INTRATHECAL BACLOFEN THERAPY FOR
TREATMENT OF SPASTICITY AND DYSTONIA
IN CHILDHOOD

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ABSTRACT

Spasticity is a common presentation in a wide variety of neurological disorders like cerebral palsy (CP), multiple sclerosis, and spinal cord injury. Management of spasticity involves multiple modalities such as physical and occupational therapy, oral medicines, Botulinum toxin injection, and orthopaedic and neurosurgical intervention. Intrathecal Baclofen (ITB) therapy is one neurosurgical intervention to control spasticity in CP patients. The ITB pump is implanted subcutaneously or sub-facially in the abdomen which delivers the baclofen directly to the intrathecal space via a catheter. As a result of by-passing the blood-brain-barrier, intrathecal administration of a hundredth part of the oral baclofen dose is sufficient to relieve spasticity and therefore preventing the peripheral side-effects seen with oral administration.

Although the ITB delivery systems demonstrate significant effectiveness in improving spasticity, the ITB delivery system is associated with a high complication rate which could interfere with the desired effect of ITB therapy. Therefore, in a retrospective observational study we aimed to analyse the ITB complications in a large (n=222) consecutive series of patients. The complication rate in relation to the long period of follow-up (939 pump years), was found to be similar or less than those reported in literature. Dystonia, young age and presence of gastrostomy tube were significantly associated with infective complications. Catheter complications were influenced by presence of dystonia and the surgical technique, whether it was a subfascial or subcutaneous implantation.

The pump is refilled by baclofen solution. The frequency of refilling is dependent on the daily dosing regime and the concentration of the aqueous
solution of baclofen in the pump. Baclofen solutions are available as commercial and compounded products. An experimental controlled study was conducted to evaluate the safety of using higher concentrations of compounded baclofen in comparison to commercial baclofen. Baclofen concentration of the compounded solution was found to be less accurate than the commercial product although it was within an acceptable range from the expected value. The number of invisible particulates was significantly higher in the compounded solution than in commercial baclofen. However, no clinical complications were reported in the compounded or in the commercial baclofen groups.

As patients receiving ITB therapy may have clinical benefits of reduction of the severity of spasticity, they could also have improvements in their functional status and quality of life. A survey study to evaluate changes in functional status and health related quality of life, showed improvement in both aspects, moreover, the improvement in the health related quality of life was more significant than the change in functional status.
This thesis is dedicated to the children and their families whose lives have been affected by spasticity and cerebral palsy.
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Ughratdar I1, Muquit S, Ingale H, Moussa A, Ammar A, Vloeberghs M.

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ABBREVIATIONS

4CPP: 4-(4-chlorophenyl)-2-prolidinone

AC: Arm circumference

AHC: Anterior horn cell

ASA: American Society of Anaesthesiologists

BCM: Boots Contract Manufacturing

BDNF: Brain-derived neurotrophic factor

BMI: Body mass index

BPC: British Pharmacopoeia

BTX: Botulinium toxin

CA: Cornu Ammon

CareQ: Care and Comfort Caregiver Questionnaire

CDCP: Centres for Disease Control and Prevention

CGC: Clinical Governance Committees

CHQ: Child Health Questionnaire

CHIP: Coping Health Inventory for Parents

CNS: Central Nervous System

COPM: Canadian Occupational Performance Measure

CP: Cerebral palsy

CPCHILD: Caregiver Priorities and Child Health Index of Life with Disabilities

CPQOL: Cerebral palsy quality of life questionnaire

CQ: Caregiver Questionnaire

CSF: Cerebrospinal fluid

DBS: Deep brain stimulator

DDS: Drug device system

DRT: Dorsal Reticulo-Spinal Tract

DVT: Deep Venous Thrombosis

EMG: Electromyography
EORTC: European Organization for Research and Treatment of Cancer
ES: Effect Size
ESAs: Erythropoiesis-Stimulating Agents

FDA: Food and Drug Administration
FIM: Functional Independence Measure

GABA: Gamma Aminobutyric Acid
GAD: Glutamic Acid Decarboxylase
GDNF: Glial Cell Line-Derived Neurotrophic Factor
GMFCS: Gross Motor Function Classification System
GP: General practitioner

HRQOL: Health related quality of life

ICD: International Classification of Disease
ICF: International Classification of Functioning, Disability, and Health
ITB: Intrathecal Baclofen.
IVB: Intra-Ventricular Baclofen

LM: Leptomeningeal Metastases
LO: Light Obscuration

MLR: Multivariate Linear Regression
MPOC: Measure of Process of Care
MRC: Medical Research Council
MRT: Medial Reticulo-Spinal Tract

NCIC: National Cancer Institute of Canada
NICE: National Institute for Health and Care Excellence
NHS: The National Health Service
NHST: Null Hypothesis Significance testing
NotIS: Nottingham Information System
NUH: Nottingham University Hospitals
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>NRS</td>
<td>Numeric rating scale</td>
</tr>
<tr>
<td>PEG</td>
<td>Percutaneous Endoscopic Gastrostomy</td>
</tr>
<tr>
<td>PVL</td>
<td>Periventricular Leukomalacia</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-Adjusted Life-Year</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SBNS</td>
<td>Society of British Neurological Surgeons</td>
</tr>
<tr>
<td>SCI</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>SSI</td>
<td>Surgical Site Infection</td>
</tr>
<tr>
<td>SDR</td>
<td>Selective dorsal rhizotomy</td>
</tr>
<tr>
<td>SPASM</td>
<td>Support Programme for Assembly of a database for Spasticity Measurement</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristic</td>
</tr>
<tr>
<td>SPOS</td>
<td>Single Particle Optical Sensing</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>UMN</td>
<td>Upper motor neuron</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WeeFIM</td>
<td>Functional Independence Measure for children</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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1 Chapter One : General Introduction
1.1 Neurophysiology of spasticity

One of the vital functions of the human motor system is to regulate the correct joint positions and movements. Furthermore, a motor system also integrates the motor intention and the muscle tone and body position information from the musculoskeletal system to maintain the individual’s posture and makes a state of readiness for the muscle to act quickly and smoothly to carry out a future task (1).

Muscle tone is the constant muscular activity or resistance that is necessary as a background to actual movement in order to maintain the basic attitude of the body particularly against the force of gravity (2). This resistance or muscle tone is controlled by two factors (3): firstly, a non-neuronal factor caused by elasticity and compliance of the tissues that is due to viscoelastic properties of connective tissue, tendons and muscles crossing the joint, secondly, neural control of the stretch reflex which is modulated by supraspinal and spinal pathways (4). The stretch reflex is a simple reflex in which the muscle contracts in response to a stretching force applied to it. The muscle spindle is the sensory receptor for this reflex. Muscle spindles are innervated with sensory neurons (Ia and II afferents) that relay information to the spinal cord about changes in muscle length. Type Ia and II afferent neurons synapse with α-motor neurons in the anterior horn cells (AHC) in the spinal cord grey matter, which, in turn, innervate the muscle. Lengthening of the muscle fibres stretches muscle spindles and consequently stimulates the sensory neurons (Ia and II) leading to the release of excitatory

*Viscosity is the resistance of tissue to deforming forces whereas elasticity is the ability of a tissue to return to its original position after being stretched. Viscosity resists stretch; elasticity pulls the muscle back to its original position (4).*
neurotransmitters; aspartate or glutamate. Subsequently, glutamate stimulates α-motor neurons in the spinal cord, causing a rapid contraction of the stretched muscle to counter muscle lengthening (5).

In normal states, the supra-spinal pathways send their balanced input to α-motor neurons. The α-motor neurons send the contraction signals to the muscle. However, feedback regarding the activity of the muscle cell is controlled by stretch reflex (5).

The supra-spinal pathways are descending motor tracts, originating in the cerebral cortex or brain stem, that directly or indirectly influence the excitability of the lower motor neuron or AHC. These pathways include the cortico-spinal (or pyramidal) tract from the cortex, which conveys direct excitatory input to the AHC. In addition, there are descending motor pathways originating in the brain stem that indirectly influence the excitability of the AHC. These include the predominantly excitatory medial reticulo-spinal tract (MRT) and lateral vestibule-spinal tract, and the inhibitory dorsal reticulo-spinal tract (DRT). The inhibitory DRT receives facilitatory input from the cortex via cortico-reticular fibres. Importantly, the DRT runs close to the cortico-spinal tract. Accordingly, both are usually simultaneously affected by the same pathologic condition (2, 5). However, the DRT is the main inhibitory pathway that releases the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (6).

The mechanisms causing spasticity are not well understood. However it is hypothesised that it is caused by the increase in the reaction of the stretch reflex, as a consequence of loss of inhibitory signals from the cerebral cortex to α- motor neurons of the spinal cord. Damage to the cerebral cortex (as in cerebral palsy, cerebral stroke, traumatic brain injury, multiple sclerosis), or the cortico-spinal tract (as in cases of spinal cord injury, spinal tumour,
epidural abscess, and transverse myelitis) results in a decreased inhibition of the stretch reflex therefore causing spasticity (5), Figure 1-1.

1.2 Spasticity

1.2.1 Definition

Several attempts have been made to define spasticity. The most often cited definition is the one by Lance in 1980 “A motor disorder characterised by a velocity dependent increase in tonic stretch reflexes and increased tendon jerks resulting from disinhibition of the stretch reflex, as one component of an upper motor neurone lesion” (7). According to this definition, it is only the increased resistance to passive movement (i.e. muscle tone) that is defined as spasticity. Other features of the upper motor neurone (UMN) syndrome, such as spasms or clonus that are characterised by brief frequent repetitive episodes of muscle contraction, are excluded.

However, in 2005 the Support Programme for Assembly of a database for Spasticity Measurement (SPASM) project, as a part of a review of spasticity measurement and evaluation, defined spasticity as “disordered sensorimotor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles” (8). Nevertheless, this description is broader and less specific and lets more features of the UMN syndrome to be involved under the definition of spasticity, such as spasms and clonus (8).
The motor cortex is responsible for planning voluntary movement.

The nerve impulse arising from the cerebral motor cortex is also sent to the basal ganglia and the extrapyramidal system nuclei.

The cerebellum coordinates the speed and direction of movement.

Muscle spindles in the contracting muscle, golgi tendon organs in the tendons and mechanoreceptors in the joints send information on the degree of contraction to the medulla spinalis, cerebellum and the somatosensory cortex.

The corticospinal pyramidal tracts carry movement order to the lower motor neuron.

The extrapyramidal system corrects the force of contraction of the muscles.

The lower motor neuron sends contraction impulse to the muscle through the peripheral nerve. This is the final common pathway from the nervous system to the muscle.

**Figure 1-1 Neural control regulating muscle contraction**
1.2.2 Causes of spasticity in children

Following the successful eradication of poliomyelitis and the dramatic fall in the prevalence of spina bifida, the most common motor disorder in children in developed countries is cerebral palsy (CP) which is the most frequent cause of spasticity in children (9). In their observational study, Hutchinson and Graham reported that 79% of spasticity in children is due to cerebral palsy, followed by acquired brain injury in 6%, then spina bifida in 5%, spinal cord injury in 2%, and other causes in 8% (10).

In the UK, the incidence of cerebral palsy is not known, but its prevalence is 186 per 100,000 population, with a total of 110,000 people affected (11). The prevalence of spasticity in CP has been reported in two studies where spasticity occurred in over 90% of all CP cases (12). In addition, Yeargin et al. stated that spasticity was found in 77% of CP patients in three centres in the United States (13).

1.2.3 Consequences of spasticity

Although the primary upper motor neuron lesion inducing spasticity is non-progressive, the resulting pathology is permanent and its consequences are progressive over time. Prolonged disinhibition of the stretch reflex results in a decreased stimulation threshold in response to triggers and physiologic shortening of the muscle fibres to the extent that complete relaxation becomes difficult and patients lose their range of motion (14). Furthermore, spasticity causes apparent muscle shortening due to a decrease in the number of sarcomeres along the myofibrils (15).

Long-term spasticity leads to muscle tightness and contractures. Once contractures have occurred, they are difficult to treat and can lead to major functional implications such as decreasing joints’ range of motion; limiting the
sitting posture and putting the patients at risk of pressure sores and frequent infections (16). They also impede self-care functions such as feeding, dressing, and bathing. Increasing spasticity also hinders the nursing care such as urinary catheterisation and hygiene procedures especially with severe spasticity of hip adductors (17). This can put children at risk of pressure sores and frequent infections, which in turn may increase severity of spasticity and spasms. These consequences lead to restricted community mobility and increasing social isolation (16, 18).

These children are dependent on their caregivers for most of their activities of daily living which has a significant and lifelong impact on the children, their caregivers and families, and on the agencies responsible for their wellbeing (19).

Sleep disorders are more common in children with spastic CP than in typically developing children (20). The prevalence of sleep difficulties in children with CP was reported by Newman et al, to be as high as 44% (21). Sleep disturbance was attributed to various elements that are common in CP such as muscle spasms, other forms of movement abnormalities, and the decreased ability to change body position during the night (21). Moreover, chronic pain, a frequent secondary problem in 60% of children with CP, was also reported to contribute to sleep disturbances (22, 23).

These difficulties can result in high demands for long-term care that by far exceed the usual requirements for typical children. These children are dependent on their caregivers for most of their activities of daily living. Such dependence has a significant and lifelong impact on the children, their caregivers and families, and the agencies responsible for their wellbeing (19).
1.2.4 Cognitive state and spastic cerebral palsy

Although CP is predominantly a disorder of movement and posture, there is a correlation between severity of motor deficit and a group of developmental disorders such as disturbances of sensation, perception, cognitive difficulties, communication disorders, behavioural disorders, and seizures (24, 25).

Bilateral spastic CP is predominantly associated with periventricular leukomalacia (PVL) which is a type of brain damage that encompasses dilation of the ventricles and reduction of the white matter. Interruption of the motor tracts is the cause of movement deficits in children with bilateral spastic CP. However, it has been hypothesised that white matter tracts connecting prefrontal and posterior brain regions, the basal ganglia, and related dopaminergic pathways may also be compromised, affecting the fine tuning of brain functioning and the development of cognition (26-28).

Middle cerebral artery infarction in children with CP can affect normal cognitive development. The middle cerebral artery supplies the lateral cortical surfaces of the parietal and temporal lobes, in addition to subcortical areas such as basal ganglia, internal capsule, and thalamus. Early brain stroke of these areas affect the development of focused attention, motor-executive function and language functions (29, 30).

Children with CP frequently have learning and memory problems (31). Memory can be impaired either due to lesions affecting neural framework as basal ganglia or the hippocampus, or as a result of encoding difficulties due to primary perceptual impairments (30).

Himmelmann et al. reported that the rate of learning disabilities varies depending on the clinical type of CP. It occurred in 100%, 17%, 49% and 62%
in quadriplegics, hemiplegics, diplegics, and in dyskinetic types, respectively (32).

1.2.5 The impact of caring for a child with spastic cerebral palsy

The parental caregiving is a natural role of being the parents of a young child. However, this role can be utterly different when a child experiences functional limitations and possible long-term dependence such as in CP. One of the central challenges for parents is to cope with their child’s chronic health problems effectively while maintaining the requirements of everyday living. In some cases, the delivery of such care can be detrimental to parents’ physical health and their psychological well-being. Furthermore, it has an impact on family income, family functionality, and sibling adjustment (33).

A Canadian population-based study has demonstrated that parents of children with CP suffered greater distress and more emotional and cognitive problems than the general population of caregivers. Further, they had a greater likelihood of physical problems, including back problems, migraine headaches, gastric ulcers and high blood pressure. These results demonstrate that CP can have a profound impact on the quality of life (QOL) of parents (34).

