at least 10 years and were asymptomatic when diagnosed with cytoscopy (n=5), and 2) those who had not been routinely screened and were symptomatic at presentation (n=14). Those receiving annual screening had a higher cancer-specific survival (100% compared to 50% in the symptomatic group). In addition, the stage of disease was less advanced at presentation in the screened group. In the non-screened group pathological stage was more advanced at diagnosis, with 7 patients at stage pT3a or pT3b, 1 with pT1N0M0, and 1 at stage pT2N0M0. By contrast in the screened group 3 patients were at pT1n0M0, 1 was at pT3aN0M0 and 1 had pT3bN0M0 disease. However these differences were not statistically significant.

RENAL SCINTIGRAPHIC SCAN

Spinal cord injury

One study (n=160) reported that there were no significant differences between patients with spinal cord injury who had missed two or more consecutive annual examinations compared with patients who were compliant with their annual examinations on mean- adjusted Effective Renal Plasma Flow (ERPF) (left kidney 311 vs 308 mL/min, right 301 vs 276; ns) [228].

14.1.1.2 Economic Evidence

No relevant economic evaluations comparing monitoring strategies or surveillance protocols were identified.

We conducted an original economic analysis to assess the costs related to different guideline management programmes for the monitoring of patients with incontinence from neurological disease.

Model overview

Our model compared follow-up strategies for renal surveillance and monitoring of incontinence as defined in different guidelines. The population considered was patients with neurological conditions with or at risk of incontinence.

The base case time horizon was 10 years but this was varied between 1 and 20 years in a sensitivity analysis. We adopted a NHS and Personal Social Services perspective and used a 3.5% discount rate.

Deviations from NICE reference case

Our model considered a 10 year time horizon (altered in a sensitivity analysis); in fact, a lifetime analysis was unfeasible due to the fact that no average age of the population could be obtained from any of the sources.

No outcome or quality of life data were used due to the unavailability of this data. A threshold analysis was conducted to determine the number of QALYs that would be required by each strategy to make it cost effective at a willingness-to-pay of £20,000/QALY and £30,000/QALY.

Approach to modelling

There is no data available comparing the effectiveness or outcomes of different intensity of monitoring and surveillance strategies for patients with bladder dysfunction of neurological origin. However, the GDG considered this question a high priority for economic analysis due to the likelihood of a high cost impact. This impact is likely to be dependent on the cost and intensity of the resources used in each strategy. Therefore an analysis on the cost of monitoring strategies recommended by national and international guidelines on neurological incontinence was undertaken.

Identification of strategies

We carried out a systematic review of guidelines that included key neurological conditions and neurological incontinence. The search identified guidelines, studies that evaluated guidelines and discussions of guidelines and various other types of recommendations. Only the actual guidelines or papers that made recommendations on assessment or monitoring were included for further analysis. Each of the guidelines was then studied to identify the recommendations made on monitoring and renal surveillance. Those that made no specific recommendations were immediately excluded from further analysis. Many guidelines which made recommendations on assessment but not monitoring or surveillance were excluded after discussion with the GDG. The papers that were excluded can be found in **Table 115**

Table 115: Excluded Guidelines

Guideline	Authors	Reason for Exclusion
1. Bladder Management for Adults with Spinal Cord Injury: A Clinical Practice Guideline for Health-Care Providers. 2006	Consortium for Spinal Cord Medicine (US)	No recommendations made on diagnosis or follow up. Refers to the VHA Handbook 1176.1.
2. Parkinson's Disease. National clinical guideline for diagnosis and management in primary and secondary care. 2006	National Institute for Health and Clinical Excellence (UK England and Wales)	No recommendations made on diagnosis or follow up.
3. Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. 2010	Scottish Intercollegiate Guidelines Network (UK Scotland)	No recommendations made on follow up; recommendations made on assessment.
4. A UK consensus on the management of the bladder in multiple sclerosis. 2009	Fowler C J, et al.	Recommendations made but not detailed enough to breakdown.
5. Guidelines on Paediatric	European Association of	Recommendations made but not

Guideline	Authors	Reason for Exclusion
Urology. 2009	Urology. Tekgul et al.	detailed enough to breakdown.
6. 4th international consultation on incontinence. 2010	Abrams et al.	No recommendations made on diagnosis or follow up
7. Neurologic urinary incontinence 2010	Wyndaele et al.	This paper documents the discussion in one of the working groups of the 4th international consultation. And makes no recommendations on follow up.

Of the four guidelines included (

Table 116), one made recommendations for neurological patients generally, two for specific diseases (spinal injury and multiple sclerosis) and one for children. The strategies that each guideline outlined were extracted and broken up into their constituent parts, which are described in

Table 116.

Table 116: Included Guidelines

Guideline	Monitoring strategy	Frequency
General guidelines		
1. M. Stöhrer et al. Guidelines on neurogenic lower urinary tract dysfunction. (NLUTD) European Association of Urology 2010	Urinalysis (UTI etc.) checked by patient [dip stick]	2 months
	Upper urinary tract, bladder morphology, and residual urine [ultrasound]	6 months
	Physical examination, blood chemistry and urine laboratory [urine culture]	12 months
	Detailed specialist investigation. Minimum: video-urodynamic investigation and should be performed in a leading neuro-urological centre [urodynamics]	18 months (1-2 years)
Disease specific guidelines		
2. Spinal Cord Injury and Disorders system of care procedure (SCI) VHA Handbook 1176.1 2005	Urine examination including UA [dipstick] and C&S [urine culture]	12 months
	Serum creatinine and BUN [blood chemistry]	12 months
	Anatomical exam (US or CT) and/or test of renal function (creatinine clearance or renal scan) [ultrasound]	12 months
	Cystoscopy - assumed 50% of population (±30%)	10 years
	Counselling regarding the advantages and disadvantages of prostate specific antigen testing [nurse specialist consultation]	12 months
	Urodynamic evaluation should be performed when objective information on voiding function is needed [Urodynamics]	Assumption - 1st year, 0.17 (±10%) in the 2nd year, every 5 years beyond that
3. Sèze et al. The Neurogenic bladder in multiple sclerosis: review of the literature and proposal of	a) Low risk	
	Three day voiding chart [nurse specialist consultation]	12 months
	Uroflowmetry and Postvoid residual measure [30mins nurse specialist]	12 months
	Urodynamic study	every 3 years

Guideline	Monitoring strategy	Frequency
management guidelines. (MS) 2007	b) High risk	
	Three day voiding chart [nurse specialist consultation]	12 months
	Postvoid residual measure [30mins nurse specialist]	12 months
	Ultrasound scanning of the urinary tract	12 months
	Urinary creatinine clearance [blood chemistry]	12 months
	Evaluation of QoL relative to VUD	12 months
	Urodynamics and Cystometry [Urodynamics]	2 years (every 1-3 yr)
	Morphological study to explore UUT dysfunction [ultrasound]	2 years (every 1-3 yr)
Paediatric guidelines		
4. Beattie Guidelines on the management of Neuropathic Bladder. (RPB) Scottish Renal Paediatric Group 2006	a+b) Low and High Risk	
	Ultrasound (<1 yr)	3 months
	Ultrasound (1-3 yr)	6 months
	Ultrasound (>3 yr)	12 months
	DMSA scan for renal function	3-6 months, 2 year follow-up
	Isotope GFR	2 years
	b) High Risk	
	Urodynamics	12 months
	a) Low Risk	
	No urodynamics	

Definition of Risk

2 studies divided patients up into high and low risk. The guidelines define the risk as the following:

Strategy from guideline 3[231] (MS):

High Risk – at least one definite **risk factor or more than** two probable **risk factors (see Table 117: Definition of Risk factors in Strategy 3**

- Low Risk – **no definite** risk factor and no more than **two probable** risk factors

Table 117: Definition of Risk factors in Strategy 3

Definite risk factors:	Probable risk factors
MS duration beyond 15 years	Detrusor-sphincter dyssynergia
Indwelling urinary catheter	Age over 50 years
Ample uninhibited contractions of the detrusor	Male sex
High detrusor pressure	

- Strategy from guideline[232] 4 (RPB):
  - Move from low risk to high risk in the case of:
    - New onset hydronephrosis
    - Febrile urinary tract infection

- Evidence of urinary retention

Model structure

The Model is a cost analysis constructed in Windows Excel. It is worked out so that the costs were calculated for each strategy in one year cycles (no movement between heath states). Each monitoring or surveillance strategy (strategy 1-4, outlined in

Table 116) was modelled over a ten year time horizon with the costs discounted at the NICE reference case discount rate of 3.5% per year. The costs were applied to interventions/tests according to the frequency indicated in the guidelines. If an intervention/test was less frequent than 12 months, it was assumed that it happened in the first year and then at the specified interval after that. Where the frequency was expressed as a range, the midpoint was taken for the base case and an extreme scenario sensitivity analysis was carried out on the maximum and minimum frequencies. If data was unavailable on frequency or populations that require the intervention, the GDG made appropriate assumptions. For the frequency of urodynamics in strategy 2, we assumed that everyone would have it in the first year and then every five years subsequently, with one in six people requiring it in the second year. In the case of cystoscopy in strategy 2, we assumed that 50% of the monitored population would fall into the indications described in the strategy.

Uncertainty

In order to take into account the uncertainty around the costs in the model we carried out various sensitivity analyses. Where the frequency of a test was expressed as a range an extreme scenario sensitivity analysis was carried out on the maximum and minimum frequencies. The various strategies were also analysed over different time periods: 1 year, 5 years and 20 years.

The parameters in the model were made probabilistic by defining a probability distribution for each model input parameter. When the model was run, a value for each input was randomly selected from its respective probability distribution simultaneously and mean costs of each strategy calculated using these values. The model was run repeatedly – in this case 1000 times – and results are summarised. This averaging of results can provide a more accurate measure of the average cost. It also provides an estimate of the uncertainty brought about by random variation, in the form of confidence intervals. Probability distributions in the analysis were based on error estimates from data sources, for example confidence intervals.

Where the NHS Reference costs were used, the uncertainty around each cost was available in the form of an upper and lower quartile range. A gamma distribution was assumed for the costs in the model as this prevents 'negative costs' from occurring. For the costs obtained from the Personal Social Services Research Unit (PSSRU) and the NHS Supply Chain Catalogue this uncertainty was not available so these costs were not made probabilistic.

Resource use and cost

With the identification and breakdown of each of these strategies it was possible to cost them. The costs for the constituent parts of each comparator strategies were identified (Table 3) using national data sources. In order to take into account the uncertainty around the costs in the model, the data was made probabilistic.

Certain assumptions were made that enabled the costs to be applied. Uroflowmetry and postvoid residual measures were assumed to take 30 minutes of specialist nurse time. A three day voiding chart and counselling were both assumed to be equivalent to the cost of a consultation with a specialist nurse.

Table 118: Resource Costs

Resource	Cost	Inter-quartile range	Source
Urinalysis (Dipstick)	£0.05	N/A	NHS Supply chain catalogue 2011[133]
Urine culture	£8	£6 - £10	NHS Reference Costs 2009-2010[12]
Blood chemistry	£3	£2 - £4	NHS Reference Costs 2009-2010[12]
Physical examination (consultant)	£88	£73 - £101	NHS Reference Costs 2009-2010[12]
Urodynamics	£154.00	£103 - £194	NHS Reference Costs 2009-2010[12]
Cost of US less than 20 min	£55.00	£40 - £66	NHS Reference Costs 2009-2010[12]
Cost of US more than 20 min	£71.00	£54 - £83	NHS Reference Costs 2009-2010[12]
Cystoscopy (adult)	£422.67	£198.89 - £524.75	NHS Reference Costs 2009-2010[12]
DMSA Scan	£180.20	£130.19 - £228.88	NHS Reference Costs 2009-2010[12]
Isotope GFR	£175.87	£122.42 - £211.15	NHS Reference Costs 2009-2010[12]
Nurse Specialist Consultation	£17.00	N/A	PSSRU 2010[42]
Specialist Nurse (per hour)	£68.00	N/A	PSSRU 2010[42]

Results

Base case results

The base-case analysis, using probabilistic data (**Table 119**) showed that over a ten year period the least costly monitoring strategy was the strategy that monitored low risk patients in the MS population (strategy 3a). This strategy however is only monitoring low risk patients; the high risk patient population was considerably more expensive, almost double the cost. The lowest cost strategy that considered a mixed population was strategy 2, in spinal cord injury patients. If we consider strategy 4 separate due to it being in a paediatric population, the most costly strategy is strategy 1 for general neurogenic lower urinary tract disorders. The probabilistic analysis enables us to fit confidence intervals around both the costs and the difference in costs. It shows when each of the strategies are compared to strategy 1 - as it is the most commonly followed guideline - the average differences are significant at the p=0.05 level in all strategies apart from 4b. For the low risk strategies strategy 3a remains the lowest cost and for the mixed and high risk strategies, strategy 2 is the least costly.

Table 119: Base-case results (Probabilistic)

Strategy	Average Cost	Upper CI	Lower CI	Average incremental costs vs strategy 1	Upper CI	Lower CI
Strategy 1	£2,583	£3,335	£1,662			
Strategy 2	£1,126	£1,459	£735	-£1,458	-£709	-£2,509
Strategy 3 a (Low risk)	£844	£1,155	£525	-£1,739	-£991	-£2,872
Strategy 3 b (high risk)	£1,635	£2,109	£1,141	-£948	-£98	-£2,109

Strategy	Average Cost	Upper CI	Lower CI	Average incremental costs vs strategy 1	Upper CI	Lower CI
Strategy 4 a (low risk)	£1,628	£2,071	£1,154	-£955	-£147	-£2,128
Strategy 4 b (high risk)	£2,293	£2,892	£1,581	-£290	£601	-£1,526

As most of these strategies are for quite heterogeneous populations considering them together carries heavy limitations. Therefore considering the absolute costs is more informative. Threshold Analysis

In order to account for the lack of data on outcomes, a threshold analysis was carried out that calculated the incremental QALYs that each strategy would have to generate in order for them to be cost effective compared to "do nothing." The incremental QALYs per patient that would be required to make a strategy cost effective are calculated at two thresholds, £20,000/QALY and £30,000/QALY. It is possible to see from the results in **Table 120** that the more expensive strategies would have to generate more additional QALYs compared to 'do nothing' in order to account for the increased cost.