In a qualitative study on the QOL of parents of children with CP, parents reported that they face many challenges. In this study, parents indicated that caring for their child affected all aspects of their life (35). They specifically pointed to the intense impact of the physical demands associated with caring for a child with a physical disability on their own physical health especially when the child grows and becomes heavier.
“Physically I’m finding it challenging lately because she’s grown so much and she is so dependent mobility-wise, so I’m finding that much more demanding.” (Mother of Michelle aged 9 years, GMFCS Level V) (35).

They also indicated that caring for their child often involves interrupted sleep because of their child’s dependence throughout the night.

“Six years of her life waking up most nights. It can be anything from once to three times a night. So it’s broken sleep and it’s not great, so I find I have to pace myself.” (Mother of Meredith aged 6 years, GMFCS Level V) (35).

Moreover, marital relationships and strain on a marriage were also affected by caring a child with CP.

“Well I suppose the fact that we can’t leave her anywhere makes it really difficult because we can’t do things as a couple, so our relationship is obviously changed a lot and we always have to think about where she is.” (Mother of Molly aged 3 years, GMFCS Level II) (35).

Furthermore, due to the constant needs of children with CP, these parents feel that they have limited freedom, and they struggle to find times for themselves and often find it impossible to do their own tasks.

“Well it impacts on everything because there is nothing that you can do spontaneously. I guess I miss that at times.” (Mother of Scott aged 16 years, GMFCS Level V) (35).
1.3 Assessment of spasticity

A quantitative evaluation of spasticity and spasms is vital for assessment of potential efficacy of different treatment modalities. Appropriate measures for spasticity are also important from a research perspective to better understand the underlying pathophysiologic mechanisms associated with spasticity, and to assess the effectiveness of novel potentially beneficial treatments (36).

Spasticity may be evaluated clinically or through using laboratory tests. Clinical evaluation is usually quick, simple, and can be carried out in any environment. The Ashworth (37) and Tardieu scales (38) are frequently utilized for clinical assessment. They measure tone intensity, yet they do not assess the effect of spasticity on functional states (39). On the other hand, laboratory assessment usually requires special equipment, but has the advantage of quantifying subtle manifestations, and can provide information regarding the underlying pathophysiological mechanisms. Electromyography (EMG) and Hoffman reflex (H reflex) (40) are frequently employed in laboratory evaluation of spasticity (41).

1.4 Management of spasticity and decision-making

Treatment of spasticity involves multiple modalities that usually include observation, physiotherapy and occupational therapy, orthotics, oral

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b The Ashworth scale is a 5-point ordinal scale for ordering the resistance encountered during passive muscle stretching. A score of one represents no increase in muscle tone; two represents a slight increase in tone, giving a catch during stretch; three represents a more marked increase in tone, yet the limb is easily mobilized; four represents considerable increase in tone, making passive movements difficult; and five represents rigidity without any possible passive mobilization (37).

c Tardieu is a scale for measuring spasticity with takes into account resistance to passive movement at both slow and fast speed (38)

d Hoffman reflex is a reflectory reaction of muscles after electrical stimulation of type 1a sensory fiber which are primary afferent fibers that constantly monitor how fast a muscle stretch changes (40).
medicines, intramuscular injections, and both neurosurgical and orthopaedic surgery. Sometimes, combinations of methods are employed to increase the beneficial effects of each modality synergistically. Selection of the most suitable treatment modality for a child with spastic CP requires that all parties to be involved. These parties include the caregivers and a multidisciplinary team including: paediatricians, physiotherapists and occupational therapists, orthotists, orthopaedic surgeons, neurosurgeons, and other healthcare professionals (42).

Treatment should be adapted to meet every individual patient’s needs aiming at: i) enhancing functional activity and mobility; ii) to decrease the risk of preventable complications (e.g. orthopaedic deformity, pressure sores, surgery); and iii) to allow stretching of shortened muscles, strengthening of antagonist muscles and facilitating physiotherapy so alleviating spasm and pain (43).

1.4.1 Factors affecting decision making for spasticity treatment:
The decision-making for treating spasticity in a child with spastic CP depends on multiple factor including its duration, severity, distribution as well as the cost. The duration of spasticity has an influence on treatment goals and choice of interventions. For instance, recent UMN lesions with minimal spasticity can be managed by local chemo-denervation, oral medication and other conservative methods aiming to balance muscle tone, delaying contractures and helping the rehabilitation efforts. However, chronic spasticity may benefit from either temporary or permanent long-term management (44). The severity of spasticity governs the choice of management modalities, as mild spasticity can often be managed successfully with a combination of
physiotherapy and oral medication. However, severe spasticity may need more aggressive measures to achieve a significant change in function. In addition, the distribution of the spasticity determines whether to treat a patient focally or systemically (45).

Figure 1-2 Spasticity management modalities

The cost of spasticity treatments should be considered. It is clear that the cost of treating spasticity complications could also be extremely expensive. Contractures are one of the most significant consequences of spasticity. In 1995, the cost of surgical correction of spasticity contractures in brain-injured patients ranged from $13,000 to $21,000 per patient (46). Patients with severe spasticity could avoid high cost corrective orthopaedic surgery if they are treated early (47).

Spasticity management modalities can be classified using a four-way
compass according to whether treatments are focal or general in effect and whether the effects are permanent or temporary. According to the four-way matrix (permanent-temporary, focal-general) practical clinical guidelines may be outlined (48, 49), Figure 1-2.

1.5 Modalities of spasticity management

1.5.1 Non-pharmacological Therapy:
Physiotherapy and occupational therapy, orthotics, and casting are the foundation of spasticity treatment. The target of a physical programme is to preserve or improve the existing level of function, increase joint range of motion, strengthen muscles, decrease pain or discomfort and to avoid secondary complications such as contractures or adverse skin changes such as pressure sores (18, 50).

1.5.2 Pharmacological management of spasticity (general and reversible)
Systemic anti-spastic medications have been considered as “non-invasive treatment” in comparison to botulinum toxin and phenol injections or surgical interventions. The ability to titrate the dose with relative effectiveness, in addition to reverse the effects if necessary, are important advantages or oral medications (51). However, all anti-spastic drugs bind to various receptors in the central nervous system other than the target receptor. This can cause undesirable effects as they may inhibit higher centers leading to alternation in alertness, mood and cognitive changes which may be subtle and not easy to notice in the patients (52).
Oral anti-spastic medications are classified according the site of action into centrally acting agents as baclofen, benzodiazepine and tizanidine, or peripherally acting agents like dantrolene sodium. According to their
mechanism of action, centrally acting medications include drugs acting through the GABAergic system (baclofen, benzodiazepines, piracetam, progabide); or drugs acting as α2 adrenergic agonist (tizanidine, clonidine) (53).

1.5.2.1 Agents Acting Through the GABAergic System

Gamma-amino butyric acid (GABA) is the main inhibitory neurotransmitter in the CNS. GABA is generated from glutamic acid by the action of glutamic acid decarboxylase (GAD). GABA appears to be stored in vesicles in the nerve terminal, and is released into the synaptic cleft through a Ca2+ sensitive mechanism. Following its release, it binds to postsynaptic receptors. GABA receptors are classified into two major classes either inotropic GABA\(_{A}\) receptors (ligand-gated ion channels) or metabotropic GABA\(_{B}\) receptors (G protein-coupled) (53).

**Benzodiazepines**

Benzodiazepines were the earliest anti-spastic medications used in widespread clinical practice. Benzodiazepines are GABA\(_{A}\) agonists that facilitate the binding of existing GABA to the GABA\(_{A}\) receptor. GABA exerts its inhibitory effects by activation of the fast hyperpolarising GABA\(_{A}\) receptor at the post-synaptic site. This initiates an increase in chloride conductance through the channel facilitating chloride entry into the post-synaptic neuron resulting in hyperpolarisation. Such hyperpolarization also increases presynaptic inhibition and reduces monosynaptic and polysynaptic reflexes throughout the spinal cord by making it less excitable and decreasing the ability to raise the neuron potential to its firing threshold (54, 55).
Several trials in 1966s pointed out the effectiveness of diazepam in reducing spasticity, especially in younger children and those with athetosis (56) (57, 58). In 2005, Mathew et al. reported in a double-blind, placebo-controlled, randomised trial the clinical efficacy of a low-dose diazepam in enhancing movement in children with spastic cerebral palsy after a significant reduction of hypertonia and improvement in the range of passive movement (59, 60).

The primary side effect commonly encountered with diazepam are sedation and a general reduction in psychomotor ability (61). It can also produce tolerance and physical dependence, and sudden withdrawal can cause seizures, anxiety, agitation, tachycardia, and even death. Likewise, an overdose with diazepam can result in coma or death. Therefore, this drug might be more beneficial for the short-term management of acute muscle spasms (54).

**Gabapentin**

Gabapentin was first approved by the FDA in 1993 as a new treatment for partial seizures (62, 63). It is structurally similar to GABA (64), but it does not appear to bind to conventional GABA_A, GABA_B, glycine, or glutamate receptors. Nevertheless, Gabapentin has been shown to inhibit presynaptic glutamate release by modulating Ca2+ channels (65).

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*Athetosis is a condition in which abnormal muscle contraction causes involuntary writhing movements. It affects some people with cerebral palsy, impairing speech and use of the hands (56).*
**Baclofen**

**Historical review of Baclofen**

Baclofen was originally developed in the 1920s for use as an anti-epileptic agent. When used to treat adults with epilepsy who also had spasticity, it was noted that this drug had little effect on seizures but led to a reduction of spasticity. Such observations led to desertion of baclofen as antiepileptic drug. By the 1970s, Baclofen was first used as an oral agent in the management of spasticity (66).

Baclofen is structured chemically as beta-chlorphenyl-gamma-aminobutyric acid, which acts selectively on GABA$_\beta$ receptor (67), Figure 1-3. GABA$_\beta$ receptors are responsible for the later and slower component of inhibitory transmission (68). GABA$_\beta$ receptors are concentrated in la sensory afferent neurons or the interneurons and some are located post-synaptically at the motor neurons in Rexed laminae I–IV of the spinal cord (69). They are also found in other sites in the central nervous system especially the thalamus (70).

![Figure 1-3 - Chemical structure of Baclofen](image-url)
Pharmacodynamics

Baclofen achieves its effect by activating the GABA$\beta$ receptors presynaptically by restricting calcium influx into Ia presynaptic terminals and through inhibiting the calcium high voltage activated gates. Reducing the influx of calcium into the presynaptic terminals of afferent fibres suppresses the release of excitatory neurotransmitters such as glutamate and aspartate (71).

Baclofen can also act at postsynaptic GABA$\beta$ receptors, where GABA$\beta$ receptor effects are principally facilitated by direct binding, and hence activation of G protein-gated inwardly rectifying K+ (GIRK) channels. This leads to an outward K+ current which hyperpolarises the membrane and consequently increases the threshold of nerve cell excitability (72).

Saito, 1975 reported the analgesic effect of baclofen through specific antagonism of substance P (73). Different mechanisms have been put forward to explain the later effect. Henry in 1982 has attributed the analgesic effect of baclofen to the reduced release of sub-stance P from nociceptive afferent nerve terminals (74). However, later in 1988, Nakajima reported that substance P blocks inward rectifying K+ conductance while baclofen increases inward rectifying K+ conductance (75).

Pharmacokinetics

Baclofen can be administered systematically by oral administration or centrally by intrathecal injection.

Absorption

Baclofen is rapidly and completely absorbed from the gastrointestinal tract, with peak plasma levels achieved after 1 to 2 hours post-administration (76).

Distribution:

Baclofen is bound to plasma proteins to the extent of up to 30%. It crosses the
blood-brain barrier and its concentrations in the CSF are up to 10% of the plasma level (77).

Elimination

Baclofen plasma half-life is approximately 3.5 hours (range from 2 to 6.8 hours). Approximately, 85% of baclofen is eliminated by the kidneys in an unchanged form within 72 hours. Renal clearance of baclofen is high and equals to creatinine clearance, which signifies the importance of kidney in the excretion mechanism of baclofen. Therefore, it may be necessary to reduce baclofen oral dose in patients with renal impairment (78, 79). About 15% of a dose of baclofen is metabolised by deamination in the liver. The main metabolite by-product is 3-(4-chlorophenyl)-4-hydroxybutyric acid and is pharmacologically inactive (76).

Dosage

The recommended oral dosage in children is 0.75-to 2.5 mg/kg of body weight. The treatment is usually initiated with low divided doses four times daily, with gradual increase at approximately 3-days intervals until a therapeutic response is achieved. The maximum recommended doses for children aged 2-7 years is 30 mg up to 60 mg for children 8 years or older (53). Clinical trials involving patients with multiple sclerosis and spinal cord lesions have proven that baclofen is effective in reducing spasticity (80, 81). A large multicenter, double-blind, placebo-controlled trial involving 106 patients with spasticity secondary to multiple sclerosis has also confirmed that baclofen was effective in relieving symptoms of spasticity such as flexor spasms, clonus, pain, stiffness, resistance to passive movement of joints and tendon stretch reflex (82).
Currently, there are a few studies investigating the effect of oral baclofen in children with CP. These paediatric studies reported that oral baclofen is more effective than placebo in reducing spasticity (83, 84). Another case series study has reported the effectiveness of baclofen in children without fixed contractures facilitating the nursing care and physiotherapy (85). However, most of the studies failed to demonstrate improvement of mobility and activities of daily living performances and ambulation (86). Even though, Pedersen et al. have reported that ambulation and muscle strength have deteriorated during baclofen treatment (87). In comparative studies, baclofen has been found more effective in reducing the spasticity than diazepam (86, 88), with considerably less day-time sedation effect and without evidence of rapid drug tolerance even after many years (89).

There is a low incidence of adverse effects, and these usually take place on initial treatment with large doses or in the treatment of patients with spasticity of cerebral origin that have additional cognitive impairment (90). These adverse effects rarely require withdrawal of the medication and are frequently mild and transient. Modifying the dosage may diminish the adverse effects. For instance, transient drowsiness is a common side effect when initiating baclofen therapy, which disappears within a few days of starting the treatment (91). The most frequently reported adverse effects in clinical practice are sedation, drowsiness, weakness, paraesthesia, dry mouth, nausea and vomiting. Other reported effects also include psychosis and dyskinesias (92, 93). Baclofen may reduce the seizure threshold, so it should be used with caution in patients with convulsions. Importantly, sudden withdrawal should be avoided in all individuals, as it may precipitate seizures, confusion, anxiety and hallucinations (94).
1.5.2.2 Central α-2 adrenergic receptor agonists

Clonidine, quanfacine, and tizanidine, have α-2 adrenergic effects. They are α-2 agonists, which act at both the spinal and supraspinal levels. The physiological result of this treatment is predominantly a decrease in presynaptic activity of the excitatory inter-neurons (95, 96).

Alpha 2 adrenergic agonists have an anti-nociceptive effect, which may assist in their tone-reducing abilities because pain is known to increase spasticity. It is possible that this effect is mediated through the release of substance P in the spinal cord (97). However, little information exists to support the effectiveness of using these drugs to treat spasticity in children.

1.5.2.3 Peripheral acting muscle relaxant

*Dantrolene Sodium*

Dantrolene sodium exerts its action directly on skeletal muscle cells by inhibiting the release of calcium from the sarcoplasmic reticulum within the muscle cell during excitation. This subsequently limits myofilament cross-bridging between actin and myosin filaments resulting in decreased muscle contraction (98).
1.5.3 **Surgical management of spasticity**

1.5.3.1 Orthopaedic Surgery:

In general, orthopaedic procedures aimed to improve the biomechanics of patients with spasticity by treating the long-term consequences of spasticity on the musculoskeletal system. The general principles of orthopaedic surgery are lengthening of contracted muscles, balancing of joint forces, fusion of unstable joints, and control of painful spasticity. The surgical techniques include tenotomy, arthrodesis, osteotomy, and tendon transfer or lengthening. The procedures are individualised according to the clinical situation and age of the patient (99).

1.5.3.2 Neurosurgical management of spasticity:

Neurosurgical treatments of spasticity can be performed by: i) interrupting the stretch reflex to reduce excitation at different locations, or ii) alternatively by attempting to encourage the inhibitory influence on motor neurons in the supra-spinal centres. Neurosurgical procedures for spasticity can be categorised into peripheral procedures (rhizotomy, neurectomy, or muscle injections) or central procedures (cordotomy, stereotactic ablative procedures, or implantation of intrathecal infusion of antispasticity medication to increase inhibitory influences) (49, 100, 101).

1.5.3.3 Anterior rhizotomy and peripheral neurotomy

The efferent limb of the spinal stretch reflex arc consists of the motor neuron in the anterior horn and the motor nerve fibre running into the ventral spinal nerve root and distally in the appropriate peripheral nerve. The peripheral nerve acts on the muscle unit at the neuromuscular junction. Accordingly, spasticity can be reduced by interrupting the efferent limb of the stretch reflex at different sites along its course by anterior rhizotomy, peripheral
neurectomy, peripheral nerve block, or neuromuscular junction block (102). Anterior Rhizotomy is rarely used because of the resulting flaccid paralysis and muscle atrophy (103). Peripheral neurectomy is also not a practical procedure as the peripheral nerves are mixed nerves containing both motor and sensory fibres. Peripheral nerve division, consequently, may lead to adverse effects such as weakness, atrophy, and loss of sensation (102).

1.5.3.4 Chemodenervation

Chemodenervation, also known as neurolysis, or neuromuscular blockage, involves using injectable materials to preclude nerve muscle transmission. The most commonly used techniques are peri-neural injection of phenol, ethanol, and botulinum toxins. Phenol and ethanol cause denervation via non-permanent axonal degeneration. The duration of the effect ranges from a few months up to 2 years, till the functional re-innervation occurs (104).

Although phenol is a low-cost chemodenervation in comparison to botulinum toxin, the adverse effects like pain, dysesthesia (due to necrosis of sensory axons in peripheral nerves), lethargy and nausea limit its use in children (105).

Since 1988, injections of Botulinum toxin (BTX) have been used increasingly in place of ethanol and phenol for chemodenervation. BTX acts at the neuromuscular junction to block the release of acetylcholine at the neuromuscular junction leading to selective, temporary muscular chemodenervation for approximately 8–12 weeks. It acts locally, hence, it is not effective in reducing global spasticity (106). The general indications for BTX are for temporary management of focal spasticity and to evaluate the effects

† Lethargy and nausea are secondary effects to systemic absorption
of denervating a spastic muscle (107). Adverse effects of BTX injection are usually mild and transient, consisting of pain on injection, occasionally mild flu-like syndrome, and excess weakness. As the botulinum neurotoxin is immunogenic, repeated injections could lead to immune-resistance and loss of its effectiveness (108, 109).

1.5.3.5 Selective dorsal rhizotomy (SDR) or interruption of afferent limb of the stretch reflex

Selective posterior rhizotomy has become a widely used neurosurgical technique for treatment of lower extremity spasticity in children with CP. The principal goal of the procedure depends on a child’s motor abilities. It relieves the spasticity that is predominantly seen in the lower limbs with the main aim to improve mobility, pain, independence and easiness of care. In other words, improving the spasticity or the range of movement is not the goal of the SDR treatment but it is the means to achieve the aims (110).

1.5.3.5.1 SDR Mechanism

Spasticity prominently depends on the sensory–motor reflex arc (stretch reflex) between muscles and spinal cord nerves. The aim of SDR is to reduce the sensory input. The principle of dorsal rhizotomy is a reduction of the sensory input into the spinal interneuron pool by cutting the sensory afferent within the posterior roots. This leads to a decrease in the net excitatory output via the alpha motor neurons and ultimately reduces spasticity (111).

Strict selection criteria for the SDR are recommended, as it is a permanent and irreversible surgical intervention. It can also damage motor function by weakening the muscle and worsening gait in patients lacking sufficient antigravity strength (112). Importantly, patient selection and treatment should be evaluated by a multidisciplinary team with specialist training and expertise
in the care of spasticity, along with access to the full range of treatment options. The team could consist of the following medical professionals: paediatric neurosurgeon, a neurologist, an orthopaedic surgeon, a physiotherapist, an occupational therapist, and a nurse clinician. The team should discuss the irreversibility of the treatment, the known complications and the uncertainties over long-term outcomes with children and young people as well as their parents or carers (113).

Early in 1987, Peacock et al. suggested the SDR selection criteria. They concluded that the greatest benefit from SDR is seen in children with i) spasticity only that affects mainly the lower limbs, ii) who were able to side-sit independently with some degree of walking ability, iii) were not severely cognitively impaired and, iv) did not receive orthopaedic interventions before SDR. In contrast, they considered the presence of severe contractures, increased weakness in antigravity muscles, or a diagnosis of either marked athetosis, dystonia or ataxia as contraindications for SDR (114).

Grunt et al. have systematically reviewed the literature for SDR selection criteria. The results have demonstrated the absence of an international consensus regarding the selection of patients for SDR, despite the fact that this is an invasive and irreversible procedure that should be offered only to those who will derive substantial benefit (112).

The National Institute for Health and Care Excellence (NICE) has issued full guidance to the NHS in England, Wales, Scotland and Northern Ireland on SDR for spasticity in CP. It has recommended considering SDR to improve walking ability in children and young people with spasticity at GMFCS level II or III (Table 1-1), in children between 3 and 9 years old; abnormal tone with pure spasticity; good leg muscle strength; straight legs and minimal muscle
shortening; good selective motor control in the legs; good cognitive skills; and not being overweight (113).

1.5.3.5.2 Contraindication of SDR
The risks of inappropriate SDR decision-making are significant, with possible negative outcomes including long-term post-operative weakness and loss of postural support due to reduction in muscle tone. Therefore, it is important to confirm that the disturbance in muscle tone is due to spasticity and not due to dystonia, rigidity, athetosis or ataxia. This is because rigidity and dystonia may coexist with spasticity in patients with basal ganglia damage particularly in children younger than five years. Further, dystonia may develop anytime during the first five years of life. Thus, in the setting of basal ganglia damage, the best is to wait until the age of five when the predominance of dystonia can more reliably be ascertained (111, 112).

<table>
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<tr>
<th>Table 1-1 Gross Motor Function Classification System</th>
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<tr>
<td><strong>Gross Motor Function Classification System (115)</strong></td>
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<tr>
<td><strong>Level I</strong> Can walk indoors and outdoors and climb stairs without using hands for support Can perform usual activities such as running and jumping Has decreased speed, balance and coordination</td>
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<tr>
<td><strong>Level II</strong> Can climb stairs with a railing Has difficulty with uneven surfaces, inclines or in crowds Has only minimal ability to run or jump</td>
</tr>
<tr>
<td><strong>Level III</strong> Walks with assistive mobility devices indoors and outdoors on level surfaces. May be able to climb stairs using a railing May propel a manual wheelchair (may require assistance for long distances or uneven surfaces).</td>
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<tr>
<td><strong>Level IV</strong> Walking ability severely limited even with assistive devices Uses wheelchairs most of the time and may propel own power wheelchair Standing transfers, with or without assistance</td>
</tr>
<tr>
<td><strong>Level V</strong> Has physical impairments that restrict voluntary control of movement Ability to maintain head and neck position against gravity restricted Impaired in all areas of motor function Cannot sit or stand independently, even with adaptive equipment Cannot independently walk but may be able to use powered mobility</td>
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Children who have undergone previous orthopaedic procedures such as tendon lengthening or neurectomy should be screened carefully. The latter procedures may result in muscle group weakness, which may be exacerbated by rhizotomy (112, 116). Pre-existing scoliosis is a relative contraindication as spinal deformity can be exacerbated by a multilevel laminotomy or by a wide, single-level thoracolumbar laminectomy (112, 117).

NICE in its guidelines put the predominant dystonia, athetosis, ataxia, and severe cognitive delay, severe scoliosis or hip dislocation, as exclusion criteria for SDR surgery (113).

1.5.3.5.3 Complications of SDR
In the early postoperative phase, the complications are often quite rare. CSF fluid leak (118) and infection have been reported (119). Transient dysesthesias lasting up to a few weeks have been reported in 2.5 to 40% of patients (120, 121). Urinary incontinence is probably the most troublesome problem. Urinary retention is frequent, with an incidence of between 1.25 and 24% (122, 123). Urinary sphincter complications, including incontinence and retention, can be significantly reduced or totally eliminated by pudendal monitoring and limiting the amount of the dorsal root of S2 cut to less than 35% (111, 124).

Permanent complications are now rare after SDR (110), however Grunt et al. stated that back pain and spinal abnormalities such as kyphosis, scoliosis, lumbar lordosis, spondylosis and spondylolisthesis are frequent after SDR (125).

1.5.3.5.4 Outcome of SDR
The effectiveness of SDR has been evaluated by using quantitative assessments of spasticity as myometry, dynamometry, or the Ashworth scale.
Three randomised controlled trials have shown significant reduction of spasticity following SDR and physiotherapy compared with a control group of patients having physiotherapy alone (126-128).

Two randomised controlled studies by Subramanian and Langerak have performed long-term evaluation of the effect of SDR on patients' gait. Patients were examined preoperatively and then at 1, 3, and 10 years after surgery in both trials and at 20 years in the second trial only. A computer-assisted gait analysis system was used to assess gait performance. Locomotor function including step length and velocity had significantly improved postoperatively (129, 130).

One comparative study evaluated the long-term effectiveness of both SDR and botulinum toxin BTX injection on gait performance. BTX demonstrated rapid improvement in gait performance but the improvement became insignificant after 12 months even with repeated injections at 4-month intervals. In contrast, the SDR has resulted in slow improvement of gait parameters during the first 3 months followed by progressive improvement from 6 months (131).

In addition to the impact of SDR on the lower limbs, there have been well-documented improvements in upper limb function and speech. In his study, Fasano has initially reported these supra-segmental phenomena (132), which have been reported in several recent studies (133, 134). There is a single small study that has suggested improvement in cognitive function following SDR (135). The phenomena may be explained on the basis that posterior root neurons have collaterals that ascend in the spinal cord giving branches to spinal AHC at many levels as well as brain stem motor nuclei. Thus, upon division of the lumber posterior rootlets, facilitatory influences would be
reduced not only within the lumber segments of the spinal cord but also in motor neuron at higher levels. Improvement of upper limb functions may also be due to the patient having more stable sitting base and therefore a decreased need to use the arms to maintain his balance (136).

The effects of SDR on the need for orthopaedic surgery have been tested in some reports which showed SDR performed at an early age had lower rates of orthopaedic surgery than those for whom SDR were performed at a later age. This was particularly true for certain operations, such as heel cord, hamstring, and adductor releases, rather than for orthopaedic procedures on the bone and joint. This could be explained by the fact that SDR decreases spasticity and hence reduces the need for release procedures, whereas bone deformities are fixed and not influenced by spasticity reduction (137, 138).

Recent evidence by Rouck et al. suggests that urinary bladder volume increased and high bladder pressure decreased in 62% of the study patients after SDR (139). Chiu et al. reported that SDR significantly improved urgency, frequency, incontinence, and urodynamic bladder capacity in spastic CP children (140).
1.5.3.6 Intrathecal baclofen therapy

Oral administration of 30–90 mg of baclofen per day is associated with plasma baclofen level of 68–650 ng/ml and corresponding CSF levels of 12–95 ng/ml (77). Increasing oral levels of baclofen eventually leads to side effects, such as sedation, confusion, urinary frequency, and insomnia. Nevertheless, infusion of 400 μg$^9$ of intrathecal baclofen (ITB) per day is associated with nearly 380 ng/ml in the CSF (141, 142).

ITB infusion provides an effective improvement in the spasticity at 1000 times lower than the doses of oral baclofen with a significant reduction of side effects (143, 144). In addition, the anti-spastic effects of baclofen occur at spinal level regardless of the cause of spasticity whether being cerebral or spinal. The spinal cord being only 2% of the mass of the brain and it receives proportionately a lower blood supply as a fraction of the cardiac output. Therefore, cerebral side effects often ensue with oral baclofen before observing the therapeutic anti-spastic effects (145, 146).

In the mid-1980s, Penn and Kroin provided the first report of ITB used in adult patients with spasticity of spinal origin (147, 148). The first report of utilising the ITB therapy to treat spasticity in children with CP was published in 1980s by Dralle (149). In 1991, Albright described a double-blind screening trial of ITB therapy in children with spastic CP (150). This was followed by many studies in the 1990s demonstrating a reduction in spasticity and dystonia (151-153).

The Food and Drug Administration (FDA) approved ITB therapy in the form of Medtronic Synchromed implantable infusion pump for spasticity of spinal

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$^9$ 1 milligram mg = 1000 microgram (ug) = 1000,000 nanogram (ng)

1.5.3.6.1 Pharmacokinetics of ITB (Intrathecal distribution of baclofen)

The drug infusion into the thecal space results in its mixing with the CSF. The amount of mixing depends on the composition of the drug, its lipid solubility, density and mode of delivery, whether bolus or continuous infusion (155).

The first factor affecting the initial distribution of intrathecal drug is the baricity\(^h\) (156). The density of baclofen is isobaric (1.003) at 24 °C and hypobaric (0.999) at 37 °C body temperature which is lower than the CSF density (1.00049 -1.0007mg/mL). Therefore, baclofen behaves like a hypobaric compound with subsequent distribution against gravity (157). However, with the slow infusion rates used from implantable pump systems factors that can influence bolus injection, such as drug volume or density may have little role in the drug distribution (158, 159). Instead, the conjunction of baricity with the position of the patient during drug infusion has a determining effect on drug distribution. A recent study used animal model to administer hyperbaric baclofen (2mg/ml in 7.5% dextrose) to anesthetised pigs while positioned either horizontally or vertically. Baclofen was administered for 6 hours at T12. The spinal cord was cut into 1 cm thick sections. Each of these sections was further subdivided into anterior and posterior halves. Baclofen concentration was measured in each piece using radiotracer methods. Drug was distributed almost exclusively caudal to the T12 infusion point in the vertical position; while was distributed more symmetrically around the infusion point in the

\(^h\) Baricity refers is the ratio of the density of the infused drug compared to the density of CSF which average 1.003 g/ml at 37 °C. Baricity is used in anesthesia to determine the manner in which a particular drug will spread in the intrathecal space (156).
horizontal group. Drug concentration dropped rapidly as far from the infusion point in both groups. Based on these findings, the patterns of drug distribution in the horizontal compared to the vertical position were significantly different. However the baricity of the solution will affect drug distribution only until it sufficiently diluted by CSF (158).

Drug distribution in the CSF is also controlled by the normal circulation of the CSF from the ventricles, where it is produced, to the spinal canal along the dorsal aspect of spinal cord to sacral cul de sac. It then flows rostrally along the anterior aspect of the spinal cord to reach the basal cistern. This cycle takes 2-2.5 hours. Furthermore, the CSF moves with the to and fro pulsatile motion of the brain with each cardiac beat. These two mechanisms help in mixing and distributing of the infused drug (160).

1.5.3.6.2 Drug elimination
Baclofen is eliminated from the CSF by spinal cord uptake or diffusion to the capillary then to be absorbed by epidural fat (158). The ITB elimination half-life ranges from 0.9-5.0 hours in comparison to 3.6 hours in the plasma. However, the total clearance ranges from 8-13 hours (161).