Table 120: Threshold Analysis on number of incremental QALYs needed for a strategy to be cost effective compared to 'do nothing'

Strategy	Average incremental Cost over 10 years	Incremental QALYs over 10 years required at threshold	
		£20,000/QALY	£30,000/QALY
Strategy 1	£2,583	0.13	0.09
Strategy 2	£1,126	0.06	0.04
Strategy 3 a (risk free)	£844	0.04	0.03
Strategy 3 b (at risk)	£1,635	0.08	0.05
Strategy 4 a (low risk)	£1,628	0.08	0.05
Strategy 4 b (high risk)	£2,293	0.11	0.08

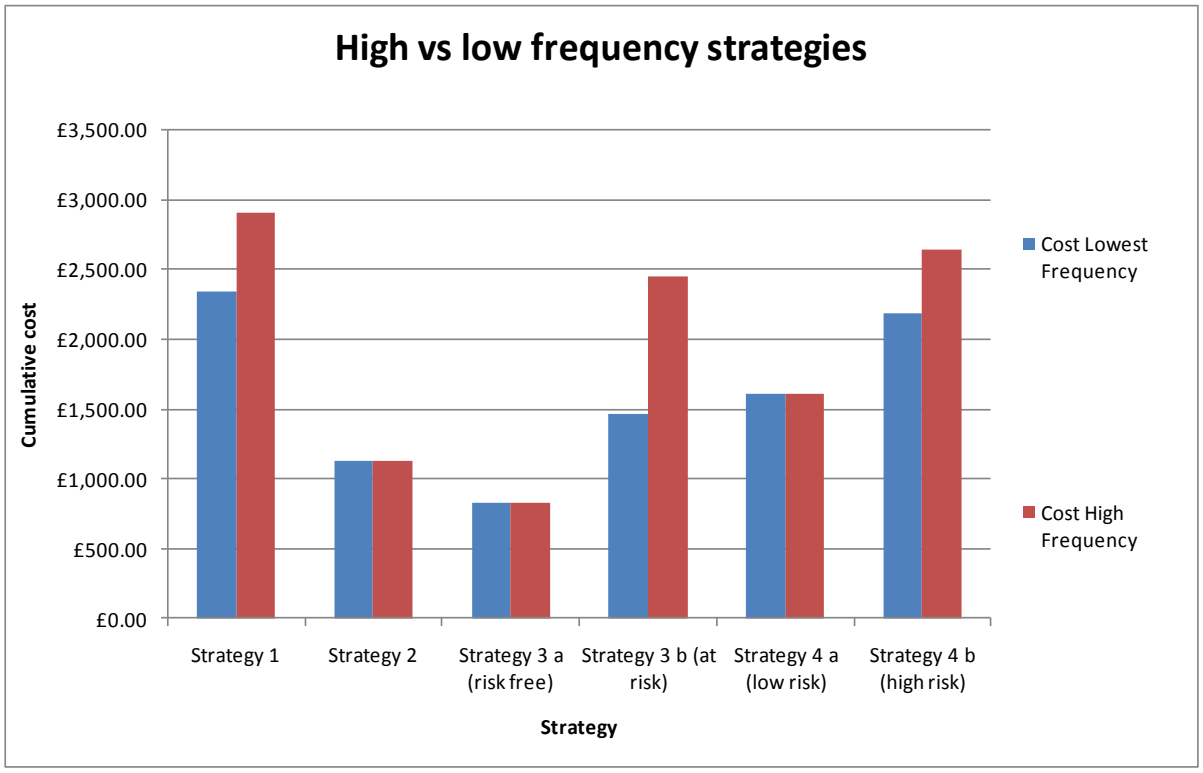
Sensitivity analysis

Where the frequency of a test was expressed as a range, an extreme scenario sensitivity analysis was carried out on the maximum and minimum frequencies. **Table 121** and **Figure 9** show that there was no change in the order of the least and most costly strategies compared to the base case analysis. The lowest cost strategies remain 3a for low risk and strategy 2 for combined and high risk populations. Strategy 3b shows the biggest difference between minimum and maximum frequency with a difference of around £1000. This means that it is probably the strategy most open to interpretation in terms of its frequency.

Table 121: Sensitivity Analysis of high versus low frequency strategies

Strategy	Cost	
	Lowest Frequency	High Frequency
Strategy 1	£2,335	£2,900
Strategy 2	£1,127	£1,127
Strategy 3 a (low risk)	£826	£826
Strategy 3 b (high risk)	£1,460	£2,451
Strategy 4 a (low risk)	£1,614	£1,614
Strategy 4 b (high risk)	£2,179	£2,647

Figure 9: Sensitivity analysis of the high versus low frequency strategies



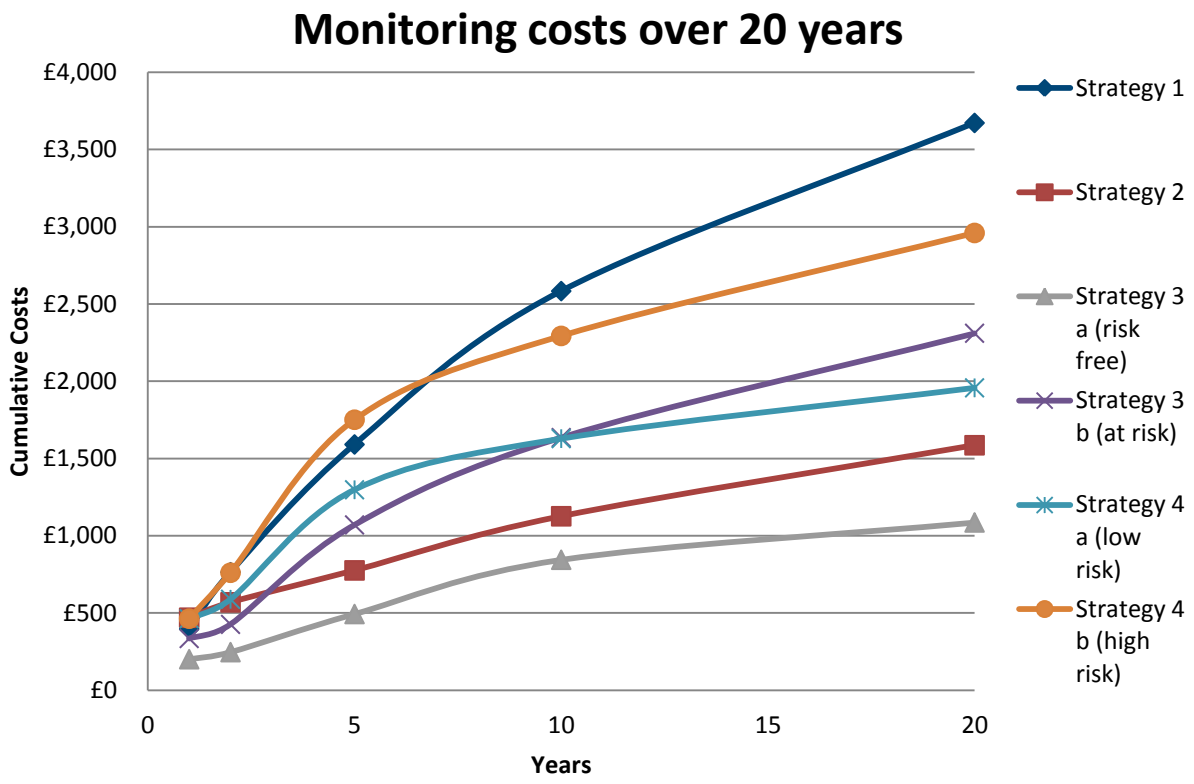
The results from varying the time horizon using probabilistic cost results can be found in Table 122. This variation shows that strategy 1 is relatively low cost in the first year but quickly becomes the most costly as the time horizon increases.

Figure 10 shows that strategy 2 increases in cost at a much slower rate over the same period. Between years ten and twenty there is very little change in the relative costs of each strategy, apart from 3b and 4a. But as these two are in different populations this is not a direct comparison. After an initial sharp increase in cost, it is possible to see the costs plateau out from around the five year mark. Despite this flattening out, strategy 1 continues to increase in cost at a faster rate than the other costs. The only point at which Strategy 1 is not highest cost of the non-paediatric strategies is at year 1.

Table 122: Sensitivity analysis varying the time horizon

Strategy	**Costs**				
	Year 1	Year 2	Year 5	Year 10	Year 20
Strategy 1	£396.30	£764	£1,591	£2,583	£3,672
Strategy 2	£469	£568	£775	£1,126	£1,585
Strategy 3 a (low risk)	£201	£246	£493	£844	£1,086
Strategy 3 b (high risk)	£334	£426	£1,070	£1,635	£2,310
Strategy 4 a (low risk)	£463	£588	£1,297	£1,628	£1,957
Strategy 4 b (high risk)	£463	£760	£1,751	£2,293	£2,960

Figure 10: Monitoring costs over 20 years



Note Strategy 1: Neurogenic lower urinary tract symptoms (European Association of Urology), strategy 2: Spinal Cord Injury (VHA Handbook), Strategy 3: Multiple Sclerosis (Sèze et al.), Strategy 4: Paediatric bladder (Beattie et al.).

Discussion

Summary of results

The probabilistic base-case results show that among non-paediatric strategies, strategy 1 is the highest cost strategy at every horizon period, apart from year 1. When comparing strategies in the low risk population, strategy 3a emerges as the least costly, while in high risk populations, strategy 2 is the least costly.

Limitations and interpretation

The results obtained in this analysis give an indication of the cost of monitoring strategies over a given time period (10 years as base case). The absolute cost of monitoring strategies over 10 years ranges between £800 and £3000 per patient depending on risk, age and condition. The cost of paediatric monitoring is considerably high, particularly in the high risk population. Even in the low risk group, paediatric monitoring has a similar cost to the strategy for high risk patients with Multiple Sclerosis (MS). The GDG believed that the strategy in the paediatric population overstated the importance of imaging and monitoring.

Strategy 1 was the most costly strategy when considering a mixed population with mixed risk levels. This strategy was also the most costly at different time horizons, different frequencies of monitoring and different risk profiles. It was the opinion of the GDG that the regular urodynamics and physical examination in a specialist urological centre determined the high cost of this strategy. This was considered to be an over-use of specialist, invasive testing.

The least costly strategy when considering a mixed population with mixed risk levels was strategy2, while in a low risk population the least costly was strategy 3 , which was the lowest cost strategy overall. The GDG noted that this shows that the risk profile is important when defining the monitoring strategy for a patient. A clear definition of high and low risk is crucial and it has been described elsewhere in the guideline (See Introduction).

No clinical outcome associated with any of the monitoring strategies was available, so it is not possible to conclude which is the most cost effective strategy. Another limitation of our analysis is that it does not consider the inevitable extra or unnecessary treatment associated with the monitoring strategies. As in any screening programme, the more often tests are done the more likely it is that false positives results will be picked up requiring an unnecessary treatment. This adds to the cost and impacts treatment effectiveness and patient quality of life. A further limitation is that the strategies are themselves based on guideline recommendations that are largely consensus driven.

In cases where the guidelines were unclear on the testing frequency, assumptions were made by the GDG. These assumptions were, however, tested extensively in probabilistic and deterministic sensitivity analyses. A further point to make is that all the populations for which the strategies are recommended are different. This limits the validity of comparisons between the strategies but not the validity of the absolute costs.

Generalisability to other populations / settings

The analysis was conducted from a UK perspective using: one international, one European, one US and one Scottish guideline. The strategies also made recommendations in different populations: general neurogenic incontinence patients, MS patients, Spinal cord injury patients and paediatric patients.

14.1.1.3 Evidence Statements

Clinical evidence statements

Two observational studies of 106 patients reported on the use of creatinine testing in patients with spinal cord injury. Neither study supported the use of creatinine for the early detection of renal impairment (5.57 yrs) (low quality)

Eight observational studies of 894 patients reported on ultrasound in patients with spinal cord injury. Overall, the studies supported the routine use of ultrasound for the detection of conditions such as hydronephrosis in patients with spinal cord injury (2 months to 23.9 yrs) (low quality)

Two observational studies of 114 patients reported on ultrasound in patients with multiple sclerosis. One study supported the routine use, and one study did not support the routine use, of ultrasound in patients with multiple sclerosis (not reported) (low quality)

Two observational studies of 65 patients reported on ultrasound in patients with spina bifida, one on adults and one on children. The study on children with normal urodynamics at birth detected no case of hydronephrosis or reflux. The study on adults supported the routine use of ultrasound (9.1 yrs) (low quality)

Two observational studies of 73 patients reported on the use of cystoscopy in patients with spinal cord injury. One study did not support its use and another was inconclusive(6-8.2 years) (low quality)

One observational study of 160 patients reported on the use of a renal scintigraphic scan in patients with spinal cord injury. The study did not support the long term, routine use of this test (not reported) (low quality)

Economic evidence statement

The absolute costs per patient of the strategies are not considered by the GDG to be extreme. However, the cost could be brought down still further as the frequency of some, but not all, of the proposed investigations is still considered to be too high in most strategies. A more realistic recommendation could be made on monitoring strategies that would better reflect best practice.

14.1.2 Recommendations and links to evidence

Recommendations:	**MONITORING AND SURVEILLANCE PROTOCOLS** **56. Do not rely on serum creatinine and estimated glomerular filtration rate in isolation for monitoring renal function[p] in people with neurogenic lower urinary tract dysfunction.** **57. Consider using isotopic glomerular filtration rate when an accurate measurement of glomerular filtration rate is required (for example, if imaging of the kidneys suggests that renal function might be compromised)[p].** **58. Offer lifelong ultrasound surveillance of the kidneys to people who are judged to be at high risk of renal complications (for example, consider surveillance ultrasound scanning at annual or 2 yearly intervals). Those at high risk include people with spinal cord injury or spina bifida and those with adverse features on urodynamic investigations such as impaired bladder compliance, detrusor-sphincter dyssynergia or vesico-ureteric reflux.** **59. Do not use plain abdominal radiography for routine surveillance in people with neurogenic lower urinary tract dysfunction.** **60. Consider urodynamic investigations as part of a surveillance regimen for people at high risk of urinary tract complications (for example, people with spina bifida, spinal cord injury or anorectal abnormalities).** **61. Do not use cystoscopy for routine surveillance in people with neurogenic lower urinary tract dysfunction.** **62. Do not use renal scintigraphy for routine surveillance in people with neurogenic lower urinary tract dysfunction.**
Relative value placed on the outcomes considered	The outcomes included in the review were: kidney function and renal disease, quality of life and hospital admissions. The GDG considered that detecting silent disease to be an important outcome as early intervention may prevent more progressive renal damage.
Quality of evidence	Seventeen observational studies evaluating creatinine, ultrasound, cystoscopy and renal scintigraphic scanning were found. The majority of studies were retrospective observational studies without a control group. The overall quality of the evidence was low. A number of the studies reported on interventions that were performed only once and therefore did not form part of an ongoing monitoring and surveillance programme.

[p] For more information on the measurement of kidney function, see 'Chronic kidney disease' (NICE clinical guideline 73).