The spinal cord presents two different environments to drug molecules. The outer layer or the white matter, which is rich in myelin and lipid, is the preferred environment for hydrophobic drugs. On the other hand, the grey matter with low lipid is an accumulating location for hydrophilic drugs. The site of action of a baclofen is in the substantia gelatinosa in the gray matter of the spinal cord (laminae II and III). Therefore, using hydrophilic baclofen intrathecally allows smaller volumes, longer half-lives, and deeper penetration into nervous tissues (158, 162).
1.5.3.6.3 Selective criteria for ITB therapy in children

Many study groups (163-165) have put criteria for the selection of ITB therapy patients. They agree broadly on these categories:

Inclusion criteria for ITB therapy

1. Severe spasticity more than 3 on Ashworth score.
2. Spasticity-causing pain, interrupts sleep, and interferes with posture or hygiene procedures.
3. Patients should be clinically stable.
4. Patient age and size: product guidelines allow treatment of children as young as 4 years, who should have sufficient body mass to support the reservoir pump (though Albright implanted ITB pump in 9-month old child weighting 9-kg (166).
5. Motivation and commitment of patients and caregivers. Patients and caregivers must be diligent with respect to follow-up responsibilities, which include scheduled pump refill at 4-12 week intervals. Caregiver must also be prepared for an effective rehabilitation program.

Exclusion criteria

1. Infection is an explicit contraindication to ITB therapy. Systemic infection may interfere with assessment of the patient response to a screening trial. In addition, infection may increase the risk of surgical complications and complicate the dosing regimen after implantation.
2. Allergy and hypersensitivity to oral baclofen is another contraindication of ITB.

The National Institute for Health and Care Excellence (NICE) in its guidelines has recommended the ITB treatment in children and young people with spasticity or dystonia that, even with the use of non-invasive treatments, still
have difficulties in posturing, pain or muscle spasms control, function and self-care (113). Furthermore, the NICE guidelines stated that patients who benefit from ITB are the children who have bilateral spasticity affecting upper and lower limbs and have moderate or severe motor dysfunction (GMFCS level III, IV or V) (11).

NICE guidelines put the small size of the children to accommodate the ITB pump and systemic intercurrent infection as contraindications to ITB therapy (113). Similarly the presence of co-existing medical conditions (such as uncontrolled epilepsy or coagulation disorders), a previous spinal fusion procedure, malnutrition or respiratory disorders with risk of respiratory failure were also considered as potential contraindications to ITB treatment (113).

Before pump implantation, a test dose is given to predict the potential therapeutic effect of ITB therapy to control spasticity. This screening process is performed by measuring the response to an intrathecal bolus of baclofen (25-50 μg) injected via a lumbar puncture or by continuous infusion of baclofen via intrathecal catheter in some conditions like dystonia (167).

The intrathecal pump is a small battery-powered device, which is implanted in the abdominal area connected to the intrathecal space by a thin flexible catheter. The pump stores and delivers baclofen into the thecal space either at a constant or variable rate that is adjusted and programmed according to clinical needs. An external programmer (telemetry) is used to communicate with and programme the pump during refill and check-up sessions (167).

Implanting techniques for the ITB pump have changed noticeably since the advent of the procedure in 1985 (148). Initially, the pump was implanted subcutaneously. However, this technique was associated with poor healing and wound dehiscence especially in children with CP (168).
In 1998, Grabb and Pittman described a subfascial technique for implanting the pump (169). This technique provided more coverage for the pump, reducing the risk of skin dehiscence, and improving the cosmetic appearance of the abdomen by reducing the pump profile in paediatric patients. Due to the underlying disease, these patients are usually significantly underweight and often lack adequate soft tissue mass to effectively cover the pump (169). The subfascial technique is performed by dissection of the subcutaneous plane until the anterior rectus abdominus and the external oblique fascia are identified. An incision is then made in the anterior rectus and external oblique sheaths. Using a combination of blunt and sharp dissection techniques, a plane is developed between the fascial and muscle layers. The final pocket lies immediately between the anterior rectus sheath and rectus abdominis muscle (169).

Implantation technique of ITB pump in the Nottingham University Hospitals (NUH) started in 1998. In the first 5 years of practice, the subcutaneous implantation was used. However, due to high rate of complications, the subfascial technique was then adapted and modified.

1.5.3.6.4 Description of subfascial technique used in NUH
After positioning the child in the left decubitus position with the hips and knees flexed to facilitate access to the thecal sac, antibiotic is administered at the time of induction of anaesthesia. The operating field is prepared with chlorhexidine and adhesive sterile draping. The preferred surgical side is usually the right to avoid scarring from previous abdominal surgery for left-sided gastrostomies (170).
A transverse skin incision is made in the right hypochondrium at the level of the upper third of a line running between the xiphoid process and the pubic ramus to allow fashioning of a pocket inferiorly and to avoid contact with the lower end of the thoracic cage (170).

The incision is deepened through the subcutaneous fat to the anterior rectus sheath (RS), and both lateral and medial edges of the rectus abdominis muscle are identified. The fascia of the rectus sheath is incised horizontally and the incision is continued laterally into the full thickness of the external oblique muscle EOM (170), Figure 1-4 A.

The anterior layer of the fascia of the internal oblique muscle merges with its posterior fascial layer over the lateral edge of the rectus abdominis (RA) muscle at a variable distance along the line of linea semilunaris. Cutting in between these internal oblique layers helps to open a natural plane between the external oblique muscle anteriorly, and the internal oblique, transversus abdominis, and peritoneum posteriorly (170), Figure 1-4 B.

Figure 1-4 Intraoperative photograph of dissecting RS from RA, (B) Illustration of cutting the anterior layer of the IOA
The implantation pouch is created starting beneath the anterior rectus sheath medially, continuing laterally under EOM. The internal oblique, the transversus abdominis, and the peritoneum constitute the posterior wall of this pouch, Figure 1-5 (170).
The subfascial implantation technique is not novel and has been described with its outcomes and complications (169, 171-174). Albright et al. have described incising the covering fascia of the external oblique muscle laterally and the fascia of the rectus abdominis muscle medially, and then degloving the fascia to fashion a subfascial pocket cranially and more caudally to the transverse fascial opening. This would leave the suture line of the fascia crossing over the pump increasing risk of infection and dehiscence (172).

Kopell et al. have modified the same technique by cutting the linea semilunaris, which provides an adequate pouch for the pump below the fascia, but we assume this could interrupt the integrity of the anterior wall of the pouch (169).

In the Nottingham University Hospital’s technique, the transverse opening of the fascia is extended more laterally to incise the red muscle fibres of the external oblique to allow dissection of the space between external and internal oblique muscles. This provides complete coverage of the pump by the muscle below the level of the fascial opening. Furthermore, cutting the anterior lamella of the internal oblique aponeurosis caudally under the external oblique muscle helps preserve the integrity of the external oblique muscle anteriorly (170).

Spinal Access

The catheter is tunnelled from abdominal wound toward the back to be inserted in the thecal space at level of L3–4 as it is less mobile than L4–5 (170), Figure 1-6.

Approaching the dural sac for inserting the intrathecal catheter in CP children with spinal deformities may be a challenge, due to distorted anatomy or presence of metallic instruments and the bony fusion mass that grows after
spinal fixation. In this situation, the thoracocervical approach for inserting the catheter intrathecally is an alternative to lumbar insertion of the catheter (175).

1.5.3.6.5 Maintenance of intrathecal baclofen therapy

The initial ITB daily dose after implantation is usually between 50-100 μg or twice the amount of successful trial dose. In cases of dystonia, the normal initial dose is 200 to 300 μg /day, according to severity of the condition (142, 176). The daily dose may be increased by 10–30%, to keep sufficient symptom control. Similarly, the daily dose may be decreased by 10–20% if patients experience adverse effects. On average, the dose of ITB for treatment of spasticity rises by a factor of 2.8 over the first year. Up to 86% of patients reach a steady dosage by the fifth year (177, 178).

The reservoirs of the pumps need to be refilled at various time intervals. The refill intervals depend on three elements: reservoir size, baclofen concentration, and daily dosage. The period between refills varies from every 3 weeks to every 6 months. Refills are recommended at no more than 6-month intervals because of uncertainty about baclofen stability beyond that time (179).

The FDA approved formulations of ITB are in concentrations of 500 μg/mL and 2000μg/mL. Most patients are able to achieve a period of 60-90 days between refills (180). The SynchroMed II System has enabled some patients to benefit from an increase in this refill interval. For instance, stability data in the SynchroMed II System supports refill intervals up to 180 days. However, certain populations of patients require higher daily doses of baclofen, and obtaining a desirable length of time between refills for these patients becomes difficult (181).

The sole manufacturer (Novartis Pharma) labels the stability of baclofen
intrathecal for up to 6 months in a Synchroned II delivery device. They have analysed concentrations greater than 2000 μg/mL, and concluded that the higher concentrations did not meet stability requirements without the formation of precipitates (182).

Recent research is investigating the role of microspheres coated in baclofen, injected in a gel, as an alternative vector for baclofen delivery. This may let higher concentrations of baclofen be delivered than the current form, which would be useful particularly in dystonia patients who usually need greater baclofen doses. It might also decrease the rate of pump refills, as well as device replacements (183).

However in actual practice, compounding pharmacies advertise concentrations up to 8000 μg/mL for physicians who seek to reduce the frequency of patient refills and/or reduce the cost (179, 184).

At Nottingham University Hospital (NUH), different concentrations of baclofen are used in refilling. The commercial baclofen concentrations (500 mcg/ml and 2000 mcg/ml) are used if the daily dosage was less than 100 mcg. However; the higher concentration of compounded baclofen (3000 mcg/ml) is used if the daily requirement of ITB exceeds 100 mcg

The compounded 3000 mcg/ml baclofen concentration has been used in the NUH practice from July 2002 till now. This is to maximise the benefit to the patient by longer refill intervals and accordingly decrease the risk of infection due to frequent refills.
1.5.3.6.6 Intrathecal baclofen complications
Continuous ITB infusion is associated with a significant number of potential complications in all patients groups (185). Although complication rates may vary between centres, the complication rate has been reported up to be 30% (186).

The potential ITB complications can be caused by the surgical procedure, the device fault (pump error or mechanical complications of the catheter), or pharmacological side effects of baclofen (185).

Surgical complications may include CSF leakage, accumulation of CSF subcutaneously that may cause pseudomeningoceles which are more frequent in paediatric patients, because they have smaller volumes of paraspinal muscles and subcutaneous tissues. In these cases, dural repair is essential for correction of the CSF leakage and pseudomeningocelle (187).

Other surgical complications include pump migration and flipping especially in paediatric patients due to creation of an over-sized subfascial pocket (185).

Infection is by far the most serious surgical complication of intrathecal pump systems. It can result in significant rates of morbidity that may lead to spread of infection along the catheter causing meningitis and explantation of the pumps (188).

Superficial wound infection at the site of implantation, although potentially serious, may be managed successfully with systemic antibiotics and local wound care. A deep infection at the site of the hardware, however, will likely

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1 Spinal pseudomeningoceles are extradural collections of CSF that follow a breach in the dural–arachnoid layer. They may occur due to an incidental durotomy, during surgery, or from trauma or congenital abnormality. The majority are iatrogenic and occur in the posterior lumbar region following surgery. Although they are often asymptomatic, they may cause low-back pain, headaches, and even nerve root entrapment (187).
require removal of the infected equipment to avoid meningitis; a rare but a more serious complication and difficult to treat (189, 190).

The pharmacological adverse effects of Baclofen might be seen during screening trial, immediately postoperatively, or during maintenance therapy especially after refilling. The most common acute side effect associated with ITB therapy is urinary retention, that may require intermittent catheterisation for 2–3 days (164). Nausea and vomiting, insomnia, and headache are also reported in 11–12% of the patients, which usually resolve spontaneously (181, 191).

Excess hypotonia caused by baclofen can lead to serious complications such as paralytic ileus (192), or deep venous thrombosis (DVT) due to stagnation of blood in the gastro-soleus venous plexus (193, 194).

Acute overdose or withdrawal of ITB, can be life threatening events (195). Overdosage of baclofen may present clinically as drowsiness, light-headedness, dizziness, somnolence, respiratory depression, seizures, and an altered level of consciousness progressing to coma (91). Although overdose from mechanical system malfunction has been reported (196), the literature review has shown that cases of ITB overdosage are more likely related to human errors at the time of surgery, refills, or programming (197, 198).

**Acute withdrawal syndrome**

Abrupt discontinuation of baclofen can cause acute withdrawal syndrome, which resembles Benzodiazepine and alcohol withdrawal. In April 2002, the Food and Drug Administration (FDA) of USA included a drug label warning for baclofen withdrawal syndrome (199). This most commonly occurs as a result of a problem within the delivery system. The clinical presentation includes: high fever, pruritus, hypotension, parasthesias, and altered mental status in
the form of dysphoria, visual, auditory and tactile hallucinations, and paranoia. Other clinical presentations also include exaggerated rebound spasticity, seizures, and muscle rigidity that in rare cases may advance to rhabdomyolysis, and even multiple organ-system failure (143, 200, 201).

The mechanism of withdrawal syndrome includes down-regulation of GABAβ receptors in the CNS and spinal cord after long-term ITB infusion. This lead to decreased sensitivity to baclofen (202). Therefore, abrupt ITB withdrawal results in a predominance of excitatory effects that simulates other conditions that are associated with CNS hyper-excitability, leading to severe spasticity that may not be overcome by low dosage of baclofen (203).

Several reports described varied psychiatric symptoms related to ITB withdrawal, such as “hallucinations”, “manic psychosis”, fluctuation of consciousness, memory impairments, or perceptual disturbances (204). Neuropsychiatric effects of abrupt baclofen withdrawal are thought to involve the GABA system. Baclofen, like GABA, inhibits CNS pathways involving monoamine neurotransmitter systems. Long use of baclofen can cause continuous inhibition of monamine neurotransmitter systems which leads to emergence of supersensitive dopamine and noradrenergic receptors. Sudden withdrawal of baclofen would cause a disinhibition of previously suppressed monoamine pathways, causing a release of norepinephrine and dopamine on to supersensitised receptors. This ultimately leads to autonomic arousal (e.g. tachycardia, hypertension, agitation, restlessness) and delusions, hallucinations, and delirium (204).

It is noteworthy that ITB withdrawal should be differentiated from autonomic dysreflexia, malignant hyperthermia (MH), and neuroleptic-malignant
Management of withdrawal syndrome
Definitive therapy of acute ITB withdrawal requires resuming of ITB delivery. Saulino et al. recommended starting a bolus dose of ITB via lumbar puncture or continues infusion with an indwelling catheter (205). Oral baclofen should be started for management of withdrawal symptoms until ITB therapy can be resumed as soon as possible (206). However, oral baclofen, even in amounts at or near the maximum tolerated dosage may not halt progression of the developing withdrawal syndrome (207, 208). In such cases, parenteral benzodiazepine\(^\text{j}\) (143) infusion was the most rational treatment for the loss of central GABAergic neurotransmission (195).

Drug delivery system (DDS) related complications
The baclofen delivery system consists of the catheter and the pump device. Complications related to the DDS much more often involve the catheter as compared to the pump (185).

The pump complications include overfilling of the pump, battery failure, pump torsion (or flipping) and pump failure, which requires replacement with a new device (209-211).

The catheter is the most vulnerable part of the infusion system, and its complications are the most common cause of ITB therapy failure (212, 213). The reported catheter complication rate is as high as 40% in patients with implanted ITB pumps (145, 214, 215). Common catheter-related problems include: kinking, disconnections, breaks, occlusions, and migration of the

\(^\text{j}\) Benzodiazepines activate GABAa-receptor complexes in the spinal cord to relieve spasticity by different mechanisms to baclofen. ITB-induced GABAb-receptor down-regulation should not interfere with the antispasticity efficacy of benzodiazepines. In addition benzodiazepines have antiepileptic effects (143).
catheter (216, 217).

1.5.3.6.7 Outcomes of intrathecal baclofen therapy
The first report of successfully treated children with ITB was by Dralle et al. who successfully treated a 4-year-old child with hypertonicity after brain injury caused by near drowning (149). Then, Muller reported significant improvements in spasticity in 20 children treated with ITB, where the spasticity had significantly decreased in 90%-95% of patients (218).

In 1993, Albright et al. conducted a prospective non randomised trial in 37 patients with cerebral causes of spasticity (25 were functionally capable of self-care and 12 were non-functional). The ITB infusion reduced the muscle tone in upper and lower limbs at dose of 27-800 μg/day. In the functional group, 19 patients reported improved upper-extremity function and 10 reported improved ambulation and speech, as well as scores on a personal independence scale (219).

Fitzgerald et al. reported the outcome of 52 tetraparetic children treated by ITB in Nottingham University Hospitals from 1998 to 2003. This study represented a large homogeneous series of ITB therapy in children with severe spasticity of cerebral origin. In 49 cases, carers reported improvements in nursing care. All of these saw a reduction in spasticity and an improved range of motion in unfixed joints. Of the 17 who were ambulant prior to initiating treatment, walking was improved in nine cases. Only one previously non-ambulant patient began to mobilise with walking aids. In addition, most cases had improvements in bulbar function (better speech and swallowing, less drooling) and upper limb function. In two cases pre-existing divergent squints disappeared. Many children appeared to become more socially interactive (220, 221).
Gerszten et al. have demonstrated the outcome of ITB on gait in 24 patients (21 with spastic CP and 3 with spasticity secondary to traumatic brain injury). The level of ambulation improved in 9 patients, was unchanged in 12 patients, and became worse in 3 patients. The study concluded that ITB is not contraindicated in patients who rely upon their spasticity for support during ambulation (222).

Guillaume et al. in a non-comparative, multicenter, prospective study on 129 children with intractable spasticity evaluated the impact of ITB therapy on standard measures of spasticity, pain, subjective improvement and outcomes of functional independence. A significant improvement in muscle tone (Ashworth score) was observed in both lower and upper extremities for patients with spasticity of cerebral or spinal origin. Patients’ pain assessments using a numeric rating scale (NRS)\(^k\) (160), showed significant reductions in pain after implantation. Pain relief increased steadily over the 12 months of follow-up. Both motor and cognitive functions improved after initiation of ITB therapy using the FIM instrument or WeeFIM for children. A significant improvement in motor function was observed at 12 months and in cognitive function at 3 months post-implantation. Patient performance and satisfaction on the Canadian Occupational Performance Measure (COPM) showed significant improvements (223).

Krach et al. reported the changes in function of 100 children and their caregiver assistant after ITB therapy. The results showed improvement in these function categories, positioning (69%), transfers (58%), dressing (69%),

\(^k\) In a pain assessment using a numeric rating scale (NRS), patients were asked to evaluate their pain using a numeric rating (0 [no pain] to 10 [the worst pain imaginable]) for 4 parameters: worst pain, least pain, average pain in the past week, and pain right now (160).
toileting/hygiene (51%), decreased startle (54%), improved sleep (43%), and improved comfort (53%). Although 22% of this group experienced 32 events related to the ITB hardware or surgery, 88 patients said they would undergo the ITB therapy again (224).

Gooch et al. evaluated care provider outcomes in 80 patients that had undergone ITB therapy for one year. After pump implantation, most participants had tone reduction (on the Ashworth scale) in both lower and upper extremities. All care providers reported improvement in scores of the Caregiver Questionnaire. Pain and joints deformities were decreased in 91% of patients. Ease of care improved in 88%. Ninety-five percent of the caregivers would have the implantation again (225).

**ITB outcome in dystonia**

Narayan et al. reported the use of ITB therapy effect in dystonic children. They successfully treated an 18-year-old adolescent with dystonia due to CP (226). In 1995, Penn, et al. reported that ITB improved focal dystonia in some adults (213).

In 2001, Albright et al. used the ITB in 89 children with severe generalised dystonia; mainly due to CP. In this study, dystonia improved in 90% of cases. Patients’ questionnaires have indicated that quality of life and ease of care significantly improved in 86% and speech/function improved in 33% (214).

Woon et al. reported on ITB benefits in 8 patients with dystonia. Three of them (with primary dystonia) had satisfactory results after ITB was considered with a deep brain stimulator (DPS). They have postulated that ITB is beneficial in children with both primary dystonia and dystonia secondary to CP. However, the benefit is subjectively greater in children with dystonia secondary to cerebral palsy, possibly due to the larger spastic component, which is known
to respond to ITB (227).

Recently, many other reports confirmed the effectiveness of ITB in treating focal and generalised dystonia (228-234).

**Weight and height gain after ITB therapy**
Children with spasticity are often below the normal centiles for height and weight when compared with healthy children without disability of the same age and sex (235, 236). Weight gain has been observed clinically in patients undergoing ITB therapy, although published reports of this side effect are rare. In their report, Hemingway et al. have noted that calorie requirements of a patient undergoing ITB therapy while on a calorie-controlled ketogenic diet was decreased by approximately 34%. Interestingly, this reduction corresponds to the estimates of spasticity reduction of 30% to 40% (237). Albright et al. have also noted an increase in growth parameters in children receiving ITB therapy (181). A mechanism proposed to explain weight gain is that caloric expenditure, which is spent to sustain involuntary muscular contraction owing to spasticity, could be shifted to normal linear growth (238).

**ITB therapy outcome with Orthopaedic deformities**
Gerszten et al. have retrospectively reviewed the need for orthopaedic surgery of the lower extremities in 48 patients with spastic CP who were treated with ITB. Subsequent orthopaedic surgery was planned in 28 patients (58%) at the time of pump placement. However, only 10 patients (21%) underwent orthopaedic surgery after ITB therapy, which was already planned at the time of initial evaluation for ITB therapy (47).
ITB outcome with spinal deformities
Many orthopaedic surgeons who treat spastic quadriplegic patients have reported a trend toward marked progressive scoliosis following the administration of ITB (239-241). In one retrospective study the Cobb angle of scoliosis in non-ambulant children with spastic CP was evaluated pre and post ITB implantation. The results demonstrated a significant increase in the rate of scoliotic curve progression (9.02 degrees/year) after ITB pump placement when compared with the published disease natural history data (4.5 degrees/year) (240). However, a prospective comparative study has shown no significant difference in the progression of scoliotic curve between ITB patients and the control group (242). In a recent study from the NUH, a retrospective comparison of scoliosis progression in quadriplegic spastic CP patients with and without ITB pumps, showed significant curve progression over time and the peak curve progression was similar between the groups. The investigators concluded that ITB pumps do not appear to alter the natural history of curve progression in these patients (243).

1.5.3.6.8 Relationship between ITB Pump and the patient
While the clinical outcome of ITB therapy has been discussed in many studies, only one study has reported the functional relationship between ITB therapy, and the patient. Twenty patients have been enrolled into this study (14 patients with multiple sclerosis and 6 patients had spinal cord injury). A structured questionnaire was designed to ask the patients whether they would have the pump implanted again, would be willing to implant the ITB pump privately in the absence of public funding and asked about their relationship with the pump inside them. Fifteen of the 20 patients who were unable to pay for the costs of the pump answered that they would pay for it if they could. The
pump was considered as a foreign body by two thirds of enrolled patients. In other words, these patients considered their pumps as only therapeutic tools. In contrast (35%) felt the pumps as part of their bodies and the presence of pump did not interfere with the rehabilitation or wearing of their clothes. Furthermore, the study reported that half of the patients were anxious about pump failure, and one third of them were afraid of the onset of the alarm signal. These results suggested that patients had a positive feeling about the therapeutic effect of the pump, and could also mean that there was a degree of dependence on ITB therapy (244).

1.5.3.6.9 Cost-benefit analysis
Sampson et al. have conducted a systematic review in 2002 to estimate the effect of ITB infusion on function and quality of life measures in patients with severe spasticity (245). Outcomes were related to standard QOL scores to estimate potential gains in quality-adjusted life years (QALYs) (246). Information on the costs of continuous ITB infusion was obtained from year 1999 data from three hospitals in the United Kingdom in which the operation was performed. Depending on the severity of disability, the cost/QALY(quality-adjusted life years) for ITB ranged from £6,900 to £12,800 (245), which is less than the NICE £20,000 threshold for willingness to pay for a QALY (113).

Since 2000, cost-effectiveness analyses, particularly in USA, usually use the value of $50,000 (≈ £36800) per quality-adjusted life-year (QALY) as a threshold for evaluating the cost-effectiveness of health interventions (17, 18).

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1 The quality-adjusted life year (QALY) is a generic measure of disease burden, including both the quality and the length of life lived. It is used to assess the value for money of medical interventions. The QALY is calculated by the change in utility status [Utility status of health is expressed on a numerical scale ranging from 0 to 1, in which 0 represents the “utility” of the state “Dead” and 1 the utility of a state lived in “perfect health”] induced by the treatment, multiplied by the duration of the treatment effect (246).
More recent reports from Europe and the United States, between 2007 and 2009\textsuperscript{m}, have evaluated the cost effectiveness of ITB therapy where cost per QALY ranged from $10.550 (≈ £7.800) to $19.570 (≈ £14.450) was below the $50,000 (≈ £36800) for one QALY (248-250).

\begin{footnotesize}
\footnotesize
\textsuperscript{m} In 2007, Lissovoy et al. published a study from France. The medical costs of ITB therapy were measured for the year 2006 (248). In 2009, Hoving et al. published a Dutch study of ITB costs, and the costs were estimated for the year 2003 (249). In 2009, Bensmail et al. published a study from the USA. All costs were adjusted to base year 2003 using the medical care consumer price index (250).
\end{footnotesize}
1.6 Aim of thesis and study design:

Randomised controlled trials (RCTs) are essential part of drug licensing, and considered as the gold standard in evaluating the short-term efficacy and safety of developing treatments or interventions. RCTs have long been considered the mainstay of evidence-based research due to their strong internal validity, which depends principally on the power of randomisation to confirm that the only difference between two treatment arms is the exposure to the treatment of interest (251, 252). This will optimise the internal validity, minimise the risk of bias by confounding and assess true cause and effect between an intervention and an outcome (253).

However RCTs applicability in clinical practice can be limited because the chronic conditions that affect broad and heterogeneous patient populations are under-represented in RCTs. In addition, patients and practitioners in RCTs are different from those in routine clinical practice (251). Moreover, the high financial cost of RCTs limits their ability to assess the safety of the treatment and to detect uncommon drug-related events over long-term follow-up (253). Further, research governance and administrative delays many cause additional difficulties in conducting RCTs (253).

In comparison, observational studies have been described as a way of “letting the rats out of the cage and seeing what happens in real life” (253). These observational studies are pursued to appraise how interventions work in the variety of patients treated in routine clinical practice when managed in clinical scenarios that broadly are diverse within and between countries. In addition, they rarely replicate the highly interventional nature of efficacy trials (251, 253). The principal advantage of observational studies is their proximity to
“real life situations” as the greater heterogeneity of medical interventions and patient populations are closer to clinical practice (254). Furthermore they are easily designed, inexpensive to conduct in comparison to RCTs, and are useful to explore rare outcomes and unusual side effects (255). Importantly, observational studies can be complementary to RCTs as they are crucial for creating new hypotheses and representing the external validity of RCTs that have been already completed. In addition, they can clarify which patient groups will get benefit from each alternative intervention (255, 256). RCTs typically measure efficacy (i.e. treatment effects under strictly controlled conditions), observational studies are best suited to measure effectiveness, or treatment effects under realistic conditions (257).

ITB has been established as a treatment of spasticity in CP patients through different study designs. Hoving et al. 2009, in an RCT were able to prove that continuous infusion of ITB is effective in treating spasticity in carefully selected children with intractable spastic CP after 18 months of treatment (258). Albright et al. 1993 in prospective, un-blinded trial have reported the significant reduction of spasticity of cerebral origin after the treatment with ITB (219). Moreover, the National Institute for Health and Care Excellence (NICE) has identified eight studies to establish the guidelines for indications, effectiveness and complications of ITB (11, 188, 259).

The current study is a retrospective observational study aimed at evaluating ITB practice in Nottingham University Hospitals as a regional referral centre for the procedure.

As this study is assessing the outcome of the current ITB practice against the standard national guideline, the conclusions derived from this study will be
invaluable auditing measures for the procedure and could highlight areas for improvement and provide a constructive evaluation of the quality of care.

Audit was defined by Department of Health in the white paper Working for Patients as: “the systematic, critical analysis of the quality of medical care, including the procedures used for diagnosis and treatment, the use of resources, and the resulting outcome and quality of life for the patient” (260).

Clinical audit is different from clinical research as the later aims to define the characteristics of good practice on an unknown land, while the audit compares the current practice against well-defined and established standards (261).

On the other hand, service evaluation measures how well a service is in achieving its intended aims. It is undertaken to benefit the people using a particular healthcare service and is planned and conducted with the only purpose of defining or judging the current service. The results of service evaluations are mostly used to produce information that can be utilised to inform local decision-makers (262).

1.6.1 Structure of the audit cycle (263, 264). Figure 1-7.

1-Preparation

A- Choosing the topic and defining a clear purpose

A Literature Review: To find out whether there are any recommended national standards on which to base the standards, then to find out any previous studies, which have been conducted on this topic to help in designing the method of data collection and setting standards. The aim of the current study is to evaluate the ITB implantation process in NUH and its outcome including morbidity and mortality rate, was well as patients’ quality of life.
2-Setting standards

Standards may be based on one, or any combination, of the following:

• National guidance or standards (e.g. Patients’ Charter).

• College or professional organisation guidelines.

• Laws (e.g. Mental Health Act 1983).

• Previously agreed local guidelines/protocols (e.g. through consultation with commissioners).

• Standards used locally by colleagues or competitors (e.g. your neighbouring trust, ward, etc.).

• Research evidence (from which standards can be developed).

• Literature review of other clinical audits that have published their standards/results.

• Current knowledge from clinical experience.

• Current practice (observes and assesses current practice).

For the purpose of this study; the selection criteria, which was published by NICE in 2012, were considered as the standards for ITB implantation (11)

The audit criteria for ITB outcome were based on the literature review and research-based evidence. Cochrane Database of Systematic Reviews has reported the rate of significant complications to be around 30% over the long-term in those receiving ITB therapy (device-related complications: occurring in 10% to 30% of individuals and pump-related infections: occurring in around 8% to 11%) (265).

3-Measuring level of performance

-Data collection and analysis: collecting the data will be from computerised records, manual collection, or both. It may be retrospective or prospective. Data should be stored in such a way that it is both secure and conforms to
legal requirements. All personal data on a computer should be “secure from loss or unauthorised disclosure” (Data Protection Act 1984) (263).

The collected data will be analysed to compare the actual performance with the set standards.

In this study the data were collected and ascertained manually by one investigator (AA) from medical records, clinic letters and validated questionnaires. Full details of data extraction process are provided in chapter two.

-Compare the performance with criteria:

The collected data are compared to criteria and standards to conclude how the standards have been met. In case the standards have not been met, the reasons should be identified and areas of potential improvement should be suggested.