	The GDG made recommendations on the basis of a very limited evidence base and no studies demonstrated outcomes from routine surveillance/monitoring that matched requirements for the adoption of screening programmes. The recommendations were made by consensus based on existing practice and deductions from the studies that have been examined. Eight studies on the use of ultrasound for spinal cord injury patients and two for spina bifida patients supported its routine use. The GDG noted that the studies all produced reasonable results (between 15-30%) in finding abnormalities The GDG agreed that the use of Serum Creatinine in isolation has been shown to be unreliable because of a number of factors (most importantly – muscle mass). One study on cystoscopy did not support its use and one study on renal scintigraphic scans did not support routine long term use. One study on cystoscopy suggested that it may be possible to improve outcomes for patients with spinal cord injury who develop bladder cancer through surveillance cystoscopy, but the study was inconclusive, and the GDG agreed that this study should not be considered
Trade-off between clinical benefits and harms	The GDG noted the surveillance being advocated minimises exposure to ionising radiation. The GDG agreed that abdominal X-ray should not be recommended because of the associated risks but noted that some centres continue to use abdominal radiography in this context. The GDG considered that lifelong ultrasound was appropriate for those people who were at high risk of renal complications such as the development of hydronephrosis or the formation or renal stones and this was current practice for particular groups such as those with spinal cord injury or spina bifida. The question of using cystoscopy as a screening tool for bladder cancer was considered. It was noted that while the incidence of bladder cancer is probably raised in some populations with neurogenic lower urinary tract dysfunction, it remains a relatively rare condition. Therefore the morbidity of routine cystoscopy and resource implications suggests that it is unlikely that cystoscopy would meet the requirements for use as a screening test. The GDG emphasized the importance of early referral of patients with red flag symptoms.
Economic considerations	An extensive cost analysis was done on the various monitoring programmes recommended by different published guidelines. This analysis showed that over ten years of monitoring, None of the strategies compared are associated with considerable costs. The most expensive strategy was under £3,000 for a ten year period. No effectiveness data or quality of life data could be found that matched the interventions; therefore a full economic evaluation could not be carried out. We conducted a threshold sensitivity analysis on the number of incremental QALYs that each strategy would have to generate compared to 'do nothing' in order to be cost-effective at a threshold of £20,000/QALY. Over ten years the QALYs gain would have to be 0.13 for the most costly strategy or less than this for the other strategies. The GDG considered this number to be low for a ten year period; therefore the monitoring strategies compared in the cost analysis are likely to be cost-effective. However, our analysis does not consider the unnecessary treatment associated with the 'false positive' cases resulting from the monitoring strategies. These would lead to unnecessary treatments and further investigation, making the monitoring strategy less cost effective. Strategies assessed here included regular eGFR measurements, ultrasound and cystoscopy as well as other techniques involved in renal surveillance. All of these strategies were judged to be low cost therefore lifelong renal surveillance and the individual components that make this up could be recommended.
Other considerations	The GDG agreed that isotopic techniques are widely regarded as being the most accurate of the available techniques for measuring the glomerular filtration rate. The GDG acknowledged that the interval between monitoring visits was, in general, arbitrarily set at one year. However, it was felt that it was important to tailor surveillance to the individual patient's circumstances. Some patients with adverse

	factors, such as concerning urodynamic findings or a history of frequent stone formation, might need to be seen more often than once a year. On the other hand, some patients who were in low risk groups, such as female MS patients, might not require regular surveillance investigations at all.

15 Potential complications: providing information and initial management

The management of the neuropathic lower urinary tract has, in general, had to rely heavily on expert opinion because definitive, high quality research has yet to answer many important questions about the optimal approach to maintaining continence. In addition, the dramatic improvement in survival for patients with complex disability due to long-term neurological conditions over the last century has been achieved, in part, by the adoption of a somewhat dogmatic approach to urinary tract management and patient care, notably in spinal cord injury units. However, it is now clear that there are many circumstances where the patients and their carers will be able to choose between different, clinically appropriate management regimes depending on their underlying neurological condition and individual circumstances.

There are a limited number of basic LUT management systems that can be used (see table). These can be considered as the means by which the patient drains or collects most of their urine output. They are not mutually exclusive so that some patients will use a combination of different systems. For example, a patient with multiple sclerosis might void with voluntary control as their main way of emptying the bladder but might also drain residual urine using intermittent catheterisation before going to bed in order to reduce nocturia. They might also choose to use a pad to contain incontinence when away from home.

It must also be appreciated that medical or surgical interventions are often needed in order to enable the use of a management system or optimise its use. For example, a patient with spina bifida with severe incontinence might wish to manage their LUT with intermittent catheterisation and to be reliably continent between catheterisations. This could require surgical treatment to overcome both impaired bladder storage of urine and incontinence due to an incompetent urethral sphincter mechanism.

Table 123: Urinary tract management systems for draining or collecting urine output

Lower Urinary tract Management System	Potential Indication	Example
Voluntary voiding	Patients with preservation of a degree of voluntary control over the LUT but who require additional treatment to control symptoms Voiding might not be normal as judged by urodynamic evaluation	A patient with urgency following a stroke using antimuscarinic medication A patient with cauda equina syndrome who can empty their bladder with a degree of abdominal straining
Intermittent catheterisation	Patients with impaired bladder emptying requiring catheter drainage. If urethral intermittent catheterisation is problematic, then a continent catheterisable abdominal conduit can be constructed using the Mitrofanoff principle.	A patient in urinary retention due to peripheral nerve damage after radical pelvic surgery
Containment of incontinence	Patients who have severe incontinence may be managed with a containment strategy using pads (in either sex) or a penile sheath collection system	A male spinal cord injury patient with involuntary voiding due to neurogenic detrusor overactivity
Indwelling	Suprapubic catheters are often preferred to	

Lower Urinary tract Management System	Potential Indication	Example
catheter	urethral catheters in the neuropathic population for reasons of convenience and in order to avoid urethral trauma. The option of using a catheter valve, rather than continuous drainage into a bag can be considered for some patients.	
Urinary diversion	Restricted to patients with intractable urinary tract symptoms that cannot be managed successfully using any of the above options. An ileal conduit is the most commonly used form of urinary diversion although continent diversion operations are also in use. The bladder is sometimes removed at the time of surgery in order to eliminate the risk of subsequent infection in the defunctioned organ (pyocystis).	

Given that patients, carers and clinicians can have fundamental choices to make between different treatment options and bladder management systems, it is important that there is information available to them about the effect of the different approaches on both quality of life and the accompanying risks. These judgements can be particularly difficult where a patient regards a particular approach as best suiting their circumstances even though there may be significantly greater risks attached to that management option. This can occur where major reconstructive surgical procedures are being considered, such as in a patient contemplating undergoing an augmentation cystoplasty in order to be continent while using intermittent self catheterisation. Conversely, there are occasions when a patient will choose the relative convenience of an indwelling catheter, despite the added risk of complications such as urinary tract stone formation and infection.

15.1 Intermittent Catheterisation, Indwelling Catheters and Penile Sheath Urine Collection

15.1.1 What are the long term risks associated with the long term use of intermittent catheterisation, indwelling catheters and penile sheaths?

Clinical Methodological Introduction	
Population:	Patients with incontinence due to neurogenic lower urinary tract dysfunction (NLUTD)
Intervention:	What are the long term risks (renal impairment, hydronephrosis, urinary tract stones, urinary tract infection, malignancy (bladder cancer) associated with the long-term use of intermittent catheterisation, indwelling catheters (supra pubic and urethral) and penile sheath collection/pads?
Comparison:	Not applicable
Outcomes:	• What is the quality of life associated with the above • Long term risks as specified in question

Clinical Methodological Introduction	
	• Include kidney, bladder and renal stones (urolithiasis, cystolithiasis renal lithiasis and nephrolithiasis) • Pyelonephritis

15.1.1.1 Clinical evidence

We searched for observational studies reporting on the long term risks associated with long-term use of intermittent catheterisation, indwelling catheters (supra pubic and urethral) and penile sheath collection/pads. In addition, we searched for observational studies reporting on the quality of life associated with these methods of urine collection.

Long term Risks

For the long term risk associated with catheters 17 studies were identified, with a minimum follow-up of 12 months[233 234 235 236 237 238 239 240 241 242 243 244 245 246 247,248 249].

Quality of Life studies

For quality of life, 3 papers were identified [250 251 252]. The search included observational studies. All of the studies were on adults with spinal cord injury, except for one on patients with myelomeningocele [250]. The results are reported by outcome.

Quality of studies

The majority of studies were retrospective reviews of medical records. The non-randomised comparisons between various catheterisation methods were prone to confounding from un-standardised management strategies being used for different population groups with different baseline risk profiles. In some studies statistical adjustments were made for such confounding, although in the majority of studies this did not occur. Studies were therefore categorised as very low quality.

Long term risks outcomes

Renal impairment

Study: N=70[233]

Length of follow-up: years of bladder management ranged from 2 to 33 yrs, frequency of follow up not stated

Table 124: Incidence of reflux and renal calculi

Complication	Intermittent catheterisation (n=23)	Padding (n=25)		Urethral catheter (n=22)		
Duration of follow-up	2-10 yrs (n=17)	2-10 yrs (n=7)	11-23 (n=14)	2-10 yrs (n=7)	11-23 (n=9)	24-33 (n=6)
Reflux	1	-	-	2	4	4
Renal calculi	-	-	3	-	1	2

None of the 6 patients on intermittent catheterisation for 11 to 23 yrs or the 4 on padding for 24 to 33 yrs reported any complications.

Study: N=57 [237]

Length of follow-up: 12 yrs, frequency of follow up yearly

Table 125: Incidence of renal stones and pyelonephritis

Complication	Total (n=57)	Catheterised group (n=32)	Non-catheterised group (n=25)	p-value (diff b/w catheterised and non catheterised group)
Renal stone	14	8	6	0.93
Pyelonephritis	13	8	5	0.66

Study: N=235 [239]

Length of follow-up: Duration of bladder management 24.1 yrs (range 10 to 45 yrs), frequency of follow up 70% yearly or every other year

Table 126: Incidence of renal calculi

	Participants with renal calculi (%)		Participants without renal calculi (%)	
	Initial discharge (n=46)	Follow-up (n=47)	Initial discharge (n=186)	Follow-up (n=188)
Normal bladder emptying	13	9	12	8
Suprapubic tapping	54	28	58	32
Abdominal pressure	17	19	19	15
Crede manoeuvre	2	23	6	19
Intermittent catheterisation	11	40	13	39
Urethral catheter	7	19	9	15

Study: N=140 [241]

Length of follow-up: 17 yrs, frequency of follow up yearly

Table 127: Incidence of renal stones

	Spontaneous voiding (SV)	Clean intermittent catheterisation (CIC)	Suprapubic cystostomy (SC)	Urethral catheter (UC)
Accumulated incidence (%)	6 (13)	3 (9)	4 (11)	8 (33)*
Episodes/100 person-years	0.88	0.54	0.65	2.5

* <0.05 in the SV versus the UC group, the CIC versus UC group, and the SPC versus the UC group by Fisher's exact test

Table 128: Results of multivariate analysis for renal stones

Bladder management	Renal stone OR adjusted (95%CI)	p
Spontaneous voiding (SV)	1.0	
Clean intermittent catheterisation	0.89 (0.17 to 4.6)	0.89
Suprapubic cystostomy	0.71 (0.16 to 3.2)	0.66
Urethral catheter	5.7 (1.3 to 25)	0.021

Study: N=179 [240]

Length of follow-up minimum 10 yrs, frequency of follow up yearly

Table 129: Incidence of the complications of upper urinary tract

	Urethral catheter	Intermittent catheterisation	Suprapubic cystostomy	Crede manoeuvre or reflex voiding	Condom catheter
Pyelonephritis	12 (41.4%)	20 (41.7%)	13 (31.0%)	10 (26.3%)	6 (27.3%)
Renal calculi	6 (20.7%)	6 (12.5%)	15 (35.7%)	13 (34.2%)	4 (18.2%)
Upper tract deterioration	15 (51.7%)	18 (37.5%)	11 (26.2%)	9 (23.7%)	5 (22.7%)

Table 130: Multivariate risk factors for complications of the upper urinary tract - adjusted odds ratio (95%CI)

	Pyelonephritis	Renal calculi	Upper tract deterioration
Urethral catheter	1.0	1.0	1.0
Intermittent catheter	0.930 (0.352-2.455)	0.526 (0.147 to 1.888)	0.330 (0.114 to 0.958)
Suprapubic catheter	0.532 (0.186 to 1.519)	1.827 (0.581 to 5.745)	0.097 (0.026 to 0.359)
Crede manoeuvre or reflex voiding	0.464 (0.158 to 1.366)	1.856 (0.579 to 5.955)	0.123 (0.035 to 0.428)
Penile sheath	0.502 (0.148 to 1.704)	0.746 (0.177 to 3.137)	0.200 (0.051 to 0.780)

Study: N=8314 [235]

Length of follow up: Mean 3 yrs (range 7 mths to 13 yrs), frequency of follow up yearly

Table 131: Incidence of stones in the kidney or ureter

Bladder management at discharge	N	%	No. of stones 5-yr cumulative incidence	%	P
Catheter-free	1710	20.6	20	1.6	0.002
Urethral catheter	1027	12.4	49	6.9	
Penile sheath	563	6.8	25	5.1	
Intermittent catheter	4407	53.0	179	5.0	
Suprapubic catheter	296	3.6	8	2.7	
Other	248	3.0	5	3.4	
Unknown	63	0.8	0		

Table 132: Risk factors for kidney stones occurring before and after the first year post injury – multivariate cox regression model

	Year one RR (adjusted) (95%CI)	Year 2 and later RR (adjusted) (95%CI)
Catheter-free	1.0	1.0
Urethral catheter	1.3 (0.6 to 2.7)	2.5 (1.1 to 5.7)
Penile sheath	1.3 (0.6 to 2.8)	2.0 (0.9 to 4.6)
Intermittent catheter	1.2 (0.6 to 2.1)	2.4 (1.2 to 5.2)
Suprapubic catheter	0.3 (0.1 to 1.3)	2.6 (1.1 to 6.3)
Other	0.6 (0.1 to 2.6)	4.2 (1.7 to 10.6)

Study: N=149[247]

Length of follow-up: 68 months, range 3 to 179 months, frequency of follow up variable

Table 133: Incidence of renal complications

Complication	Suprapubic catheterisation

Complication	Suprapubic catheterisation
All renal complications	20/149
Acute pyelonephritis	8/149
Renal calculi	12/149
Renal scarring	9/149
All vesicoureteral reflux (VUR) VUR with renal stones VUR with renal scarring VUR with renal stones and scarring	21/149 (bilateral in 5) 3/149 1/149 1/149

Renal scarring and calculi were more prevalent in quadriplegic than paraplegic patients. Renal scarring was generally mild, and the risk of scarring was zero if the bladder was normal or areflexic

Study: N=204 (142 followed up)[242]

Length of follow up: 12 years, frequency of follow up not stated

Table 134: Incidence of renal complications

Adverse event	Urethral catheter	Non catheterised	p
Renal stones	18/56	6/86	0.0001
Recurrent pyelonephritis	7/56	2/86	0.015
Parenchymal thinning	13/56	4/86	0.0009

Study: N=316[249]

Follow up mean 18.3 (12.4) yrs since injury, frequency of follow-up unclear

Table 135: Incidence of renal complications

Complications	Urethral n=114	CIC n=92	Spontaneous n=74	Suprapubic n=36	p
pyelonephritis	8%	1%	1.5%	3%	<0.001
Renal stone	55%	22%	20%	36%	<0.001
VUR	23%	7%	8%	28%	0.001
Abnormal upper tracts	30%	16%	27%	39%	0.038

Hydronephrosis

Study: N=70[233]

Length of follow-up: range 2 to 33 yrs, frequency of follow-up not stated

Table 136: Incidence of hydronephrosis

Complication	Intermittent catheterisation (n=23)	Padding (n=25)		Urethral catheter (n=22)		
Duration of follow-up	2-10 yrs (n=17)	2-10 yrs (n=7)	11-23 (n=14)	2-10 yrs (n=7)	11-23 (n=9)	24-33 (n=6)
Hydronephrosis	-	1	-	4	2	-

None of the 6 patients on intermittent catheterisation for 11 to 23 yrs or the 4 on padding for 24 to 33 yrs reported any complications.

Study: N=65 [243]

Length of follow-up: mean 3.7 yrs (range 1 to 7.5 yrs), frequency of follow up not stated

Findings:

0/28 of the patients had hydronephrosis

Urinary tract stones

Study: N=70[233]

Length of follow-up: range 2 to 33 yrs, frequency of follow up not stated

Table 137: Incidence of bladder calculi

Complication	Intermittent catheterisation (n=23)	Padding (n=25)		Urethral catheter (n=22)		
Duration of follow-up	2-10 yrs (n=17)	2-10 yrs (n=7)	11-23 (n=14)	2-10 yrs (n=7)	11-23 (n=9)	24-33 (n=6)
Bladder calculi	1	-	-	1	3	12

None of the 6 patients on intermittent catheterisation for 11 to 23 yrs or the 4 on padding for 24 to 33 yrs reported any complications.