![Figure 1-7 Clinical audit cycle](image-url)
4-making improvements

Data collection has no chance of making any impact unless they are conveyed to the relevant team to start the more difficult stage of implementing changes. First, the results need to be presented and discussed with the relevant teams in the organisation. Second, the results should be used to develop an action plan, specifying: i) what needs to be done; ii) how it will be done; iii) who is going to do it; and iv) when to be done.

In the current study, the results have been discussed with the clinicians who perform the procedure and have been presented at the neurosurgery clinical audit meeting as well as national neurosurgical meeting (The Society of British Neurological Surgeons).

5-Sustaining improvements

This stage is critical to the successful outcome of an audit: it differentiates whether the implemented changes had an effect in practice and whether further improvements are needed to achieve the standards required. This can be achieved by a re-audit to complete the full audit cycle using the same strategies to ensure the original audit is comparable.
2 CHAPTER TWO: COMPLICATIONS OF INTRATHECAL BACLOFEN THERAPY
2.1 Introduction

ITB has become an established treatment modality to control medically refractory spasticity (166). Nevertheless, there are frequent complications related to the intricate implantation technique and prolonged duration of ITB therapy (206). This is reflected in the literature with an increase in frequency of reported adverse events over the years in proportion to increased usage (266).

Gooch et al. demonstrated that reporting and defining the adverse events of ITB is crucial to the clinical practice for two reasons: firstly, precise information about ITB complications is essential to develop the hardware device and improve the surgical procedure. Secondly, to provide patients’ families with enough knowledge to make informed choices about the benefits and risks of implanting ITB pump (210).

These adverse events are related to surgical implantation technique, adverse effects of baclofen, and hardware related complications as for instance catheter complications or pump failure (171). The most commonly reported adverse events are infections and device related problems (164, 267). Pharmacological ITB adverse effects include sedation, lethargy, drowsiness, hypotonia, headache, nausea, vomiting, constipation and a new onset of seizures or increased seizure frequency (206).

Implantation of ITB pumps started at Nottingham University Hospital (NUH) in 1998. Since then, more than 250 pumps have been implanted to treat spasticity in the paediatric population.

All patients are followed up, and pumps refilled at NUH for a minimum of one year until the baclofen dosage is optimised. After this period, approximately
45% of patients continue to be followed at NUH annually, while the remaining patients receive ITB pump refills at their local hospitals.

2.1.1 The Aim
This chapter will explore and analyse the complications and identify the risk factors related to ITB treatment at Nottingham University Hospitals. Following reviewing the literature thoroughly, the following questions were chosen:

1. What types of complications are associated with ITB therapy?
2. What is the frequency of these complications?
3. Is there a difference between the local rate of complications and the published literature?
4. What are the risk factors for these complications e.g. surgical techniques, patient’s weight and age at implantation time, dystonia, and the presence of a gastrostomy tube?
5. Does the complication rate remain constant or improve with surgeon experience?
2.2 Material and Methods

2.2.1 Study design
This is a retrospective observational study aimed at analysing ITB pump complications and adverse effects. All patients were operated by one paediatric neurosurgeon (MHV). All ITB pumps were inserted in the Department of Neurosurgery at Nottingham University Hospital over a period of 13 years (from 1998-2011). This study has been conducted as a part of service evaluation and clinical audit (number 14-337C).

2.2.2 Data collection
The principal source of the clinical data was the patients' medical records. Laboratory results were collected from the Nottingham Information System (NotIS).

Patient population
This is a retrospective observational study of 286 consecutive cases of spasticity and dystonia referred to the paediatric neurosurgery service in NUH from October 1998 to December 2011. The study follow-up period was extended to December 2012 and thus all the patients had a minimum of one year follow up after the initial ITB implantation. This sampling period was long enough to capture a wide range of complications and possible changes in complications over time that are relevant to chosen study questions (268).

The patients’ medical records, including all data related to ITB and complications of the patients undergoing ITB implantation, were reviewed.

A literature review was conducted to develop our guidelines and to design the data extraction manual (269-271).
2.2.3 Guidelines for collecting the retrospective data

2.2.3.1 The data source and extraction method

Medical records have various sections that describe similar information. The relevant information may be dispersed throughout the clinical notes, nursing notes, drug charts, operative notes, clinic letters, and investigation reports. To increase the reliability of the medical record review (MRR), a data extraction manual was created to outline rules and considerations. This was used to identify where to find the information as well as inclusion and exclusion criteria for this data. Each variable was extracted based on the knowledge of which section of the medical records tend to hold that information consistently.

Demographic data including patient’s age, sex, ID number, and referral destination were collected from the medical notes.

Implantation date, weight at time of implantation, surgical technique (e.g., subcutaneous or sub-fascial pump placement), American Society of Anesthesiologists (ASA) grade, operative time, and any surgical revisions were extracted from the operative notes.

The date of complication was defined as the date of presentation to clinic, GP, or unplanned review in the neurosurgery department.

Distribution of spasticity (quadriplegic or diplegic), ambulatory state, and spinal deformities were collected from physiotherapy documentation in the clinical continuation sheets.

Orthopaedic deformities or complications (such as contractures or fixed deformities of the hips, knees and ankles) were identified as binary data. These data were extracted from physiotherapy assessment documentations, intraoperative assessment under sedation by operating neurosurgeon during test dose trial, and/ or from referral letters.
Associated co-morbidities such as epilepsy, visual difficulties, degree of cognitive impairment, and the presence of a percutaneous endoscopic gastrostomy (PEG) tube were collected from paediatricians’ referral and clinic letters.

Cognitive impairment was classified using information from referral letter and assessments from paediatricians, neurosurgeons, GPs and orthopaedic surgeons. This was classified into poor, fair and intact cognition.

In addition, refilling dose administered, concentration of baclofen used and interval between refills were collected from the print-out of the ITB pump programmer (telemetry).

2.2.3.2 Data abstraction tool

The list of patients, for whom ITB implantation has been performed from 1998 to 2011, has been obtained from the surgical logbook of the lead clinician (MHV). Following completion of the audit registration process, the medical notes were retrieved by Audit office from the medical records department. The medical notes were reviewed at the neurosurgery department by one investigator (AA).

An electronic data form was designed using Microsoft Access 2007. The main table was used for recording the patient’s demography, complications and other variables recorded in this investigation. Another table was designed to collect ITB refilling data (daily dose, baclofen concentration and duration between refills) for each patient, Figure 2-1.

2.2.3.3 Assessment of reliability

The data has been extracted by the one investigator (AA). To verify the collected data, intra-rater reliability of data extraction was tested in a sample
of 40 random medical records (11) (18% of the investigated cases) after 6 months from commencement of the project (272).
Figure 2-1 Microsoft Access 2007 displaying patients' records and linked to side table displaying the refill data for each record.
2.2.4 Identification of Outcomes (Dependent Variables)

In this study, the examined clinical outcomes (dependent variables) were the complications and adverse events in implanted ITB patients.

2.2.4.1 Definition of complications

Sokol et al. defined a surgical complication (SC) as any undesirable and unexpected result of an operation affecting the patient (273).

According to the literature review, ITB adverse events (AEs) were classified into three categories; (a) device-related AEs e.g. pump and the catheter complications (b) surgical procedure related e.g. infections and wound dehiscence (c) pharmacological effects of baclofen e.g. constipation, withdrawal syndrome and baclofen overdose (180, 206, 223).

In the data extraction process, major complications were defined as events that required surgical intervention (e.g. deep infections and device related complications). The number of complications experienced by each patient was documented according to the chronological occurrence, into: initial, second, third, and fourth events.

*Identification of infection complications*

Superficial wound infection, at the site of implantation, is potentially serious but it can be managed successfully with systemic antibiotics and local wound care. However, a deep infection, at the site of the hardware, will likely require removal of the infected equipment (189, 190). Therefore, it is important to differentiate between severity of ITB infection to guide its proper management (274).
According to the definitions of the Centres for Disease Control and Prevention (CDCP), ITB infections were classified as superficial, deep, and organ space infections (275, 276).

Superficial infection was defined when it included at least one of the following: (1) occurs within 30 days after the surgical procedure; (2) includes skin and subcutaneous tissue of the incision; (3) presents by purulent discharge with isolated organisms from the incisional site associated with one of cardinal signs of inflammation (pain, tenderness, localized swelling, redness or hotness); (4) intentionally explored by the physician and is culture-positive or not cultured; and/or (5) identification of superficial SSI by the surgeon or attending physician (275).

On the other hand, deep surgical site infection is diagnosed when at least one of the following were found: (1) it happens within 30 days of the surgery if there is no implanted foreign body at the surgical site or within 365 days with an implant in situ; (2) drainage of purulent discharge from the deep incision and culture positive or not cultured and associated with fever or localised pain and tenderness; (3) deep incision spontaneously dehisced or deliberately opened by a surgeon; and/or (4) diagnosed by a surgeon or a physician as deep incisional surgical site infection (275).

Organ or anatomical space surgical site infection was diagnosed if at least one of the following was involved: (1) any part of the body related to surgical procedures other than skin or muscle; (2) Occurrence within 30 days if no implant left in place or less than 365 days if implant is in situ; (3) presence of purulent discharge or isolation of organisms from the organ or body space; and/or (4) evidence of infection or abscess involving the organ or body space.
by direct examination, reoperation, or by histopathological or radiological examination (275).

Data pertaining to the causative organism of the ITB infection and time to diagnose the infection was collected from NotIS.

**Catheter complication**

Catheter-related complications included catheter dislocation, fracture, occlusion, migration, and connector breakdown. Catheter complications were identified if the patients presented with symptoms of acute baclofen withdrawal, or the patient reported a reduction in the therapeutic effect of the ITB, or being unresponsive to escalation of infusion rate (185, 212).

During follow-up visits, the ITB pump function was checked regularly and the daily ITB infusion dose was adjusted according to response of symptoms, and the clinical outcomes and possible adverse events were evaluated.
2.2.5 Statistical Analysis

2.2.5.1 Descriptive Statistics

For normally distributed variables, continuous data was presented as mean and standard deviation for normally distributed variables. For the non-normally distributed parameters, median and the interquartile range [25th–75th percentile] were used.

2.2.5.2 Logistic Regression Analysis

Spearman’s correlation co-efficient was used to define the significant associations between assumed variables (e.g. age, weight, dystonia and presence of PEG) with two outcomes; surgical site infection, and catheter complications. Potentially correlated variables for each outcome were then used in a multivariate binary logistic regression to recognise statistically significant complication predictors. A P-value < 0.05 (two-tailed) was considered significant.

2.2.5.3 Survival analysis

The functional survival of the ITB pumps and the temporal distribution of complications were analysed using univariate analyses Log-rank tests. Kaplan Meier plots were used to visualise the differences in distribution fraction of patients remaining complication free. Complication free survival was defined as the duration between catheter implantation and the diagnosis of complications. The observation period closed on 31 December 2012.
2.3 Results

A total of 286 consecutive patients were referred from 65 clinical practices either via paediatric neurology, paediatric orthopaedics or their General Practitioner. Out of 258 patients found to be responsive to ITB test dose. Thirty-six patient declined ITB treatment while the remaining 222 received in total 265 ITB implantations over the 13-year period, Table 2-1.

Table 2-1 the results of test dose screening

<table>
<thead>
<tr>
<th>Screened patients</th>
<th>286</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response to ITB test dose</td>
<td>28</td>
</tr>
<tr>
<td>Positive response to ITB test dose</td>
<td>258</td>
</tr>
<tr>
<td>• Implanted patients</td>
<td>222</td>
</tr>
<tr>
<td>• Patients declined ITB treatment</td>
<td>36</td>
</tr>
</tbody>
</table>

2.3.1 Children with failed response to ITB test dose trial

Twenty eight patients failed to response to ITB screening dose. Table 2-2 demonstrates their different diagnosis.

Table 2-2 diagnosis of the children with failed response to ITB trial

<table>
<thead>
<tr>
<th>Cerebral Palsy</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypoxic brain injury</td>
<td>17</td>
</tr>
<tr>
<td>• Neonatal intra-ventricular haemorrhage</td>
<td>2</td>
</tr>
<tr>
<td>• Perinatal encephalitis</td>
<td>6</td>
</tr>
<tr>
<td>• Foetal alcohol syndrome</td>
<td>1</td>
</tr>
<tr>
<td>• Twin to twin transfusion syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Primary dystonia</td>
<td>1</td>
</tr>
</tbody>
</table>

2.3.2 The demography and clinical characteristic of implanted cases

This cohort comprised of 222 children (135 male and 87) female. The mean age at the time of implantation was 10.9 years, (9 months-19.5 years). Nine children were below the age of 4 years old when they received ITB implantation, Table 2-3.
The cumulative follow up duration of the entire population was 11269 pump months (939 pump years) with a median 4.02 years (IQR 2.24-5.87) years. The mean daily dose of ITB that was needed to attain the optimal response in this series was 307 µg/day (range 80-1150 µg/day, SD±194).
Figure 2-2 Number of cases per referring centre to NUH
Of all the 222 patients who had ITB implantation, 203 had spastic quadriplegia, 19 patients were paraplegic, 158 patients were wheelchair bound, 59 were walking with aid and only 5 patients were independently ambulant. Ninety-one (40.9%) patients had associated epilepsy, 118 patients had severe cognitive impairment, 83 had mild cognitive impairment and 21 had normal cognition. Thirty-four (15.3%) patients had visual impairments. Twelve (5.4%) patients had prior ventriculo-peritoneal shunt implantations. Sixty-one (27.5%) patients had gastrostomy tube for feeding due to difficult swallowing and/or associated oesophageal spasm. Muscle contractures and orthopaedic deformities were manifest in 145 (65%) patients, 51 (22.9%) of whom had previous surgical corrections. Spinal deformity, such as kyphoscoliosis, was present in 103 (46%) patients. Nine patients had received spinal deformity corrective surgery prior to ITB implantation, whilst 10 patients had spinal surgery post-implantation. Four patients were waiting for correction surgery. Figure 2-3 depicts these comorbidities and their percentages.
The main indication for ITB implantation in this population was cerebral palsy which was a consequence of various neonatal causes. Other indications included primary dystonia, Table 2-4.

**Table 2-4** Indications of ITB implantation in the study population

<table>
<thead>
<tr>
<th>Indication of implantation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Cerebral palsy</td>
<td>210</td>
</tr>
<tr>
<td>- Perinatal hypoxia</td>
<td>131</td>
</tr>
<tr>
<td>- Perinatal encephalitis</td>
<td>55</td>
</tr>
<tr>
<td>- X-linked adrenoleukodystrophy Demyelination</td>
<td>13</td>
</tr>
<tr>
<td>- Neuronal migration disorder and corpus callosum agenesis</td>
<td>5</td>
</tr>
<tr>
<td>- Other congenital brain anomalies</td>
<td>5</td>
</tr>
<tr>
<td>- Chromosome 18 abnormality</td>
<td>1</td>
</tr>
<tr>
<td>2-Primary dystonia</td>
<td>7</td>
</tr>
<tr>
<td>- Hallervorden Spatz</td>
<td>3</td>
</tr>
<tr>
<td>- Idiopathic</td>
<td>2</td>
</tr>
<tr>
<td>- Leighs Syndrome</td>
<td>2</td>
</tr>
<tr>
<td>3-Traumatic brain injury (TBI)</td>
<td>1</td>
</tr>
<tr>
<td>4-Transverse Myelitis</td>
<td>1</td>
</tr>
<tr>
<td>5-Hereditary Spastic Paraplegia</td>
<td>2</td>
</tr>
<tr>
<td>6-Near drowning</td>
<td>1</td>
</tr>
</tbody>
</table>

67 patients of the 222 cerebral palsy patients had mixed spasticity and dystonia.
Chapter 2

Complications of ITB Therapy

The peak time of ITB implantation in NUH was between 2006 and 2007, Table 2-5.

**Table 2-5** Distribution of ITB implantations per years of practice

<table>
<thead>
<tr>
<th>Year</th>
<th>No of primary implantation s/y</th>
<th>Total no. of implantations/y</th>
<th>Re-implantation due to infections</th>
<th>Re-implantation after battery depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1999</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2000</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2001</td>
<td>13</td>
<td>14</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2002</td>
<td>14</td>
<td>17</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2003</td>
<td>14</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2004</td>
<td>16</td>
<td>17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td>17</td>
<td>22</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2006</td>
<td>31</td>
<td>35</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2007</td>
<td>37</td>
<td>38</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2008</td>
<td>17</td>
<td>22</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>20</td>
<td>23</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2010</td>
<td>15</td>
<td>19</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2011</td>
<td>6</td>
<td>21</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>222</td>
<td>265</td>
<td>25</td>
<td>18</td>
</tr>
</tbody>
</table>

ITB implantations was most frequent in children between 8 and 12 years old (69 patients) and the lowest number of implantations was in children below the age of 4 (9 patients). Implantation according to age group was normally distributed, Figure 2-4.
2.3.3 Implantation technique

In the first 4 years of ITB service, 35 patients received ITB implantations using the subcutaneous technique with all subsequent implants from 2003 performed with a sub-fascial implantation technique, Table 2-6.

| Table 2-6 Surgical techniques and ITB pump models used for implantation |
|---------------------------------|-----------------|-----------------|
| **Number of patients**          | 222 patients    | **Initial implantation** |
| **Total No of implantations**   | 265 (222 patients) | 43 planned replacement: |
|                                 |                 | • 25 replacements after complications (23 infections and 2 pump failures) |
|                                 |                 | • 18 elective implantation after battery depletion |
| **Level of implant**            | 35 Subcutaneous and 187 Subfascial | |
| **ITB Pump models**             | 57 EL (10 ml) 208 (II 20 ml) | |
Two hundred and twenty-one patients received ITB implants with catheter insertion at lumbar region, while 20 patients had their catheter inserted at the cervico-thoracic region due to associated spinal deformities or previous spinal surgery, Table 2-7.

<table>
<thead>
<tr>
<th>Indications of inserting baclofen catheter at the cervico-thoracic region</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe untreated scoliosis</td>
<td>4</td>
</tr>
<tr>
<td>Previous spinal surgery with fusion mass or metal work</td>
<td>9</td>
</tr>
<tr>
<td>Re-insertion of the catheter due to iatrogenic transection of lumbar ITB catheter during corrective spinal surgery</td>
<td>7</td>
</tr>
</tbody>
</table>

Of all the 265 ITB implants, 253 had implantations on the right side of the body. However, 12 patients had implants on the left side due to previous abdominal surgery or prior ITB explantation due to infection on the right side.
2.3.4 Adverse events related to screening trial:
In 286 patients who had screening trial, 20 (7.3%) patients had mild symptoms of nausea and vomiting, 12 (4.1%) patients had headache. These symptoms were managed conservatively. Seventeen (5.9%) patients had CSF leakage at lumbar puncture site that in the majority resolved spontaneously but 2 patient needed suturing of the skin to control the CSF leakage. Four patients (1.3%) experienced hypotonia and insomnia which resolved spontaneously. One patient (0.69%) had numbness in his lower limbs which recovered after removal of the lumbar catheter. None of these patients were documented to have post procedure infection.

2.3.5 Adverse events after ITB implantation
During 13 years of practice, a total of 118 adverse events were documented in 84 patients. Twenty six of these 84 patients (26/84, 30.9%) had two consecutive AEs, while 6 and 2 patients experienced three and four adverse events respectively, Table 2-8.
These 118 AEs included 29 (13%) pharmacological side effects of intrathecal baclofen, and 85 procedures and device related complications which necessitated surgical revision.
Table 2-8 Types and chronological frequency of documented complications in the study population

<table>
<thead>
<tr>
<th></th>
<th>Initial adverse events</th>
<th>Second adverse events</th>
<th>Third adverse events</th>
<th>Fourth adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patient</td>
<td>84</td>
<td>26</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Time to complications</td>
<td>253 days SD ±425 days</td>
<td>Mean 616 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6 – 2505 days)</td>
<td>SD±795 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7 - 1853 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound complications:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF leakage</td>
<td>40</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Seroma</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>28</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Catheter complication:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migration</td>
<td>38</td>
<td>10</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Iatrogenic fracture after spine surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Kink and occlusion</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fracture</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Catheter disconnection</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Device errors</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pharmacological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>24/222</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overdose</td>
<td>3/222</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2/222</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
2.3.6 Pharmacological adverse events.
Constipation was documented in 23 (10.5%) patients as the most common pharmacological side effect of ITB therapy and was conservatively managed. Urine retention and worsening of swallowing was reported only in 2 patients. Three children had overdose symptoms ranging from hypotonia, and drowsiness. One patient, of the later three, needed admission in paediatric intensive care for respiratory support due to apnoea that followed ITB pump refill. Two patients developed psychosis and presented with delusions and confusional state that was controlled by decreasing the baclofen dose.
In this series, ITB therapy did not affect the frequency of epileptic seizures, nor did it cause no complications with ventriculo-peritoneal shunts. Moreover, baclofen withdrawal syndrome was not observed in this series.

2.3.7 Surgical and device related complications of ITB.
Eighty-five secondary surgical procedures were documented in this cohort during 939 pump years of follow up. Ex-plantation was performed in 29 ITB pumps; 25 pumps were removed after deep infections in 23 patients and 4 cases due to family requests for perceived lack of efficacy. Seven patients required revision due to malfunction after spinal surgery, 47 revisions of ITB catheter due to various reasons and 2 pump replacements after recognising pump errors.
2.3.7.1 Device related complications

A total of 56 device related complications out of 265 implants (21.13 %) were recorded in (40/222, 16.3 %) patients. Pump malfunction only occurred in 2 patients (<1%) who presented with ITB under-infusion that did not improve after increasing the dose and were also associated with alarm fault. ITB pumps were replaced and the patients resumed the therapeutic effects. No cases of pump flipping or intraperitoneal migration were documented in this study.

Catheter complications were responsible for the most ITB pump revisions in this cohort, which occurred 54 times in 38 patients. The most frequent complications were catheter migrations, which occurred 23 times (8.6% of 265 implanted pumps). Spontaneous catheter fractures were the second most common complications that occurred in 12 (4.5%), followed by catheter disconnections from the ITB pump that reported in 7 (2.6%) cases. Seven (2.6%) iatrogenic catheter transection happened after spinal surgeries, and lastly, 5 (1.9%) catheters were revised due to kink or occlusion.

Ten patients required surgical revisions for catheter malfunctions on 2 occasions each, and 4 patients had revision surgery on 3 occasions. The median time between implanting the ITB pump and catheter revision was 641 days (21.6 months) and ranged from 49 to 2505 days.

2.3.7.2 Surgical wound complications

A total 51 (19.2%) surgical wound complications were found. Four events of CSF leakage occurred in 3 patients, which subsided spontaneously or by secondary suturing. Three patients had a postoperative subcutaneous seroma in the abdominal wound that resolved after aspiration under sterile conditions.
Surgical site infection
Surgical site infection (SSI) was reported in 44 (16.6%) cases out of 265 implantations. Superficial infection presenting as erythema, swelling, and tenderness was recognised in 18 cases (6.8%), who responded successfully to conservative management and antibiotic administration. Deep infection was reported in 25 cases (9.43%) and presented with erythema, purulent discharge, swelling and wound dehiscence that necessitated urgent removal of the ITB pump. One of those patients, who was under 4 years old, experienced two deep infections. One case (0.37%) of organ space infection with meningitis was reported and the patient required admission to intensive care for treatment of septic shock.

One patient had recurrent superficial infection, however salvage of the ITB pump was achieved by surgical revision, pump removal was avoided. Five patients had experienced 2 of wound complications.

The median time elapsed between ITB pump implantation and diagnosis of infection was 25 days (6-111 days).

2.3.7.3 Microbiological results
Microbiology cultures were obtained from surgical sites of all infected cases. Of the 51 surgical wound complications, organisms were isolated in 21 (41.2%) samples by microbiology culture Table 2-9.

The most frequent causative organism was *Staphylococcus aureus* that was positively cultured in 11/51 (21.5%) of all infection events. In one patient the infection was caused by 2 different types of bacteria (S. aureus and *Abiotrophia* specie). *Pseudomonas aeruginosa* was isolated in two patients (4%); one of them was colonised at their tracheostomy site and the other patient had isolated *pseudomonas aeruginosa* following spinal fixation surgery.
complicated by wound infection. Other bacteria cultivated were group A Beta-hemolytic Streptococcus in 2%, coagulase-negative Staphylococcus species (9.8%), and *Pseudomonas aeruginosa* in 4%. In 58% of cases the culture was negative.

**Table 2-9** Types of infecting organism in patients with surgical wound complications.

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>11</td>
</tr>
<tr>
<td>Group A Beta-haemolytic Streptococcus</td>
<td>1</td>
</tr>
<tr>
<td>Abiotrophia species</td>
<td>2</td>
</tr>
<tr>
<td>Coagulase negative Staphylococcus CONS</td>
<td>5</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>3</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>2</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2</td>
</tr>
<tr>
<td>Culture negative SSI</td>
<td>30</td>
</tr>
</tbody>
</table>
2.3.8 Predictive factors of catheter complications

Univariate analysis of potential risk factors related to catheter complications revealed that catheter complications were correlated with dystonia and level of implantation (subcutaneous or sub-fascial), Table 2-10.

**Table 2-10** Correlation of risk factors and catheter complications (Spearman’s correlation test)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia</td>
<td>0.398</td>
<td>0.002*</td>
</tr>
<tr>
<td>Implantation level (subcutaneous and subfascial)</td>
<td>-0.163</td>
<td>0.015*</td>
</tr>
<tr>
<td>Distribution of spasticity</td>
<td>0.086</td>
<td>0.200</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>-0.081</td>
<td>0.228</td>
</tr>
<tr>
<td>Spinal deformity</td>
<td>0.047</td>
<td>0.480</td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>-0.040</td>
<td>0.553</td>
</tr>
<tr>
<td>Insertion method of the catheter (LP or Laminectomy)</td>
<td>0.033</td>
<td>0.623</td>
</tr>
<tr>
<td>Weight at implantation time</td>
<td>0.029</td>
<td>0.670</td>
</tr>
<tr>
<td>Operative duration</td>
<td>0.014</td>
<td>0.830</td>
</tr>
<tr>
<td>Age of implantation</td>
<td>-0.003</td>
<td>0.969</td>
</tr>
</tbody>
</table>
The multivariate binary regression analysis revealed that dystonia and the level of ITB implantations were the most significant factors that determine the frequency of catheter complications (p =0.001 and 0.02 respectively). Distribution of spasticity (quadriplegia or diplegic), associated epilepsy, degree of spasticity, spinal deformity, and presence of gastrostomy was not statistically significant, Table 2-11.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>P value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia</td>
<td>0.001*</td>
<td>8.970(3.970-20.2690)</td>
</tr>
<tr>
<td>Level of implantation(subcutaneous /sub-</td>
<td>0.020*</td>
<td>0.322(.124-.835)</td>
</tr>
<tr>
<td>fascial technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insertion method of the catheter (LP or</td>
<td>0.198</td>
<td>0.344(.0671-.765)</td>
</tr>
<tr>
<td>Laminectomy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.368</td>
<td>0.682(0.296--0.570)</td>
</tr>
<tr>
<td>Spinal deformity</td>
<td>0.426</td>
<td>1.378(0.6263-.029)</td>
</tr>
<tr>
<td>Distribution of spasticity (Diplegia or</td>
<td>0.493</td>
<td>1.806(.3339-0.792)</td>
</tr>
<tr>
<td>Quadreplegia)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.3.9 Predictive factors of wound infections

Univariate analysis of risk factors associated with intrathecal baclofen infections was conducted to investigate the predictive factors of infection, Table 2-12.

**Table 2-12 Correlation of risk factors and wound infections (Spearman’s correlation test)**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrostomy</td>
<td>0.410</td>
<td>0.001*</td>
</tr>
<tr>
<td>Age at implantation time</td>
<td>-0.298</td>
<td>0.005*</td>
</tr>
<tr>
<td>Associated dystonia</td>
<td>0.279</td>
<td>0.001*</td>
</tr>
<tr>
<td>Weight at implantation</td>
<td>-0.174</td>
<td>0.009*</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>-0.027</td>
<td>0.689</td>
</tr>
<tr>
<td>VP shunts</td>
<td>0.015</td>
<td>0.826</td>
</tr>
<tr>
<td>ASA grade</td>
<td>0.118</td>
<td>0.101</td>
</tr>
<tr>
<td>Previous procedures</td>
<td>0.12</td>
<td>0.079</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.059</td>
<td>0.378</td>
</tr>
<tr>
<td>Operative time</td>
<td>0.066</td>
<td>0.327</td>
</tr>
<tr>
<td>Level of implantation</td>
<td>0.007</td>
<td>0.919</td>
</tr>
</tbody>
</table>

Significant associations were found between occurrence of infection and; young age and low weight at implantation time, associated dystonia, and the presence of gastrostomy tube. However, no significant correlations were found with operative duration, technique of pump implantations (subfascial or subcutaneous), distribution of spasticity (quadriplegia or diplegic) visual impairment, ventriculo-peritoneal shunt, associated epilepsy, ASA grade and previous revision surgery.
The multivariable binary regression model for infection complications showed that most surgical site infections had significant associations with age, dystonia, and presence of gastrostomy. On the other hand, there were no significant associations with weight, operative time, ASA grade, and previous surgical revisions, Table 2-13.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>P value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia</td>
<td>0.0001*</td>
<td>0.162 (0.065-0.405)</td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>0.002*</td>
<td>0.084 (0.028-0.254)</td>
</tr>
<tr>
<td>Age at implantation time</td>
<td>0.02*</td>
<td>0.982 (0.972-.994)</td>
</tr>
<tr>
<td>Operative time</td>
<td>0.090</td>
<td>1.015 (0.997-1.033)</td>
</tr>
<tr>
<td>Infection after secondary procedure</td>
<td>0.305</td>
<td>1.681 (0.623-4.534)</td>
</tr>
<tr>
<td>Weight at implantation time</td>
<td>0.825</td>
<td>0.995(0.955-1.037)</td>
</tr>
<tr>
<td>ASA grade</td>
<td>0.932</td>
<td>1.034 (0.478-2.236)</td>
</tr>
</tbody>
</table>
2.3.10 Complication free pump survival

The Kaplan Meier curve showed the cumulative complication-free pump survival for all the patients. The plot in Figure 2-5 presented 2 curves illustrating catheter (blue curve) and infection (green curve) complications over time. The X-axis represents the time in months. As the graph demonstrates, infections events happened earlier following pump implantation, while catheter complications have been reported at any time during patients’ follow-up. Infection tended to occur only during the first 8 weeks following implantation, with no further infections reported later on during the follow-up time. Interestingly, complications were not observed after a period of 82 months, even after planned pump replacement.
Figure 2-5 Kaplan Meier plot showing complication free patient survival of all patients with an ITB pump.
2.3.11 Complication rate throughout practice

The complications rate was higher in early practice; however, it gradually declined with time. Figure 2-6 demonstrates increased implantation rate throughout years of practice however, the major complication did not parallel this. Figure 2-7 shows the percentage of complications per year.