Study: N=140 [241]

Length of follow-up: 17 yrs, frequency of follow up yearly

Table 138: Incidence of bladder stones

	Spontaneous voiding (SV)	Clean intermittent catheterisation (CIC)	Suprapubic cystostomy (SPC)	Urethral catheter (UC)
Accumulated incidence (%)	14 (30)	5 (15)	15 (42)*	5 (21)
Episodes/100 person-years	2.0	0.89	5.1	1.7

* <0.05 in the CIC vs SPC group by chi-square test

Table 139: Risk of bladder stone – results of multivariate analysis

Bladder management	Bladder stone OR adjusted (95%CI)	p
Spontaneous voiding (SV)	1.0	
Clean intermittent catheterisation	0.53 (0.16 to 1.8)	0.30
Suprapubic cystostomy	1.5 (0.56 to 3.9)	0.43
Urethral catheter	0.89 (0.24 to 3.3)	0.86

Study: N=57 [237]

Length of follow up: 12 yrs, frequency of follow-up yearly

Table 140: Incidence of bladder stones

Complication	Total (n=57)	Catheterised group (n=32)	Non-catheterised group (n=25)	p-value (diff b/w catheterised and non catheterised group)
Bladder stone	18	13	5	0.10

Study: N=457 [246]

Length of follow-up: median 60 months, frequency of follow up yearly

Table 141: Risk of bladder stones

Bladder management type	Mean follow-up(years)	No. of bladder stones/no. of pts	% forming bladder stones (no./ total no.)	Total group follow-up (years)	% absolute annual risk stone formation
Penile sheath + sphincterotomy	8.4	0	0 (0/55)	463	0
Intermittent self catheterisation (ISC)	6.75	1/1	1.5 (1/70)	480	0.2
Expression voiding with or without penile sheath	6.3	7/7	3 (7/240)	1,515	0.5
Urethral catheter	5.9	59/35	23 (35/152)	789	4% (first stone), 16% (subsequent stones)

Results of Cox- regression analysis: Although age, sex, and injury level were not significantly explanatory variables, degree of injury was considered (p=0.02) in the model. After correcting for degree of injury, both suprapubic and urethral forms of indwelling catheter were found to have a high risk of bladder stone formation compared with ISC or condom drainage with or without sphincterotomy.

The hazard ratio was 10.5 (p<0.0005, 95% CI 4.0-27.5) for patients with supra pubic catheters and 12.8 (p<0.005, 95% 5.1-31.9) for those with urethral catheters. Bladder stones were no more likely to form in patients with supra pubic catheters than in those with urethral urethral catheters (hazard ratio 1.2, p=0.6).

Study: N=149[247]

Length of follow-up: 68 months, range 3 to 179 months, frequency of follow up variable

Table 142: Incidence of bladder stones

Complication	Suprapubic catheterisation
Bladder stones	33/149

Higher incidence in quadriplegics (26/96 quadriplegics versus 7/68 paraplegics). There were frequent recurrences, leading to a total of 56 episodes.

Study: N=204 (142 followed up)[242]

Length of follow up: 12 years, frequency of follow up not stated

Table 143: Incidence of bladder stones

Adverse event	Urethral catheter	Non catheterised	p
Bladder stones	34/56	10/86	0.0001

Study: N=35[249]

Length of follow up: 6 years (range 2-12 years), frequency of follow up 6 monthly for two years then yearly

Table 144: Incidence of recurrent bladder stones

Adverse event	Urethral catheter	Intermittent catheterisation	p

Adverse event	Urethral catheter	Intermittent catheterisation	p
Recurrent bladder stones	13/13	0/13	Not stated

Study: N=316[249]

Follow up mean 18.3 (12.4) yrs since injury, frequency of follow up unclear

Table 145: Incidence of bladder stones

Complications	Urethral n=114	CIC n=92	Spontaneous n=74	Suprapubic n=36	p
Bladder stone	28%	0%	8%	22%	<0.001

Urinary tract infection

Study: N=129 [236]

Length of follow-up: One yr

Table 146: Incidence of upper tract infection (data extracted from graph)

Bladder management	Urinary tract infection % (95%CI)
Normal voiding	6 (2 to 36%)
Controlled voiding	20 (5 to 50%)
Clean intermittent catheterisation	70 (43 to 90)
Mixed (using clean intermittent catheterisation plus other method)	72 (58 to 90)
Suprapubic tapping	48 (30 to 68)
Compression or straining	31 (11 to 59)

Study: N=65 [243]

Length of follow-up: mean 3.7 yrs (range 1 to 7.5 yrs), frequency of follow up not stated

Findings:

12/28 patients had received treatment for one or more urinary tract infection

Study: N=125 [245]

Length of follow-up: One yr

Findings:

Table 147: Episodes and timing of urinary infections post admission

Timing (weeks)	Urethral catheterisation (n=85)	Supra-pubic cystostomy (n=40)	Total (n=125)
1,2	12 (20%)	6 (14%)	16 (13%)
2,4	10(16%)	3 (21%)	13 (10%)
4,6	33(52%)	1 (7%)	34 (27%)
6,8	4 (6%)	2 (14%)	6 (4%)
8,10	2 (3%)	1 (7%)	3 (2%)
10,12	2(3%)	1 (7%)	3 (2%)

Study: N=149[247]

Length of follow-up: 68 months, range 3 to 179 months, frequency of follow up variable

Table 148: Incidence of urinary tract infection

Complication	Suprapubic catheterisation
All symptomatic UTIs	45/149
Cystitis	38/149
Epididymo-orchitis	3/149

Some had more than one episode.

Study: N=204 (142 followed up)[242]

Length of follow up: 12 years, frequency of follow up not stated

Table 149: Incidence of urinary tract infections

Adverse event	Urethral catheter	Non catheterised	p
Symptomatic UTIs (1 episode)	6/56	35/86	0.0001
Symptomatic UTIs (> 1 episode)	42/56	11/86	0.0001
Urosepsis	12/56	7/86	0.023
Leading to death	2/56	0/86	

Study: N=64[248]

Length of follow up: 1 year, frequency of follow up monthly

Table 150: Incidence of urinary tract infections

Adverse event	Intermittent catheterisation	Condom and collection bag	p
Urinary tract infection	17.2 infections/ person-year	18.9 infections/ person-year	NS

Study: N=35[244]

Length of follow up: 6 years (range 2-12 years), frequency of follow up 6 monthly for two years then yearly

Table 151: Incidence of urinary tract infections

Adverse event	Urethral catheter	Intermittent catheterisation	p
Symptomatic (febrile) UTIs	12/13	7/22	Not stated

Study: N= 705[234]

Length of follow up: 1 year

Findings:

At discharge there was no significant difference in rate of bacteriuria with fever (BWF) between those with self intermittent catheterisation, those with intermittent catheterisation by someone else and those with a urethral catheter.

Table 152: Rates of BWF at hospital discharge and at 1 year follow up N (%)

	At discharge	At 1 year follow up
Self intermittent catheterisation	77/155 (50)	33/62 (53)
Intermittent catheterisation by other	60/103 (58)	20/24 (83)
Urethral catheter	48/114 (42)	25/57 (44)

Examining only those who were on the same system of drainage at discharge from the initial rehabilitation and at year 1 follow-up, the patients on intermittent catheterisation by someone else

(ICO) were more likely to have experienced at lease one episode of BWF than the group on self intermittent catheterisation and patients with urethral catheter ($p<0.025$).

Bladder cancer

Study: N=3670 [238]

Length of follow-up: mean 2 yrs

Findings:

Analyses of potential risk factors for bladder cancer revealed a significantly greater proportion of participants who used an indwelling urethral catheter (IDC) (46% of IDC group, 39% of multi group (using both dwelling and non dwelling)) developed bladder calculi compared with 10% in the non-urethral catheter (NIDC) group ($x2 =537.64$, $p<0.001$) .

Age- adjusted analyses revealed that increasing exposure to IDC use was associated with bladder cancer in spinal cord injury. The IDC group had an age –adjusted rate of 77 per 100,000 person-years, compared with rates of 56.1 and 18.6 per 100,000 person-years in the multi and NIDC groups, respectively.

After age and gender adjustment, participants with spinal cord injury were 15.2 (95% CI, 9.2 -23.3) times likely to develop bladder cancer than the general population. Of those using IDC only as their method of bladder management, the observed 15 cases of bladder cancer were compared with an expected 0.6 cases, yielding a ratio of 25.4 (95%, 14.0 -41.9).

Calculations of attributable risk (AR), revealed that IDC was responsible for 34.1 cases of bladder cancer per 100,000 person-years of SCI. This yielded an AR percentage of 55.8% for IDC use, whereas male gender and bladder calculi were responsible for fewer cases of bladder cancer, at 32.9% and 10.7% respectively. In those using IDC only, IDC was responsible for 58.4 cases per 100,000 person-years, or 64.8% of all bladder cancer occurring in the IDC population.

At the completion of the study, 13 persons with bladder cancer had died, with the cause of death identified as bladder cancer in 12. Of the 12, 10 had solely used IDC, where as 2 used multiple techniques. There were no bladder cancer deaths in the NIDC group.

Study: N=149[247]

Length of follow-up: 68 months, range 3 to 179 months, frequency of follow up variable

Table 153: Incidence of cancer

Complication	Suprapubic catheterisation
Low grade superficial transitional cell carcinoma	1/149

Quality of life outcome

Study: N=22[250]

Young patients with spina bifida (Myelomeningocele MMC) aged 13-26 who had been using clean intermittent catheterisation (CIC) independently for at least 5 years. This was a qualitative study, using semi-structured interviews, to elicit attitudes to their condition and CIC. The study was conducted in Sweden.

Telling peers of their use of CIC was deemed as difficult but important and satisfying. Peer reactions ranged from disgust (catheter insertion) to childish (use of diapers) to admiration. Those not in

wheelchairs experienced less belief from others about their CIC use, and some of these wished they were in a wheelchair to increase acceptance of their CIC use. Lack of medical staff understanding of CIC was perceived as a major problem.

All disliked being catheterised by someone else, but in medical appointments most were reticent at stating this, and the clinician would do the catheterisation.

Most of the participants rated their incontinence as a mild disability, and rated non-MMC disabilities they didn't have, such as blindness, as more severe.

Eight participants had no friends at all. Two others spoke of friends, but on later investigation these were really casual acquaintances. 12 had a best friend. 15 found it easy to make friends but harder to keep them. Barriers to friendship were perceived as an inability to run, the use of crutches or the need for diapers. 12 were currently involved with a partner. Finding a partner was strongly desired by 17, but they found it difficult to realise this wish. None knew of the effects of their condition on sexual function, and felt that a medical professional should give them more information on this. Some could not imagine a future without children of their own. 19 were preoccupied with thoughts of parenthood in the future, but 9 were unsure if they would be able to do this. Of the 3 female adults in a relationship, one had had a healthy baby. At the end of the interview the participants were invited to ask anything. Two males and two females asked: "How am I going to find someone to marry?"

Overall all participants were satisfied with CIC and would not want to return to their previous voiding technique. Most, after five years experience, did not find it a problem in daily life. Overall, CIC was regarded as positive and most of the children's negative experiences were related to their overall disability, independent of CIC.

Study: N=41[252]

SCI patients, mean age 39.5 yrs. Mean time post SCI 4 years. The study was conducted in Germany. Patients divided into "treatment successes" and "treatment failures". Success determined by a bladder capacity of >360 mL, absence of autonomic dysregulation and continence

Table 154: Qualiveen scale scores in relation to bladder function after correction for depression

	Bladder management mean (SD)		
Scale	Success (n=14)	Failure (n=27)	P value
Limitations	37.2 (22.10)	48.6 (18.29)	.0544
Constraints	39.2 (21.44)	52.9 (25.68)	.0377
Fears	20.0 (16.40)	44.7 (19.65)	.0014
Feelings	12.7 (15.22)	39.8 (27.69)	.0182

Study: N=132[251]

Follow up: 24 months. SCI patients using clean intermittent catheterisation, compared to healthy controls.

Effect

Comparison of SF-36 scores of patients and controls (general population) with respect to gender.

Table 155: Comparison of SF-36 scores of patient and controls (general population) with respect to sex

	Male mean (SE)			**Female mean (SE)**		
Domain	Patients (n=81)	Controls (n=90)	P value	Patients (n=51)	Controls (n=60)	P value
Physical	18.4 (3.2)	85.3 (1.7)	<0.001	28.3 (4.4)	72.0 (2.3)	<0.001

	Male mean (SE)			Female mean (SE)		
functioning						
Role-physical functioning	26.2 (4.5)	81.8 (2.9)	<0.001	30.9 (5.7)	71.2 (3.6)	<0.001
Role-emotional functioning	29.2 (4.8)	70.2 (3.4)	<0.001	38.6 (6.4)	60.8 (3.9)	0.002
Vitality	43.6 (2.4)	52.7 (2.0)	0.005	42.3 (3.0)	48.8 (1.9)	0.064
Mental health	55.6 (2.4)	67.2 (1.7)	<0.001	51.9 (3.1)	64.6 (1.7)	<0.001
Social functioning	49.5 (2.9)	85.2 (1.8)	<0.001	54.4 (4.0)	81.7 (2.1)	<0.001
Bodily pain	62.4 (3.3)	81.4 (1.8)	<0.001	60.5 (4.0)	70.9 (2.1)	0.025
General health	46.9 (2.1)	54.7 (1.5)	0.002	44.0 (2.3)	51.7 (1.8)	0.013

Table 156: Comparison of SF-36 scores of patients and controls (general population) with respect to age

	< 50 yr			≥ 50 yr		
Domain	Patients (n=90)	Controls (n=100)	P value	Patients (n=41)	Controls (n=50)	P value
Physical functioning	20.1 (3.0)	83.5 (1.7)	<0.001	27.1 (5.1)	74.9 (2.3)	<0.001
Role-physical functioning	28.3 (4.2)	81.0 (2.9)	<0.001	27.4 (6.6)	73.0 (3.6)	<0.001
Role-emotional functioning	32.6 (4.7)	66.9 (3.4)	<0.001	33.3 (7.0)	64.4 (4.0)	<0.001
Vitality	46.8 (2.1)	51.0 (1.9)	0.146	34.9 (3.5)	50.9 (2.1)	<0.001
Mental health	56.2 (2.2)	63.7 (1.7)	0.005	49.7 (3.7)	68.4 (1.8)	<0.001
Social functioning	54.0 (2.8)	84.2 (1.7)	<0.001	45.7 (4.3)	83.3 (2.2)	<0.001
Bodily pain	64.4 (2.9)	80.0 (1.7)	<0.001	55.7 (5.2)	72.7 (2.3)	0.004
General health	47.1 (1.8)	54.4 (1.6)	0.003	42.9 (3.2)	52.1 (1.6)	0.006

The results of this study demonstrate that a treatment regimen leading to favourable urodynamic data and continence correlates with better quality of life.

15.1.1.2 Economic evidence

No relevant economic evaluations comparing the short and long-term use of intermittent catheterisation, indwelling catheters and penile sheath collection/pads were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 157: Resource costs

Item	Cost*	Frequency †	Cost per year
Average cost of indwelling catheters:	£5.31	8.7/year	£245.00
Average costs of intermittent catheters	£0.75	5/day	£1,365.93
Average cost of pads	£0.25	5/day	£456.25
Average cost of sheaths	£4.84	1/day	£1,766.6

*Source: *NHS Supply Chain Catalogue (2011)[12] †GDG opinion.*

Economic considerations

The economic issues in this question are dependent on the degree of choice available in selection of intervention leading to two situations:

1. The choice of intervention is limited by what the patient can manage or by the indication for their condition.
2. The patient and clinician have a choice over the intervention on the basis of comfort, convenience and prevention of adverse events.

In the first situation the economic considerations are not particularly important as the choice has already been made on other grounds. In the second situation, the economic considerations are around the risks of adverse events. The incidence of adverse events is considerable, as reported in the clinical evidence. Since these adverse events would require some costly treatment, we believe that those interventions that produce the lowest rates of adverse events will result in the lowest overall cost.

15.1.1.3 Evidence Statements

Clinical evidence statements

9 studies of 9664 participants reported on the incidence of renal impairment (follow-up 3 mths to 33 yrs) (very low quality)

1 study of 135 participants reported on the incidence of hydronephrosis (follow-up 2 to 33 yrs) (very low quality)

8 studies of 1428 participants reported on the incidence of urinary tract stones (follow-up 3 mths to 33 yrs) (very low quality)

8 studies of 1476 participants reported on the incidence of urinary tract infections (follow-up 3 mths to 12 yrs) (very low quality)

2 studies of 3819 participants reported on the incidence of bladder cancer (follow-up 3 months to 179 months) (very low quality)

2 studies of 154 participants reported on quality of life (unclear) (very low quality)

Economic evidence statement

The choice of intervention should be based on the results of the clinical review as the incidence of adverse events associated with each intervention will be the main driver of cost-effectiveness. The intervention with the lowest rate of adverse events is likely to be the lowest cost.

15.1.2 Recommendations and links to evidence

Recommendations:	**RENAL IMPAIRMENT** **63. Discuss with the person and/or their family members and carers the increased risk of renal complications (such as kidney stones, hydronephrosis and scarring) in people with neurogenic urinary tract dysfunction (in particular those with spina bifida or spinal cord injury). Tell**

	them the symptoms to look out for (such as loin pain, urinary tract infection and haematuria) and when to see a healthcare professional. **64. When discussing treatment options, tell the person that indwelling urethral catheters may be associated with higher risks of renal complications (such as kidney stones and scarring) than other forms of bladder management (such as intermittent self catheterisation).** **65. Use renal imaging to investigate symptoms that suggest upper urinary tract disease.** **<u>BLADDER STONES</u>** **66. Discuss with the person and/or their family members and carers the increased risk of bladder stones in people with neurogenic lower urinary tract dysfunction. Tell them the symptoms to look out for that mean they should see a healthcare professional (for example, recurrent infection, recurrent catheter blockages or haematuria).** **67. Discuss with the person and/or their family members and carers that indwelling catheters (urethral and suprapubic) are associated with a higher incidence of bladder stones compared with other forms of bladder management. Tell them the symptoms to look out for that mean they should see a healthcare professional (for example, recurrent infection, recurrent catheter blockages or haematuria).** **68. Refer people with symptoms that suggest the presence of bladder stones (for example, recurrent catheter blockages, recurrent urinary tract infection or haematuria) for cystoscopy.** **<u>BLADDER CANCER</u>** **69. Discuss with the person and/or family members and carers that there may be an increased risk of bladder cancer in people with neurogenic lower urinary tract dysfunction, in particular those with a long history of neurogenic lower urinary tract dysfunction and complicating factors, such as recurrent urinary tract infections. Tell them the symptoms to look out for (especially haematuria) that mean they should see a healthcare professional.** **70. Arrange urgent (within 2 weeks) investigation with urinary tract imaging and cystoscopy for people with:** • **visible haematuria *or*** • **increased frequency of urinary tract infections *or*** • **other unexplained lower urinary tract symptoms.**
Relative value placed on the outcomes considered	The evidence review was designed to assess the long-term risks that are attached to the use of different LUT management systems. The GDG considered that the outcomes under consideration are of high importance.
Quality of evidence	The majority of studies were retrospective reviews of medical records. The non-randomised comparisons between different catheterisation methods were prone to

	confounding from un-standardised management strategies being used for different population groups with different baseline risk profiles. Studies were therefore categorised as very low quality. Studies were mainly restricted to patients with spinal cord injury. Overall, the evidence suggested an increased risk of stones, hydronephrosis and scarring associated with all bladder management systems compared to spontaneous voiding. Comparisons of the risks associated with different management systems were very limited, but there was some suggestion that urethral catheters were associated with a higher risk of complications compared to other bladder management systems.
Trade-off between clinical benefits and harms	The information presented in the evidence review is of relevance to clinicians, patients and carers when choices between management systems are under consideration. However, an analysis of the balance between benefit and harm is necessary. This should include an assessment of the possible benefits of the different management systems in the individual patient's circumstances. The review has not included an assessment of such benefits so that no statement can be made in relation to the benefit/harm relationship. Although the evidence was confined largely to spinal cord injury patients the GDG view was that the risks were applicable to a wider population.
Economic considerations	No health economic evaluations were found for this question. The clinical review showed that the incidence of adverse events is considerable. Since these adverse events would require some costly treatment, and might be quite serious, those interventions that produce the lowest rates of adverse events are more likely to be least costly. Some interventions might be contraindicated for some patients; in these cases economic considerations are not particularly important when deciding the intervention.
Other considerations	The GDG agreed complications associated with long term use of catheterisation needs to be discussed with patients prior to making decisions on bladder management. Patient GDG members acknowledged that potential kidney complications was a worry to patients and that it was important clinicians provided clear information and ensured patients knew where to go to obtain help when needed. The GDG were aware that the incidence of cancer of the bladder in patients with NLUTD remains uncertain and might not differ greatly from that in the general population but when cancer does occur in a neurological population it is more invasive and aggressive. The GDG noted that there has been a lot of debate on what the incidence is and that it is difficult to come to conclusions based on the evidence included. They noted that the studies that addressed this issue in the evidence revue were those that looked at rates of bladder cancer in relation to bladder management system. Studies looking at bladder cancer rates that did not include management system comparisons were not included. However, such studies were known to have produced a range of different estimates of the risk of bladder cancer, with most studies looking at spinal cord injury patients (Bladder cancer in patients with spinal cord injuries. K Subramonian, RA Cartwright, P Harnden and SCW Harrison. British Journal of Urology International. 2004, 93,739-743.) The recommendations were made on the basis of the information that arose from the literature review and the clinical experience of the GDG members. It was recognised that current practice, both in the UK and internationally, is to offer upper urinary tract surveillance to patients with neurogenic lower urinary tract dysfunction who are in groups (such as spinal cord injury) which have both a significantly increased risk of renal complications and a good prognosis with respect to their underlying neurological condition. Although there is no evidence that directly validates this approach, the GDG concluded that there is sufficient evidence of increased risk to suggest that current practice should be continued although it is hoped that future studies will evaluate the costs and benefits associated with upper tract screening. The GDG recommended referral for cystoscopy in patients with suspected bladder stones on the basis that cystoscopy is the most reliable investigation for detecting bladder calculi (which can be small and poorly calcified in some cases).

	The benefits of detecting and treating complications that include renal and bladder stones, hydronephrosis and bladder cancer were felt to be self-evident. The value to the patient of detecting minor degrees of renal scarring is uncertain

15.1.3 Research recommendations

Intermittent Catheterisation, Indwelling Catheters and Penile Sheath Urine Collection

5. What are the long-term risks and effects on quality of life of different bladder management strategies for lower urinary tract dysfunction in people with neurological disease?

- **Why this is important**

  The range of bladder management strategies available to manage lower urinary tract dysfunction in neurological disease includes permanent urethral catheterisation and suprapubic catheterisation, intermittent self-catheterisation, penile sheath collection systems and pads. However, there is very sparse evidence about which strategies are most acceptable to patients and/or their family members and carers. The current research base relates mainly to the spinal injury population but may be relevant to people with other neurological diseases.

  Bladder management strategies are a long-term treatment with implications for maintaining health and quality of life. In order to make informed choices about the most appropriate method of bladder management, patients and/or their family members and carers require information about the risks and benefits of the available options. There is currently little evidence about which methods are most likely to produce long-term complications (renal impairment, urinary stones and infections, hydronephrosis, bladder malignancy). The effect on quality of life for patients and/or their family members and carers of different bladder management strategies is not known. There are methodological difficulties due to the heterogeneity of the population with neurological disease, the long time course of treatments and the presence of cognitive impairment in some sub-populations.

  Proposed studies could include prospective cohort studies of disease-specific populations examining the effect of each method on quality of life using both generic and disease-specific assessment methods. In addition, prospective screening for complications including renal impairment, stone formation and infection should be carried out and comparisons made for each bladder management method. Particular emphasis should be placed on quality-of-life outcomes for family members and carers, especially for those looking after people with cognitive impairment.

16 Access to and interaction with services

The current organisation of services for patients with NLUTD is the result of diverse influences rather than objective planning. Regional spinal cord injury units were developed to meet the needs of casualties of warfare and high risk industrial activity and placed management of the urinary tract as a high priority. In contrast, patients with multiple sclerosis and Parkinson's disease have traditionally been managed in general neurology clinics which have often lacked the facilities to address urinary tract issues; the development of disease-specific specialist nursing for these conditions offers the prospect of improved urinary tract care for these patients. Furthermore, there are still many patients with symptoms from NLUTD who are largely managed in primary care; elderly patients with cerebrovascular disease or dementia will often have limited access to specialist management for urinary symptoms.

There is a need to understand what specialist expertise is available to meet the needs of patients with NLUTD and to use that resource effectively. Such efficiency depends not only on specialist services being accessed appropriately but also on the timely transfer of responsibility back to non-specialist clinical teams, when they are equipped to meet the patient's needs, so as to avoid congestion within specialist care.

Given the diversity of neurological conditions that are associated with NLUTD and the variable way in which patients' urinary tracts can be affected, it is not possible to design rigid referral pathways for NLUTD. However, the concept of "red flag" symptoms, signs and investigation results can be adapted to this clinical field although red flags can only represent an aid to appropriate referral as there will inevitably be other valid indications to seek specialist input.

While there needs to be effective interchange with timely communications between general and specialist services, there is also a need for high quality interaction between specialists. This need is particularly evident at the times of transition between paediatric and adult services and, again, when transferring patients into elderly care services. The need for a considered and structured transition from paediatric services has been recognised in areas such as cardiology and oncology, and furthermore it is recognised that transition is a process rather than being a discrete event at a point in time. Patients with complex NLUTD are also likely to benefit from a well-conducted transfer into adult services.

16.1 Access to and interaction with services

16.1.1 For patients and their carers with lower urinary tract dysfunction associated with neurological disorders, what are the experiences of access to and interaction with services that address these issues?

Clinical Methodological Introduction	
Population:	Neurological disease Patients/Carers
Intervention:	Primary, Secondary and Tertiary Services
Comparison:	Specialist versus non-specialist services
Outcomes:	• Quality of life • Patients satisfaction

We searched for observational and qualitative studies reporting on patient and carer experiences of access to and interaction with services. Preliminary searches found very little literature available on this topic therefore the search was widened to include patients with neurological disease or injury only. In addition, we searched the websites of registered stakeholders for audit or survey data.

16.1.1.1 Clinical Evidence Review

Two qualitative studies were identified that answered this question [253]; [254]. In addition, one focus group and one audit were identified [255]; [256].

One study [253] reported on 60 patients with Parkinson's disease or informal carers. All were living independently. Focus groups were organised and the responses to a series of open ended questions were recorded.

One study [254] reported on 11 patients with multiple sclerosis who met with a continence adviser. Participants were sent a survey to complete by mail.

There was one focus group with people with neurological conditions (number not specified) [255] and one survey of patients with multiple sclerosis (N=24) [256].

A summary of the characteristics of these studies is presented in the table below:

Table 158: Summary of study characteristics

	Population	Methods	Relevance	Quality
Wollin 2005[254]	Self-selecting sample of multiple sclerosis patients. Australia	Methods poor described. Results adequately reported.	Only a small proportion of patients had lower urinary tract symptoms. Only a small proportion of participants had engaged with continence services.	Low
Van der Eijk 2011[253]	Self-selecting sample of patients with Parkinson's disease. The Netherlands	Methods appropriate. Results well reported.	The number of patients with lower urinary tract symptoms was not specified. Focus of study was patient-centeredness.	Moderate
MS Trust 2001[256]	Neurologist and self selecting sample of patients with multiple sclerosis. UK	Methods appropriate. Results well reported	The number of patients with lower urinary tract symptoms was not specified. Focus of the study was MS specialist nurses	Moderate
NCS 2009[255]	Self selecting sample of patients with neurological conditions. UK	Methods unclear. Data collection unclear	The number of patients with lower urinary tract symptoms was not specified. The focus of the study was participants' experiences of neurological services.	Low

Experiences of staff groups

Specialist services and specialist nurses

Since consulting with a continence adviser, one study [254] reported that:

- the majority of patients noted an improvement in continence status and bladder issues.
- Some patients noted an improvement in lifestyle activities, with a significant increase in self confidence.

One study [253] reported that patients with Parkinson's disease wanted to have easy access to interim telephone and mail contact. There was a perceived increase in access to hospital care as a result of a specialised nurse in the department. This study also identified the lack of multidisciplinary collaboration and communication between healthcare providers as a significant contributor to existing bottlenecks in access to services.

One focus group report [255] found that:

- Not everyone had access to specialist nurses, but those who did were very positive about them, finding it helpful to have support from someone who knew about the complexities of their condition.
- People's experiences of specialist teams were positive.

One audit [256] reported that specialist nurses:

- Provided support during diagnosis and longer-term.
- Improved access to services.
- Co-ordinated care.
- Acted as an adviser to other health professionals.

Neurologists

One report [255] on focus groups, noted that:

- Those who did have check-ups with their neurologist described them as being very brief and offering no support or information, and only occasional drug reviews. There were a couple of instances of lack of flexibility within neurology services e.g., accessing services outside of their regular visits.

General Practitioners

One [255] focus group report found that:

- GPs were unable to be proactive in their support, relying on the patients to ask for specific treatments, or telling the person to return to their specialist for support. The lack of GP awareness did have particular consequences for some people, with people reporting being prescribed drugs for other conditions that were not suitable for someone with a neurological condition, or which reacted to existing drugs. GP education was considered to be vital. Continuity of GP was highlighted as important.

One study [253] reported that:

- Patients felt that late recognition of early symptoms and delayed referrals by GPs were major problems.

Access to services

One [255] focus group report found that:

- People noted difficulty with physically accessing services e.g., parking was lacking, need for accessible transport.
- There were several people who had been helped by specific treatments to which they no longer had access.

Continuity of care

One [255] focus group report found that:

- People mentioned instances of lack of communication and co-ordination between services and that people became lost to services in the transition from child to adult services and also post 65.

Support

One study [253] reported that:

Patients and informal care caregivers both expressed the need to be instructed on how to cope with the disease. This was seen as especially important for maintaining employment for as long as possible.

Patients wanted to be treated with respect and taken seriously. Paying attention to the 'person behind the disease' and providing customised care to individual preferences were greatly appreciated. Involvement and support of the informal caregiver was felt to be necessary in order to prevent overburdening.

One audit [256] reported that:

The role played by spouses or partners both at the time of diagnosis and later, in terms of continued care and support, in some cases over many years, could not be overestimated

One focus group report[255] found that:

In most areas people said that their carers received little or no support. It was suggested that carers rarely knew they were also entitled to have an assessment of their needs, and were often unaware of the relevant allowances and benefits.

Involvement in decision making

One study [253] reported:

- Many patients and informal caregivers expressed a desire to be actively involved, and to be able to participate in shared decision making with their professional caregivers. However, they identified a current lack of information to do so. Patients also valued the freedom to request a second opinion, and to self-select their professional caregiver or institution.

Treatment plan

One focus group report[255] found that:

- Very few people had care plans, although there was some confusion as to what constituted a care plan. Despite this, a number of people felt that they were as involved as they wanted to be in their care. Not many people had a key worker or care co-ordinator, but people said they knew who they would contact if their needs changed.

16.1.1.2 Economic evidence

No economic studies were identified on experiences of access to and interaction with services that address issued of lower urinary tract dysfunction associated with neurological disorders.

16.1.1.3 Evidence Statements

Clinical Evidence Statements

One study noted improvements in continence associated with a continence advisor (low quality)

One study noted positive experiences of specialist nurses (low quality)

One study noted that some patients and carers experiencing some lack of support, for example a lack of information, with respect to their appointments with neurologists and GPs (low quality)

One study noted that some patients and carers experienced delay in diagnosis (moderate quality)

One study noted that some patients and carers have difficulty accessing services either due to physical reasons or due to availability (low quality)

One study noted that some patients and carers experienced lack of communication and coordination (low quality).

One study noted that some patients and carers wanted help coping with their condition, especially for maintaining employment (moderate quality)

One study noted the important role of carers (high quality) and one study noted that carers received little or no support (low quality)

One study noted that patients and carers desired to be actively involved in their care but some lacked the information to do so (moderate)

One study noted that some patients felt as involved in their care as they wanted to be (low quality)

Economic evidence statements

No economic studies were identified for this question. It was not possible to present any short or long term costs for this issue. However, a better informed patient and good communication between service providers and patients will result in fewer long term costs due to better adherence to treatment and a better understanding of self care. There was recognition of the need for good quality information to be provided and this would incur staff time cost especially when provided through face to face training by clinical staff.

16.1.2 Recommendations and links to evidence

Recommendations:	**ACCESS TO AND INTERACTION WITH SERVICES** **71. Provide contact details for the provision of specialist advice if a person has received care for neurogenic lower urinary tract dysfunction in a specialised setting (for example, in a spinal injury unit or a paediatric urology unit). The contact details should be given to the person and/or their family members and carers and to the non-specialist medical and nursing staff involved in their care.**

	72. Provide people with neurogenic lower urinary tract dysfunction, and/or their family members and carers with written information that includes: • **a list of key healthcare professionals involved in their care, a description of their role and their contact details** • **copies of all clinical correspondence** • **a list of prescribed medications and equipment.** **This information should also be sent to the person's GP.** **73. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in 'Patient experience in adult NHS services' (NICE clinical guideline 138). Recommendations on tailoring healthcare services for each patient can be found in section 1.3 and recommendations on continuity of care and relationships can be found in section 1.4 of NICE clinical guideline 138.**
Relative value placed on the outcomes considered	The GDG put a high priority on patient satisfaction and quality of life; however there were no data available for quality of life in the evidence that was under consideration.
Quality of evidence	The quality of evidence was low to high quality. All the studies included in the review had only a small proportion of patients with urinary tract symptoms or the number was not specified. The recommendations made were based on the experience of the GDG members which was broadly in agreement with the conclusions from the qualitative studies and surveys included in the review. In Two studies [254], [255] patients reported a benefit from having access to specialist nurses or continence advisor and the GDG agreed that patient access to specialist nursing provided them with information and support which was not necessarily available from neurology or GP services. Particular areas of concern reported by patients in the studies included: a lack of communication between health professionals, a lack of co-ordination between services, a lack of support for carers, poor information provision for both patients and carers and limited involvement in decision-making about treatment and care. The group acknowledged that multidisciplinary collaboration and communication amongst health professionals was frequently suboptimal and could lead to a less satisfactory patient experience. The GDG felt that the generic recommendations made in the Patient Experience Guideline were highly relevant to this population and agreed these should be incorporated into the guideline.
Trade-off between clinical benefits and harms	The GDG agreed that providing patients and carers with information on who is involved in their care and how to access services would have a positive impact on the patient's experience.
Economic considerations	No economic studies were identified for this question. It was not possible to present any short or long term costs for this issue. However, a better informed patient and good communication will result in fewer long term costs due to better adherence to treatment and a better understanding of self care. There was recognition of the need for good quality information to be provided and this would incur staff time especially where provided through face to face training by clinical staff.
Other considerations	The GDG noted that GPs are often not given information about service access and contact details for the care provided to patients by other health professionals. The GDG agreed that individual care plans are now more widely used and are recognised as a means of improving information-sharing. They can also empower the patient and their carer by indicating the level of care and access to services they can expect to receive.

16.2 Transfer from child to adult services

16.2.1 What interventions or configuration of services improve outcomes when a patient is transferred from child to adult services?

Clinical Methodological Introduction	
Population	Patients with NLUTD Patients <19 yrs
Intervention	Specialist Adolescent Care Services (transition management)
Comparison	Usual Care
Outcomes	Patient Experience Quality of Life Morbidity (renal impairment, incontinence, urinary tract infections) Continuity of Care Readmission to hospital

We searched for any studies evaluating specialist adolescent care services (transition management) in patients with NLUTD.

16.2.1.1 Clinical Evidence Review

Ten studies of relevance were found. Only one study was found that addressed the effects of a specific transition intervention (Sawyer[257]). Respondents were the patients themselves. The other studies did not impose an intervention, but instead adopted an observational approach to evaluating current practice. Three of these quantitatively assessed the extent to which a family-centred, or "Medical Home" approach affected transition (Lotstein[258], Duke [259], Scal [260]). The respondents were the parents or guardians of the patients. The remaining six were qualitative studies attempting to elicit perceptions of current transition services (Osterlund[261], Davies [262], Fiorentino[263], Reiss[264], Stewart[265], Young[266]) with the aim of using such perceptions to inform better practice. Respondents were a mixture of patients, family members and health care providers.

Seven of the nine studies (Sawyer[257], Osterlund[261], Davies [262], Fiorentino[263], Reiss[264], Stewart[265], Young[266]) provided information relevant to the protocol outcome of 'patient experience', but none of the other outcomes were covered by these studies. The three studies addressing the value of the 'Medical Home' approach (Lotstein[258], Duke [259], Scal [260]) evaluated whether a certain level of transfer-related 'guidance and support' had been achieved, based on the answers to three questions. Although this measure is somewhat arbitrary, it does have some face validity as an indirect measure of patient experience, since the sense of feeling guided and supported through the transfer process is likely to lead to an improved experience.

All but four of the nine studies (Sawyer[257], Osterlund[261], Davies [262], Young[266]) included non-neurologically impaired participants in their samples although, unless there was evidence to the contrary it was assumed that they would include some neurologically impaired patients. Despite this population heterogeneity, it was deemed that these studies would contain relevant information applicable to patients with NLUTD.

All studies were from the USA, except:
Davies [262]: Canada
Fiorentino [263]: UK

Young[266]: Canada
Stewart[265]: Canada
Sawyer[257]: Australia

Table 1 summarises the nine included papers. Table 2 provides information on the quality of the reporting in the included qualitative studies.

Table 159: Summary of studies included in the clinical evidence review

Study	Underlying pathology; country of study	Age of patients	Respondents	Intervention details	Outcomes reported	Analysis
Pilot trial of a transition strategy						
Sawyer[257] n=10	Spina bifida; Australia	>18 yrs	Patients	Use of a **transition co-ordinator**, to transfer paediatric patients with spina bifida to the adult setting with a transfer summary record, and to make a case presentation to the adult medical centre. An initial assessment by the adult medical centre was also carried out by a nurse in the patient's own home. Finally a review was carried out by the medical team at the adult centre.	**Patient experience**	Qualitative analysis (no details given)
Studies quantitatively assessing a family-centred approach to transition (all used data from the 200-2001 National Survey of Children with Special health care needs)						
Lotstein[258] n=5533	Children with special health care needs; USA	13-17yrs	Parent/guardian	**Participants were categorised into those whose current care complied with the notion of a "Medical Home", and those who did not**. Criteria for having a Medical Home were: 1. a usual provider of care, a personal physician or nurse, 2. no problems obtaining referrals or effective care, and 3. receiving family-centred care	Whether or not the participant received guidance and support in the transition to adulthood, in terms of: 1. the provider having discussed changing health needs in adulthood, 2. having addressed a plan for tackling these changing	Simple comparison of proportions of those meeting the criteria of receiving guidance and support or not across the two groups formed by 1) those meeting the criteria of having a Medical Home and 2) those not meeting the criteria.

Study	Underlying pathology; country of study	Age of patients	Respondents	Intervention details	Outcomes reported	Analysis
				(all had to be met).	needs, and 3. having discussed the need for transfer to adult care (all had to be fulfilled).	
Duke [259] n= 18,198	Children with special health care needs; USA	12-17yrs	Parent/guardian	**Participants were categorised into those whose current care complied with the notion of a "Medical Home", and those who did not**. This was characterised by a measure of family centred care (FCC). It is a measure of the: 1. visit time adequacy, 2. provider listening quality, 3. provider sensitivity to family issues, 4. receipt of necessary health information, 5. partnering in an adolescent's care, and 6. the presence of interpreting services, if appropriate. This was converted into an overall continuous variable score (0-5), with a higher score	Whether or not the participant received guidance and support in the transition to adulthood, in terms of: 1. the provider having discussed changing health needs in adulthood, 2. having addressed a plan for tackling these changing needs, and 3. having discussed the need for transfer to adult care	There was a logistic regression analysis of the relationship between each of the 3 outcome measures (each bivariate, and each dealt with separately) and continuous FCC values, adjusting for potential confounders.

Study	Underlying pathology; country of study	Age of patients	Respondents	Intervention details	Outcomes reported	Analysis
				denoting a better parent-provider interaction. This score was dichotomised to >3.6/5 (higher) and <3.6/5 (lower).		
Scal [260] n=4332	Children with special health care needs; USA	14-17yrs	Parent/guardian	**Participants were scored on the main explanatory variable of parent provider interaction**. This was assessed with the same questions as for Duke 2011, except for the question on interpreters, which was not used. The score from the 5 questions were summed, with a higher score denoting a better parent-provider interaction.	Whether or not the participant received guidance and support in the transition to adulthood, in terms of: 1. the provider having discussed changing health needs in adulthood, 2. having addressed a plan for tackling these changing needs, and 3. having discussed the need for transfer to adult care A composite variable was created as the sum of the scores on these questions (1= yes,	Linear regression model evaluating the relationship between level of parent provider interaction (score of 0-5) and score relating to receiving adequate guidance and support (score 0-3). Other explanatory variables in the model were demographic and socioeconomic data, and illness severity and complexity.

Study	Underlying pathology; country of study	Age of patients	Respondents	Intervention details	Outcomes reported	Analysis
					0=no). Thus the score ranged from 0-3.	
Qualitative studies attempting to elicit perceptions of current transition services through interviews and focus groups						
Davies 2011 [262]	Complex neurological conditions with intellectual impairment	18-21 yrs	Parents=17	Experiences and perceptions about the transition process, with the aim of eliciting information that would inform good practice	**Carer experience**	Constant comparison method to analyse semi structured interviews
Osterlund[261] n=13	Spina bifida and SCI; USA	18-21 yrs	Patients=6, family members=6, private nurse=1	Opinions were sought on the perceived benefits of better medical record management during transition.	**Patient/carer experience**	Grounded theory analysis of the focus group and interview data.
Fiorentino[263] n=77	Physical disability; UK	16-24 yrs	Patients=50, carer=22	Experiences and perceptions about the transition practices already in use in this area were sought, with the aim of eliciting information that would inform good practice.	**Patient/carer experience**	Thematic analysis of the semi-structured interview data
Reiss[264] n=143	Chronic disability; USA	13-35yrs	Patients=49, family members =44, health care providers=50	Experiences and perceptions about the transition practices already in use in this area were sought, with the aim of eliciting information that would inform good practice.	**Patient/carer experience**	Content analysis of the focus group and interview data.
Stewart[265] n=34	CP, Spina Bifida, SCI, Head injury, and some non neurological cases; Canada	19-30 yrs	Patients=21, parents=12, health care providers=1	Experiences and perceptions about the transition practices already in use in this area were sought, with the aim of eliciting information that would inform good practice.	**Patient/carer experience**	Thematic analysis of the focus group and interview data.

Study	Underlying pathology; country of study	Age of patients	Respondents	Intervention details	Outcomes reported	Analysis
Young[266] n=60	CP, Spina Bifida and acquired brain injuries; Canada	20-33Y yrs	Patients=30, Parents=30	Experiences and perceptions about the transition practices already in use in this area were sought, with the aim of eliciting information that would inform good practice.	**Patient/carer experience**	Constant comparative method analysis of the interview data.

Table 160: Quality of reporting in qualitative studies included in the clinical evidence review

Study	Population	Methods	Analysis	Relevance to guideline population	Quality*
Sawyer[257]	Well reported	Poorly reported	Poorly reported	Moderate relevance: Spina Bifida patients in Australia.	Moderate
Osterlund[261]	Well reported	Well reported	Well reported	Moderate relevance: Spina bifida and SCI patients in USA.	High
Davies [262]	Well reported	Well reported	Well reported	Moderate relevance: Complex neurological conditions with intellectual impairment in Canada	High
Fiorentino[263]	Well reported	Poorly reported	Poorly reported	Limited relevance: Study was from the UK, but the population was defined as “physical disability” and will have contained a limited number of people within the guideline population.	Low
Reiss[264]	Well reported	Well reported	Well reported	Limited relevance: USA study, and the population was defined as “chronic disability”. This will have contained a limited number of people within the guideline population.	Moderate
Stewart[265]	Well reported	Well reported	Well reported	Moderate relevance: CP, Spina Bifida, SCI, Head injury, and some non neurological cases from Canada.	High
Young[266]	Well reported	Well reported	Well reported	Moderate relevance: CP, Spina Bifida and acquired brain injuries from Canada.	High

***Quality score based on the rating for population, methods and analysis**

Pilot trial of a transition strategy

Sawyer[257] (moderate quality)

This qualitative study reported the use of a transition co-ordinator. However, respondents did not focus specifically on the particular benefits or disadvantages of this intervention. Instead, responses reflected general dissatisfaction with the overall transfer experience.

Pre-transfer interviews suggested anxieties about leaving paediatric care, focussed around concerns about leaving familiar and trusted health care professionals and clinical environments, and about having to meet and develop rapport with new health professionals. There were specific fears about how well the medical record would be passed to the adult facility.

Post-transfer interviews showed there were three main sources of dissatisfaction:

- Time delay between planned transfer date and actual date, which was up to 3 months in 5 cases
- The assessment and review were regarded as insufficient, and it was believed that the prospect of the annual review in the adult service was not as good as the paediatric service
- Uncertainty about future care at the adult institution

Summary
The use of a transition co-ordinator did not appear to lead to a positive perception amongst respondents. Time delays, and the perception of insufficient assessments and review procedures, were the main sources of negative opinion on experience.

Quantitative assessment of a family-centred approach to transition

The quality of these studies could not be assessed

Lotstein[258]

Having a 'Medical Home' significantly increased the odds more than twofold of meeting the goal of getting guidance and support in transition (table 2).

Table 161: Results from Lotstein 2005

Outcome	Existence of a medical home	No medical home	
Receiving guidance and support in the transition to adulthood (needed to answer 'yes' to all three questions, as in Duke 2011 below)	20.1%	11.4%	adjusted OR: 2.1 (1.6-2.8)

Duke [259]

Having higher levels of family-centred care (FCC) led to significantly higher odds that the provider would engage in activities aimed at providing guidance and support during transition.

Table 162: Results from Duke 2011

Outcome (indicative of receiving guidance and support in the transition to adulthood)	Effects of Family Centred Care (FCC) on each outcome
Did the provider review future health needs?	OR: 2.3 (2.07-2.57); p<0.001 Higher levels of FCC (a score of >3.6/5) led to a 2.3x increased odds of future health needs being reviewed, compared to lower levels of FCC. This was after adjustment for all potential confounders.
Did the provider encourage the patient taking his/her own responsibility for care?	OR: 3.93 (3.51-4.40); p<0.001 Higher levels of FCC (a score of >3.6/5) led to a 3.9x increased odds of being encouraged to take responsibility for care, compared to lower levels of FCC . This was after adjustment for all potential confounders.
Did the provider discuss future transfer to adult providers?	OR: 1.63 (1.38-1.92); p<0.001 Higher levels of FCC (a score of >3.6/5) led to a 1.63x increased odds of transfer to adult providers being discussed, compared to lower levels of FCC. This was after adjustment for all potential confounders.

Scal [260]

Linear regression modelling showed a significant association between higher provider-parent interaction and a higher tendency to receive guidance regarding transfer (Regression co-efficient =0.0831, t =7.24, p<0.001) after adjustment for potential confounders. Other significant correlates of outcome were female gender, age and the number of needed services.

Summary

All three studies showed a consistent result: having a family-centred care model, with a high level of family involvement, led to a greater likelihood of gaining guidance and support in the transfer process. It is reasonable to assume that any greater guidance and support may indirectly and positively influence the outcome of patient experience.

Qualitative study attempting to elicit perceptions of current transition services

Davies, 2011 [262] (high quality)

Perceptions of transition to care

Parents felt a sense of abandonment by the health care system. They felt that had received little, if any, preparation for the eventual transition. There was limited discussion about the process in the year preceding the transition, and it was generally only at their young adult's last appointment in the pediatric setting that future care was discussed. Parents reported feeling fear and uncertainty during transition. They were fearful of the unknown in relation to the availability of appropriate services to address the needs of the family, as well.

Parental resourcefulness (for example using an informal support network) and having a family support system were thought to facilitate the transition.

Factors that were perceived as hindering the transition included inadequate resources (there were few resources available to meet the complex needs of their young adults), insufficient coordination,

compromised parental health (the process of transition was an extremely stressful time and this compromised parental health) and the vulnerability of the young adult.

Osterlund, 2005 [261] (high quality)

Management of patient records during transition

Patients felt that primary care physicians and school were not good at maintaining records that would be helpful in the transition process. Medical forms were felt inadequate to capture the rich detail of a true case. There was also the perception that no healthcare provider had the whole story of their case. Parents felt that the best documentation of the care their children had received was carried in their own heads, and worried that once their children took over independent responsibility for their own care they would not have this information. The patients were aware they did not carry such detailed memories of all the necessary information as their parents, and saw their parents as essential in managing their records. Parents thus felt compelled to make their own written care records.

Parents felt that they were not given adequate access to their own official medical records, although they felt this should be their right. They were enthusiastic about the concept of on-line records that they could access. They felt that having access to certain information, such as a baseline CT scan, would save much time and stress when going to hospital during emergencies, or when away from home.

Parents felt that sharing of information between institutions was inadequate, and they often felt that they were the only ones capable of initiating and facilitating that sharing. No patients reported access to transition notes.

Subsequent recommendations by Osterlund and colleagues:

1. Research into electronic health records, and how they could utilise the position of parents as the central information manager, should be carried out.
2. Efforts should be made to help parents transfer the information management role to their children
3. Internet-accessible records would be very useful
4. Future medical information systems could learn from current parental information strategies.

Fiorentino[263](low quality)

Carer perceptions of transition

The perception of problems was greater for the carers than the patients, the latter often lacking interest in their health. Carers often felt disturbed by the perceived reduction in service quality and quantity after transition, and the authors suggested that transition should be handled sensitively and gradually. Carers felt that the sudden onus on the patient taking responsibility for their own health excluded them from the care process. One important feeling was that information about transfer was not communicated smoothly.

Patient perceptions of transition

None of the young people felt that transition to adult services was smooth. Many young people were expected to contact their new consultants independently, which was, in the authors' opinion, often not done through disinterest, lack of confidence or moving away from the area. Often young people were unaware of the name of their new consultant.

Special units versus mainstream

Children from special units within mainstream schools seemed to have a smoother transition than those from mainstream schools without a special unit: the former had better continuity of care, and less loss of services such as physiotherapy, and this was attributed by the authors' to the child being networked better into the services system.

Reiss[264](moderate quality)

Preparatory steps

Preparatory steps should be taken early to prepare children for the adult world, and specifically for being an adult patient. In the earlier years this should involve asking the parents about their future wishes and desires for the child, thus instilling a sense in the child as being on a pathway to adulthood, and thus affirming the importance of teaching independence. Later, children should be given tasks to develop independence and self-care.

Closure

There should be a chance for the paediatric provider and the patient/family to say goodbye and to mark the important stage with some kind of rite of passage. Otherwise there is a sense of abandonment that may aggravate negative feelings towards the new provider.

Comparisons

Paediatrics was seen as friendly and patient/family-centred, but adult care was seen as "quick and dirty" and disease-centred. Patients, parents and paediatric providers lacked trust in the ability of the adult providers to provide an adequate service.

Working together

Paediatric and adult care were thought to represent two different philosophies, each with their advantages and disadvantages. The need for them to work together was emphasised. Parents often felt disenfranchised which limited their ability to share important information with providers.

Other perceptions

Attention should be given to any cognitive deficits for transfer to work optimally. If a disease is progressive and prognosis is poor, patients should be allowed to stay under paediatric care. Transition should be based on maturity, not age.

Stewart[265](high quality)

There was a feeling of doors being shut, being dropped, and feeling cut off at transition. It was felt too abrupt, often when the patients were not ready for it.

As a consequence, most respondents wanted the opportunity to build their own bridges between the paediatric and adult services. To do this they needed the help and support of others to assist them in communicating their needs, asking for assistance appropriately and making decisions. This was felt especially important since many had not, because of their condition, had the opportunity to develop these skills throughout childhood.

It was also perceived that service providers should communicate better with each other to improve service co-ordination. Negative attitudes from service providers were also seen as negative.

The participants suggested the following changes to transition services:

1. Involve patients and their families in the planning and delivery of transition services
2. Shift the focus of services from therapy to supports, including information, advocacy and education, peer support, and sharing knowledge
3. Provide individualised services in the local community
4. Start early to help a young person develop the skills and supports to lead a full life
5. Improve co-ordination and communication among community services
6. Share service providers' knowledge and expertise to guide and support the person in transition.

Young[266] (high quality)

The main challenges occurring in transition were:

1. Lack of access to health care. In particular the concern was in the loss of access to healthcare providers with whom a relationship had been built, and who had a historical knowledge of the condition. The sense of being left in the dark, with no knowledge of what health care was available for access, was expressed.
2. Lack of professional's knowledge. Adult providers were often viewed as having little relevant knowledge or training, and were perceived as afraid of treating people with disabilities.
3. Lack of information provided. Many felt that information from someone who knew how the system worked would have been helpful. Transition co-ordinators were suggested.
4. Uncertainty about transition. Many did not know what to expect.

Two solutions were identified:

1. Early provision of detailed information. Some youths wanted information to be directed at them and not just their parents. Some felt that the paediatric clinicians should give the information. Those who had already been through transition stated how helpful more information would have been in terms of knowing what to expect and what was available.
2. More extensive support throughout the clinical transition process. Again, a transition co-ordinator was suggested. There was also talk of support to help shift the role of advocate from parent to child

Summary of all qualitative studies

Record keeping was perceived as insufficient to assist a smooth transfer. Parents felt they were the only ones carrying the full story of their child's care, and were anxious about the ability of their child to take on that knowledge. The concept of making records more freely available electronically was suggested.

Transfer was often perceived as too sudden, and accompanied by too little warning or prior information. Patients and parents reported a sense of loss of health care providers that knew them and their case, and felt abandoned and unaware of what to do next. The chance to say goodbye to the paediatric provider was emphasised, in order to allow the children to move on. Parents often felt excluded by the transfer to adult services.

Patients were often lacking in an independent attitude to their own health. The need to start prompting children to become more independent from an early age was stressed. Proper preparation in terms of helping children to build their own bridges between services was viewed as important. Additional support throughout the transfer process was also perceived as a requirement, and some suggested a transfer co-ordinator would help.

Patients, parents and health providers often perceived the adult care system and its providers negatively. Communication between paediatric and adult care was viewed as inadequate, but there was a perception they should work together more. Families should be centrally involved in the process.

16.2.1.2 Economic evidence

No economic studies were identified that compared the cost effectiveness of different strategies for dealing with transitions.

16.2.1.3 Evidence Statements

Clinical Evidence Statements

One study comprising 10 patients suggested that the use of a transition co-ordinator did not lead to a positive patient or carer perception in terms of improving the transition process. (moderate quality)

Three studies comprising 28063 participants (though there is very likely to be some overlap of participants between studies) suggested that a family-centred care model, with a high level of family involvement, led to a beneficial effect on the likelihood of gaining guidance and support in the transfer process. low quality

Six studies comprising 317 participants suggested that transfer was perceived as too sudden and poorly communicated, that record keeping and inter-disciplinary communication were poor, and that patients should be given more help in adopting a more adult attitude to their own healthcare. (low to high quality))

Economic evidence Statements

No economic studies were identified that compared the cost-effectiveness of different strategies for dealing with transitions. The GDG recognised that there are costs involved in establishing a transition service. However, there are also costs attached to the patient disengaging from care and suffering from complications at a later date.

16.2.2 Recommendations and links to evidence

Recommendations:	**<u>TRANSFER FROM CHILD TO ADULT SERVICES</u>** **74. When managing the transition of a person from paediatric services to adult services for ongoing care of neurogenic lower urinary tract dysfunction:** • **formulate a clear structured care pathway at an early stage and involve the person and/or their parents and carers** • **involve the young person's parents and carers when preparing transfer documentation with the young person's consent** • **provide a full summary of the person's clinical history, investigation results and details of treatments for the person and receiving clinician** • **integrate information from the multidisciplinary health team into the transfer documentation**

	• **identify and plan the urological services that will need to be continued after the transition of care** • **formally transfer care to a named individual(s).** **75. When receiving a person from paediatric services to adult services for ongoing care of neurogenic lower urinary tract dysfunction:** • **review the transfer documentation and liaise with the other adult services involved in ongoing care (for example, adult neuro-rehabilitation services)** • **provide the person with details of the service to which care is being transferred, including contact details of key personnel, such as the urologist and specialist nurses** • **ensure that urological services are being provided after transition to adult services.** **76. Consider establishing regular multidisciplinary team meetings for paediatric and adult specialists to discuss the management of neurogenic lower urinary tract dysfunction in children and young people during the years leading up to transition and after entering adult services.**
Relative value placed on the outcomes considered	Patient and parent/carer experiences of the transition process from paediatric to adult services were considered to be important in themselves and particularly important in establishing positive engagement with the adult care team. The risks of failed transition arrangements were considered to be serious as they include disengagement with continuing care which could affect quality of life and lead to serious morbidity from renal impairment, incontinence, urinary tract infections or readmissions to hospital.
Quality of evidence	The evidence was assessed as low to high quality. The methodology of these studies was felt to be appropriate in the context of the clinical question. Evidence was limited to observational studies of patient and carer experience. However, given the nature of the question, the evidence was felt to be valuable in informing discussion. Although many of the studies included a non-neurological population the GDG considered the studies to contain relevant information that is applicable to a neurological population. The GDG noted that only one of the studies provided information from a UK population. Six studies [257], Osterlund[261], Fiorentino[263], Reiss[264], Stewart[265], Young[266]) provided information on the patient experience outcome as specified in the protocol, but none of the other outcomes were covered by the studies included in the review. Three studies that quantitatively assessed a family-centred or 'medical home approach' (Lotstein[258], Duke [259], Scal [260]) demonstrated that a high level of family involvement led to a greater likelihood of obtaining support and guidance in the transfer of care which may result in a more positive patient experience. These studies all used high quality nationally collected data and were assessed as having used appropriate analytical techniques. Five qualitative studies (Osterlund[261], Fiorentino[263], Reiss[264], Stewart[265], Young[266]) considered the perceptions of current transition services. The participants were a mixture of patients, family members and health care providers. The studies reported examples of poor communication amongst health professionals and inadequate patient record keeping. Patients reported that transfer was often sudden with little warning or information and inadequate communication between paediatric and adult services. The GDG recognised that the findings of these studies provide a limited insight into the issues that can impact on the success of the process of transferring care between different services. However, the issues raised were felt to chime with some of the

	experiences of GDG members.
Trade-off between clinical benefits and harms	More structured, proactive, transition processes are very unlikely to cause clinical harm but may be of substantial benefit.
Economic considerations	No evidence is available that addresses the issue of cost-effectiveness of transition services. The GDG recognised that there are costs involved in establishing a transition service. However the GDG also recognised that the savings may fall out of better continuity of care (e.g. savings from fewer later complications, from patient's disengagement from care).
Other considerations	The transfer of urological care from paediatric to adult services has to be undertaken in the context of the overall transfer of care of the underlying neurological condition. A number of patients with neuropathic urinary tract disorders will have multiple and complex associated needs. The GDG recognised that there are particular skills (such as adolescent health expertise, multi-agency working, communication counselling) required in the effective management of young people. The transition process is recognised to include the involvement of parents and carers as well as patients. For example, providing parents with information to allow them to support their child's transition into adulthood may be of value.

17 Glossary: methodology

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Bivariate	Bivariate data, that shows the relationship between two variables
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative,

	in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Cox- regression analysis	Method for investigating the effect of several variables upon the time a specified event takes to happen. The method does not assume any particular "survival model" but it is not truly non-parametric because it does assume that the effects of the predictor variables upon survival are constant over time and are additive in one scale.
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based

	on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard See 'Reference standard'GRADE.	GRADE / GRADE profile A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.

Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Healthcare Resource Group (HRG)	A grouping consisting of patient events that have been judged to consume a similar level of resource
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity Or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Internal validity	Measure in quantitative studies, where it ensures that a researcher's experiment design closely follows the principle of cause and effect.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and

	specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Loss to follow-up	This represents the number of participants in a study who were not available for follow-up measurements after an intervention. Loss to follow up can create bias if two groups have a differential percentage of loss to follow up, and bias can also be created between groups through a breakdown of randomisation.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV) [In screening/diagnostic tests:]	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
Net monetary benefit (NMB)	The value (usually in monetary terms) of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the NMB is calculated as: (£20,000 x QALYs gained) – cost. This value can then be compared easily against other interventions.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening/diagnostic tests: A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct.

Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	For diagnostic tests. The proportion of patients with that particular test result who have the target disorder (post test odds/[1 + post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.

Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
SF-6D	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases

	incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

18 Glossary: clinical

Alpha-blockers(Alpha adrenergic antagonists)	(Also known as alpha adrenergic blocking agents or alpha adrenergic antagonists): drugs that inhibit the response to sympathetic impulses by blocking the alpha receptor sites of effector organs. Also known as alpha adrenergic blocking agents or alpha adrenergic antagonists. Because they inhibit the contraction of non-vascular smooth muscle such as the trigone and sphincter muscles of the urinary bladderthat found at the bladder neck and within the prostate, aAlpha-blockers are sometimescommonly used to treat bladder outflow obstruction in men with normally innervated urinary tracts.
Anticholinergic	An anticholinergic agent is a substance that blocks the neurotransmitter acetylcholine in the central and the peripheral nervous system.
Antimuscarinic drugs:	An anticholinergic agent that specifically blocks the muscarinic form of the cholinergic receptor. Because they decrease the bladder tone and the amplification of contractions of the urinary bladder and counteract the relaxation of the trigone and external sphincter responsiveness of the bladder wall muscle to stimulating nerve impulses, Antimuscarinic drugs are used in the management of the overactive bladder.
Appendicovesicostomy	Surgical transference of the isolated appendix so that it can be used as a conduit for urinary diversion from the bladder to the skin in children with cloacal exstrophy or neurogenic bladder, making a route for insertion of a catheter.
Areflexic	Absence of reflexes.
Asymptomatic bacteriuria	Significant number of bacteria in the urine that occurs without usual symptoms of infection such as, burning during urination or frequent urination.
Augmentation cystoplasty	Surgical reconstruction of the bladder using an isolated intestinal segment to augment bladder capacity.
Auto augmentation	Surgical procedure in which the detrusor muscle of the bladder is removed, leaving the bladder epithelium otherwise intact.
Autologous fascial sling surgery	A procedure to treat stress urinary incontinence , in which a harvested strip of rectus fascia is used to provide support to the urethra.
Autonomic dysreflexia	Condition associated with damage to the spinal cord above the mid thoracic level characterized by a marked increase in the sympathetic response to minor stimuli such as bladder or rectal distention. It may be triggered by distension of the bladder or colon; catheterization of or irrigation of the bladder; cystoscopy; or during transurethral resection Manifestations include severe hypertension; bradycardia; flushing; and excessive sweating. This is a potentially life threatening condition which should be considered a medical emergency requiring immediate attention.
Autonomic dysregulation	Malfunctioning of the autonomic nervous system (the portion of the nervous system that conveys impulses between the blood vessels, heart, and all the organs in the chest, abdomen, and pelvis and the brain (mainly the medulla, pons and hypothalamus).
Bacteriuria	Presence of bacteria in urine.
Behavioural management programmes	Behavioural therapies are usually used to treat urge urinary incontinence and mixed urinary incontinence. Such therapies include: Timed voiding where the person is asked to void at set time intervals, rather than in response to a sense of bladder filling. Bladder retraining where intervals between voids are progressively increased or the patient is asked to delay voiding for a specific time when they experience

	the need to void. Habit retraining involves identifying an incontinent person's toileting pattern and developing an individualized toileting schedule in order to pre-empt episodes of incontinence.
Biofeedback	The process of becoming aware of various physiological functions using instruments that provide information on the activity of those same systems, with a goal of being able to manipulate them at will.
Bladder retraining	See behaviour management programmes.
Bladder stone	Stone found in the urinary bladder formed by crystallization and concretion of salts from the urine usually in stagnate urine, and containing phosphate and oxalate salts of calcium or ammonium. Stones typically form in conjunction with bacterial colonization of the urine, for example when an indwelling catheter is present or bladder emptying is incomplete..
Bricker anastomosis	Technique for performing ureteroenteric anastomosis. This is the joining site of the ureters and the section of intestine used for the diversion for example in an ileal conduit.
Cauda equina compression	serious condition caused by compression of the nerves roots in the lower portion of the spinal canal that supplying the lower limbs and, crucially the bladder and urethral sphincter.
Congenital sacral dysgenesis	A congenital disorder in which there is abnormal foetal development of the sacrum. This can result in major malformation of the lower vertebrae and pelvis, affecting the spinal nerves in the region with resulting neurological impairment.
Crede manoeuvre	Use of manual pressure on a bladder, particularly an acontractile bladder, to express urine.
Cutaneous diversion	Surgical procedure that diverts urine to an abdominal wall stoma. For example a ureterostomy is formed by detaching one or both ureters from the bladder, and bringing them to the surface of the abdomen with the formation of an opening (stoma) to allow passage of urine. An ileal conduit is another form of cutaneous diversion.
Cystectomy	Surgical removal of all or part of the urinary bladder.
Cystometric capacity	Volume of urine that can be held in the bladder.
Detrusor	Detrusor urinae muscle, also detrusor muscle, muscularis propria of the urinary bladder and (less precise) muscularis propria, contracts when urinating to squeeze out urine.
Detrusor overactivity (formerly detrusor hyperreflexia)	Frequently occurring condition characterized by frequency, urgency and urge incontinence. Detrusor overactivity is defined as the presence of involuntary detrusor contractions seen during the filling phase of a urodymnamic study.
Electomyography (EMG)	Technique for evaluating and recording the electrical activity produced by skeletal muscles.[1] EMG is performed using an instrument called an electromyograph, to produce a record called an electromyogram. An electromyograph detects the electrical potential generated by muscle cells[2] when these cells are electrically or neurologically activated. The signals can be analyzed to detect medical abnormalities, activation level, recruitment order or to analyze the biomechanics of human or animal movement.
Epididymo-orchitis	Inflammation of the epididymis and/or testis. It is usually due to infection, most commonly from a urine infection or a sexually transmitted infection.
Febrile UTIs	Urinary tract infections resulting in fever.
Filling cystometry	Part of urodynamic testing in which the bladder is slowly filled with liquid while pressure and volume measurements are taken in order to assess bladder function.

Gore-tex bladder neck sling	Sling made of synthetic material compressing the bladder neck with the aim of preventing stress urinary incontinence
Habit retraining	See behaviour management programmes.
Hydronephrosis	Distension and dilation of the renal pelvis and calyces, usually caused by obstruction of the free flow of urine from the kidney. Untreated, it leads to progressive atrophy of the kidney as a result of back pressure.
Ileal conduit diversion	Surgical technique for the diversion of urine into a specially formed reservoir from a section of the ilieum with a stoma after a patient has had their bladder removed. Urine is transported from the ureters (the tubes draining urine from the kidneys) to a stoma on the abdominal wall using an isolated segment of small intestine.
Ileal loop	An alternative term for ileal conduit.
Ileocecal	A segment of the intestine which comprises part of both the small intestine (ileum) and the large intestine.
Ileocystoplasty	Augmentation cystoplasty using an isolated segment of the ileum for the graft.
Ileum	Final section of the small intestine
Isoperistaltic	Performed or arranged so that the grafted or anastomosed segment of bowel (or other peristaltic tube) exhibit peristalsis that facilitates propogation of material through the bowel segment.
Klebsiella	Frequent human pathogen which can lead to a wide range of disease states, notably pneumonia, urinary tract infections, septicemia, ankylosing spondylitis, and soft tissue infections.
Lipoma of cauda equine	A benign spinal tumour that is predominantly comprised of fat and can cause cauda equina compression or be associated with mal development of the spine and spinal nerves.
Locus of control	Theory in personality psychology referring to the extent to which individuals believe that they can control events which affect them.
Marlex mesh	Used surgically as a reinforcing mesh for example in inguinal hernia repair.
Medullary lipoma	Benign, soft, rubbery, encapsulated spinal cord-tumor, usually composed of mature fat cells.
Meningocele	Type of spina bifida in which the spinal cord develops normally but the meninges protrude from a spinal opening.
Myelitis	Disease involving inflammation of the spinal cord, which disrupts central nervous system functions linking the brain and limbs.
Myelodysplasia	A congenital disorder resulting in a neural tube defect causing defective development of any part of the spinal cord.
Neurogenic	Originating in the nerves or nervous tissue.
Neurogenic bladder	Lower urinary tract dysfunction due to disease of or damage to the nervous system supplying the lower urinary tract.
Neuromusclar electrical stimulation	Procedure used to strengthen healthy muscles or to maintain muscle mass during or following periods of enforced inactivity. This helps to maintain or gain range of motion, to facilitate voluntary motor control, and temporarily reduces spasticity when the nerve supply to the muscle is intact. This procedure involves sending small electrical impulses through the skin to the underlying nerves and muscles to create an involuntary muscle contraction.
Neuropathic	Any pathology of the nervous system.
Neuroradiological	Related to the branch or type of radiology that deals with the nervous system.
Nocturia	Waking from sleep one or more times to urinate.
Non-neurogenic etiology	Originating outside the nerves or nervous tissue.

Overactive bladder:	Produces symptoms of urinary urgency, with or without urge incontinence, usually with an increased frequency of micturition. It is characterised by the presence of involuntary bladder contractions that are seen during bladder filling. These are sometimes termed “bladder spasms”.
Pelvic floor muscle training	Daily training programme to strengthen the muscles that support the uterus, bladder and other pelvic organs and help prevent accidental urine leakage. Also called Kegel exercises or pelvic muscle rehabilitation.
Perineal	Pertaining to the perineum. A region of the body including the genitals and anus.
Pressure-flow studies	Simultaneous measurement of bladder pressure and flow rate during the voiding phase of the micturition cycle. The test is used to assess the process of bladder emptying. For example bladder outflow obstruction can be diagnosed if there is a low urinary flow rate in conjunction with a raised bladder (detrusor) pressure during voiding.
Pelvic Floor Prolapse	Loss of muscle tone and or ligamentous elasticity resulting in the descent of the uterus or other pelvic organs into the vagina. If severe, the prolapse can protrude out of the vaginal orifice.
Prompted voiding	This is used to encourage people to initiate their own toileting. It usually involves positive reinforcement. It involves the use of a carer to take the person with incontinence to the toilet, and so involves education of both the person with incontinence and their carer.
Pseudomonas	Clinically significant and opportunistic pathogen, often causing hospital-acquired infections.
Puboprostatic sling suspension	Support structures, made from natural or synthetic materials, that are implanted so as to support the urethra, to treat urinary stress incontinence.
Pyelonephritis	Ascending urinary tract infection that has reached the pyelum or pelvis of the kidney. It is a form of nephritis that is also referred to as pyelitis.
Pyocystitis	Inflammation involving the accumulation of pus within the urinary bladder. It is typically seen in patients in whom urine has been diverted away from the bladder (for example by an ileal conduit diversion).
Pyuria	Urine which visibly contains pus or microscopically contains an excess of white blood cells.
Qualiveen	A disease specific quality of life measure for individuals with spinal cord injury who have urinary disorders. It has 30 items that focus on four aspects of patients’ lives: bother with limitations, frequency of limitations, fears, and feelings. Response options are framed as five-point scales with 0 indicating no effect of urinary problems on health-related quality of life and four indicating a high adverse effect
Rectus fascia	Connective tissue that surrounds, the paired muscle running vertically on each side of the anterior wall and all the blood vessels, and nerves, binding those structures together.
Rectus sheath	Consists of two lamina, the anterior sheath and the posterior sheath. The sheath is made up of the aponeuroses of the three anterolateral abdominal muscles as they converge at the linea alba. The makeup of the anterior and posterior sheaths vary depending on the level of the abdominal wall examined.
Renal calculi	Stones in the kidney, usually formed in the urine-collecting area of the kidney (kidney pelvis). Their sizes vary and most contain calcium oxalate.
Sacral agenesis	A condition that exists when either part or all of the sacrum is absent. It is usually associated with impaired development of sacral spinal nerves and with consequent pelvic organ and lower limb dysfunction.
Sacral teratoma (Sacrococcygeal teratoma)	Tumour occuring in the sacrococcygeal region, usually noted at birth or appearing soon after.

Renal Scintigraphy	photographic recording, with the use of a gamma camera, of the distribution of a radioisotope (radioactive substance) given by injection which accumulates in the kidneys and allows the production of pictures offering details on both kidney structure and function.
SF-36	A multi-purpose, short-form health survey with only 36 questions. It yields an eight-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.
Sigmoid	Segment of the colon between the descending colon and the rectum.
Spina bifida	A condition in which the bones of the spine do not close. In cases of myelomeningocoele, the bony abnormality is accompanied by abnormal development of the spinal cord or nerves and their covering membranes, which leads to abnormalities in the nerve supply to the lower limbs and pelvic organs.
Spinal cord lipoma	Fatty non-cancerous tumour within or around the spinal cord without any skin or bony abnormalities. Most commonly these lesions are located within the thoracic spinal cord and may cause symptoms of spinal cord compression. They appear most often in adults.
Spinal dysraphism	A general term that encompasses a number of different developmental abnormalities of the spine and spinal cord, of which spina bifida is an example.
Stomal stenosis	Narrowing of the stoma.
Timed voiding	See behavioural management programmes.
Transverse colon	The part of the large intestine that runs from the ascending colon, across the abdomen, to continue as the descending colon.
Transverse myelitis	Neurological disorder caused by inflammation within a localised section of the spinal cord. Damage and scarring can occur affecting the function of the nerve connections crossing that segment
Ureteroileal stenosis	Narrowing of the tubes that carry urine from the kidneys at the point where they are joined to an ileal conduit.
Urethral	Related to the canal through which urine is discharged from the bladder
Urethral tape and sling surgery	A procedure that restores bladder control for people who lose urine when they cough or exercise. The urethral tape procedure involves positioning an artificial tape under the urethra, which is the tube that runs from the bladder through which you urinate. The tape will then rest like a hammock under the urethra, giving support and maintaining continence. A urethral tape consists of a thin mesh ribbon that is placed in order to provide support to the urethra. Urethral sling surgery involves placing a sling around the urethra to lift it back into a normal position and to exert pressure on the urethra to aid urine retention. The sling is attached to the abdominal wall. Also, please see: Autologous fascial sling surgery.
Urge incontinence	See overactive bladder.
Urinary diversion	Surgical procedure to reroutes urine flow from its normal pathway either temporarily or permanently.
Urodynamic investigations:	Investigation of the function of the lower urinary tract (the bladder and urethra) using physical measurements such as urine pressure and flow rate, as well as clinical assessment. Video-urodynamic investigations involve using a dye to fill the bladder enabling X-rays of the lower urinary tract to be taken during filling and emptying of the bladder.

Stress incontinence	Stress urinary incontinence describes a symptom, a sign and a diagnosis, although it is only following urodynamic investigation that a diagnosis of urodynamic stress incontinence can be made. This condition is defined as 'the involuntary leakage of urine during increased abdominal pressure in the absence of a detrusor contraction'.
Uroflowmetry	Diagnostic test used to measure the flow of urine during urination.
Urosepsis	A systemic inflammatory response to urinary tract infection which may result in septicaemia, multi-organ failure and death if severe. The term is used occasionally used to mean any urinary tract infection.
Vesicoureteral reflux	Retrograde flow of urine from the urinary bladder up the ureter. This is may be due to a congenital abnormality of the vesicoureteral valve, recurrent infection or raised intravesicular pressure as a result of bladder outlet obstruction or neuropathic bladder sphincter dyssynergy.
Vesicovaginal fistula	Abnormal fistulous tract extending between the bladder and the vagina that allows the continuous involuntary discharge of urine into the vaginal vault.
Visual analogue scale	Psychometric response scale which can be used in questionnaires . It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured.

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