![Figure 2-6 Number of major complications related to number of implantations per year.](image-url)
2.3.12 Mortality with ITB therapy

Eight patients (3%) died with no evidence that their death was related to ITB therapy. All of them had severe grade of cerebral palsy with impaired mobility and cognitive impairment and died due to causes related to the underlying cerebral palsy.
2.4 Discussion

2.4.1 The demography and clinical characteristic of implanted cases

The indication for ITB therapy in this study conforms to previous series (which was conducted on 90% of this cohort) as cerebral palsy was the commonest indication for ITB therapy in children and most of the patients had spastic quadriplegia 88% (181, 185, 210, 266, 277, 278).

The annual implantation rate increased gradually from 1998 until the peak in 2007, and then gradually decreased after 2008 due to commencement of selective dorsal rhizotomy as a surgical treatment for spasticity in paraplegic patients.

The male to female ratio in this cohort was approximately 3:2, in concordance with previous studies (181, 225, 278), which is partly explained by the greater preponderance of cerebral palsy in males compared with females (2.2 and 1.7 per 1000 births respectively) (279, 280). An alternative theory proposed is that parents of female patients are dissuaded by the large abdominal incision required for implanting the relatively sizeable pump, in comparison to parents of male patients who might pursue more aggressive treatments in the hope of increasing their activities (181).

In the present study, more than two thirds (71%) of implantations occurred in children above 8 years and the mean age at time of implantation was 10.9 years. This is slightly younger than average in other series, which vary between 11.2-13.6 years (173, 210, 274, 277, 278). The development of spasticity in children with cerebral palsy usually increases up to the age of 4 years, then decreases gradually to 12 years of age. After the age of 12 years children will retain that level of spasticity (281).
2.4.2 Screening trial

Gilmartin et al. reported that 94% of patients with spasticity of cerebral origin have demonstrated a positive response to the screening test for ITB therapy (188), and Penn et al. reported 97% response in patients with spasticity of spinal origin (145). Albright et al. stated that 90% of 69 patients who had dystonia responded to ITB trial by decreased dystonia scores (214). Philips et al. have reported 89.7% response to ITB trial in a cohort of adults with multiple diagnoses (282).

In the current study 28 (9.7%) out of 286 children has failed the ITB test dose and the response rate was 90.3%. This finding broadly agrees with the previous studies (145, 188, 214, 282). The observed low response in this cohort could be related to possible association of spasticity with other neurological conditions such as severe dystonia which was difficult to be confirmed through this retrospective review.

Furthermore, a thorough literature search revealed no mention of using the ITB therapy for treating twin-twin transfusion syndrome\(^\text{\tiny n}\) (283) or foetal alcohol syndrome\(^\text{\tiny o}\) (284).

Future prospective studies on the ITB therapy should take into account the prevalence and causes of failed trial dose.

\(^{\text{n}}\) Twin-twin transfusion syndrome is a condition that affects identical twin pregnancies. It results from intertwine vascular connection within the placenta. It is associated with a high risk of perinatal mortality of around 90%, and neurological sequelae are found in 20-40% (283).

\(^{\text{o}}\) Foetal alcohol syndrome: a group of conditions that can occur in children, and is associated with heavy maternal alcohol consumption. Foetal death is the extreme outcome of this syndrome. Other features include: an abnormal facial appearance, short height, low body weight, small head size, poor coordination, low intelligence, behaviour problems, and problems with hearing or seeing (284).
2.4.3 Pharmacological adverse events related to ITB

There is paucity in reporting drug related adverse events of ITB therapy in the literature (10) as the majority of publications focus on infection and device related complications (278). The most common ITB adverse effects reported in the literature include constipation (10–31%) (209, 214, 285), nausea and vomiting (11–14%) (181, 191), headache (11–12%) (168, 181), and new onset or increased frequency of seizures (13%) (206, 286). Constipation is the commonest problem in the CP population and is exacerbated after ITB therapy (287). In this study 11% of the patients experienced worsening constipation which was managed conservatively.

Psychosis or personality changes occurred after an over-dosage of ITB in 0.9% of this cohort which goes in line with the results of another study that reported it in less than 1% (166).

Withdrawal syndrome is one of the most crucial drug related adverse event of ITB therapy, and may be life threatening (288). It has been documented in ITB patients as case reports (207, 289-293). Studies suggest that patients could experience withdrawal symptoms close to their scheduled refill dates. Catheter-related complications, infected pump removal, empty reservoir volume, end of battery life and iatrogenic programming error are considered as causes of ITB withdrawal syndrome (195). Rebound spasticity is the earliest symptom of withdrawal and can be associated with tachycardia and fever. Samson-Fang et al. stated that identification of withdrawal syndrome is very difficult in patients with cerebral palsy (207), especially if they present to a clinician who is unfamiliar with ITB therapy (206).

In this cohort, no clear documentation of ITB withdrawal symptoms was found. However, reduced effect of ITB due to catheter malfunction might be
considered as mild or early symptoms of withdrawal. Intermittent catheter dysfunction, due to partial occlusion or kink, can cause mild symptoms such as increasing spasticity (185, 294). These early, mild symptoms might be managed promptly before progression to abrupt withdrawal.

No withdrawal symptoms were found after acute removal of infected pumps. This is because the infection usually happens early after ITB implantation before GABA\(\beta\) receptor down-regulation has occurred (274). Additionally it is routine practice to start oral baclofen replacement once the clinician has removed the infected pump (205).

Withdrawal symptoms are similar to other serious conditions e.g. autonomic dysreflexia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome (295), and status dystonicus (296). Alden et al. suggested checking the functional integrity of the ITB system in all children with ITB therapy if they present with fever or unexplained systemic illness (289). Coffey et al. recommended meticulous care to ITB pump refilling and programming, in addition to educating the caregivers and paediatric emergency team to recognise the symptoms of withdrawal syndrome (143).

2.4.4 Surgical and device related complications of ITB therapy

Previous studies (166, 173, 206, 274, 297) reported a complication rate ranging from 20\%–30\% in ITB therapy patients. However these values and the rate of each event may vary among published works according to the features of the assessed population, the implantation technique, and the follow-up period. Furthermore, many complications could be reported under several different categories. For instance, a kinked catheter could be categorised under catheter problems, device-related problems or baclofen
Chapter 2

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withdrawal. Also, different methods are used to calculate rates which can be reported as simple frequencies, number of events, or by frequency of events by treatment years (266).

2.4.4.1 Pump malfunction
Several studies stated that the effectiveness of intrathecal baclofen therapy in treating spasticity and dystonia could be compromised by device related complications such as catheter and pump related complications (214, 298, 299).

In the present study, only 2 (1%) patients experienced pump error that required ITB pump replacement to resume therapeutic effect. This result is consistent with Motta et al. who reported 4 incidents in 430 patients ≈ 1% (278). However, Borowski et al. reported 4 (2.4 %) pump failure in 161 implants (173).

In general, device-related errors are rare with the existing ITB pump systems (299), although the possibility of errors has been described by the device manufacturer (Medtronic, Inc, Minneapolis, MN). They recommend routine verification of pump function at each refill where the actual delivered volume should be within 10% of the intended volume determined by the pump. They stated potential causes for pump errors are; exposure to MRI, missing pump propellant, and gear shaft wear. The commonest error is related to pump switch off after exposure to MRI. Hence, it is crucial to interrogate all ITB pumps after MRI exposure, to confirm their functional status to avoid an abrupt change to ITB delivery (300).

2.4.4.2 Catheter complications
In this study, catheter complications were the main cause of surgical revision of ITB implantation and occurred in 20% of implantations.
In early practice of ITB therapy, Albright et al. (301) and Penn et al. (212) both reported that frequency of catheter complications may be as high as 31-40%. Furthermore long-term follow-up studies have suggested higher rates of around 37%-55% (302, 303). Cochrane Database of Systematic Reviews revealed the rate of device related complications to be between 10%-30% over the long term in those receiving ITB (265).

Catheter migration is the single most common complication encountered with pump catheters in this study, which is consistent with previous studies (304, 305). However, Vender et al. found pump connector fracture and disconnection to be the most frequent catheter complication (185). Gooch et al. had the same results.(210) The higher rate of hub connector fractures was attributed to the old straight connector that was used in early ITB practice. This complication has been reduced since introduction of a new hub connector angled at 45° which reduces the strain and decreases the risk of fracture (185). In comparison to the above, this cohort had lower catheter complications. In addition hub connector fracture was seen less than other catheter complication types. This could be explained by the early adoption of the modified 45 degree connector.

2.4.4.3 Surgical site infection after ITB implantation

Postoperative surgical site infection is a major problem in ITB practice, especially when it occurs in a compromised host such as a child with CP (274). Comparing infection rates between studies could be difficult as many studies report their infection rate per patient rather than per number of procedures.
Furthermore, few studies only define the severity of infections such as being superficial or deep infection (274). In this cohort, the infection rate was recorded per number of procedures.

Infection in this cohort is the second most commonly documented type of complication. Deep infection occurred in 9.43% of patients which necessitated explantation of the ITB pump.

Since introducing ITB as a treatment of spasticity in children, the ex-plantation rates after deep ITB infection reported in literature vary from 4-44% (168, 185, 285, 301, 306).

However, our rates seem to be similar to recent studies. Fjelstad et al reported deep infections in 10% of 91 paediatric patients (307). Motta et al. reported 30 pumps (7%) explantations in 430 patients due to infection (278). Bayhan et al. reported 29 ITB infections in 298 children with cerebral palsy (308). Cochrane Database of Systematic Reviews revealed that the rate of infections to be around 8% to 11% (265).

In our study, the average time for infection to manifest, was less than one month. This finding is consistent with those of Dickey et al. who reported the median time to have ITB infection was 14 days (274), and similarly Fjelstad, et al. reported the same observation in a series of 163 patients (307). These findings further support the idea that Staphylococcus colonisation happens early at the time of device implantation (309). It happens by inoculation with only a few microorganisms from the patient's skin during implantation or the pathogens may be transmitted from surgical or clinical staff (310-312). Albright et al. asserted that when infection occurred within 8 weeks postoperatively, it should be classified as a procedure related complications (181).
In this study, *Staphylococcus aureus* was the most frequent cultivated organism followed by Coagulase-negative staphylococci\(^p\). *Staphylococci* organisms have the ability to adhere to the devices and to build a biofilm. The later film acts as a mechanical barrier allowing colonisation of the organisms and preventing the patient’s immune mechanisms from eradicating the bacteria related to the infected device. In addition, antibiotics are rarely capable of treating these infections, in spite of the use of the sensitive antibiotics which are of proven in vitro activity. Therefore it has been established in clinical practice, that staphylococcal infections of implantable devices generally necessitate removal (310). However, in one of our patients who had previous ITB pump explantation after deep infection, wound dehiscence and signs of infection developed 10 days after elective pump replacement. An attempt to salvage the device was considered to circumvent the necessity for removal of the device. The surgical wound was revised in theatre by debridement, washing with antiseptic solution, followed by 4 weeks of intravenous antibiotics tailored to the pathogen. The procedure successfully allowed the pump to survive.

This manoeuvre had been tried successfully in previous studies when the infection was caused by non-adherent bacteria which are not capable of producing the biofilm, thus allowing the patients to respond to treatment by antibiotics (189, 309, 313, 314).

\(^p\) Coagulase-negative staphylococci are by far the most common cause of bacteraemia related to indwelling devices. Most of these infections are hospital acquired, and studies over the past several years suggest that they are often caused by strains that are transmitted among hospitalized patient (310).
2.4.4.3.1 Culture negative infection
In this study, the causative organism was identified only in one third of the infected cases whilst the rest did not show bacterial growth. Negative culture or no bacterial growth is a common difficulty in the treatment of postoperative SSI. Previous studies have reported the incidence of culture negative SSIs up to 30% (315).

Several explanations have been given for culture negative infection at surgical sites. The most common reason is commencing antibiotics before culturing the infected site. Secondly, the infection may be caused by atypical organisms that do not grow on standard culture media or grow rather slowly resulting in discarding the plates before the bacteria becomes apparent (315). Lastly, common contaminants such as *Staphylococcus epidermidis* or *Corynebacterium species* are generally not considered pathogenic, though they may actually be responsible for the infection at a surgical site (316, 317).

Surgical site infection increases the cost to the health service. Generally, the cost of (SSI) is tripled due to the expense of hospital stays, the economic burden on community health services, and the increase in social and financial dependency of the patient (318).

In the United States, postoperative SSI cost was estimated to be three times the cost on uncomplicated postoperative course. (319) In the UK, the Public Health Laboratory Service (PHLS) estimated a 2.5 times cost increase for patients who was complicated with SSI compared to patients without postoperative SSI. Furthermore, it valued the cost of the patients SSI episode in 2000, on average between £1618 and £2398 per patient (320). No previous study has investigated the cost of ITB pump infection; however ITB implantation is already an expensive procedure which costs £13,895
according to the NICE guidelines in 2012. The NICE calculated the costs of implanting the ITB pump from Sampson et al, study in 2002 and converted to 2010/11 costs by using the hospital and community health services pay and prices index uplift (113).

2.4.5 Complication free survival in ITB patients
Both catheter and infection complications, in this cohort were infrequently observed after 6.8 years. Catheter complications occurred within an average of 2 years post-implantation, and were rare after 6.8 years. The clustering of catheter complications in the first two years could be related to incomplete therapeutic effect of baclofen during the first 12 to 18 months of ITB therapy when the individual dose titration is managed (321). Subsequently the uncontrolled spastic movements and differential motion generated between the pump in the abdomen and spine may contribute to repetitive pulling on the catheter, leading to its disconnection or migrations (322). The low incidence of late catheter complications was related to body tolerance to ITB catheter (278), in addition to reaching the therapeutic effect of the ITB (322).

Ghosh et al. suggested that better tolerance of the foreign body produces little reaction after several years (277). Furthermore improvement in weight (238, 323), and immunity with age are possible reasons to explain such results (277). This also accords with earlier observations, that adults have less complication than children (185, 307).
2.4.6 Predisposing factors for ITB pump complications

2.4.6.1 Age at implantation time

The occurrence of infection in this cohort was negatively correlated with the age at implantation time. This finding is consistent with Albright et al’s results, that the incidence of serious ITB complications is significantly higher in children younger than 8 years old (181). Similarly, Murphy et al. who reported that ITB explantation rate was more often in their young than in their older patients (168). Further work is required to establish the safety and effectiveness of ITB therapy in paediatric patients below the age of 4 years (324).

2.4.6.2 Gastrostomy tube

The presence of gastrostomy tube was found as a risk factor of infection developing. Jevsevar and Karlin stated that the nutritional status of CP patients is a significant risk factor for developing infection (325). This is because malnourished CP children often have disturbances in their immune systems, predisposing them to infections (169, 326). Therefore, gastrostomy often helps in the nutritional optimisation especially in the perioperative period. However, in this study the presence of a gastrostomy tube was associated with SSI.

Murphy et al. also reported that patients with gastrostomy tubes are more liable to ITB pump infection and ex-plantation (36). In multivariate analysis to identify the risk factors of ITB pump infection, Fjelstad, et al. stated that the frequency of deep SSI was significantly related to the presence of gastrostomy tubes (168, 307). In addition, it was also found to have a significant correlation with deep wound infections after instrumented spinal fusion in children with cerebral palsy (327).
A gastrostomy tube is a foreign body, and hence it creates and maintains a potential focus for bacterial colonisation (328). One tenth of children with gastrostomies develop erythema and tenderness around insertion site of tube (329), with a tendency to harbour polymicrobial colonies of organism (330, 331).

Increased bacterial colonisation is sometimes difficult to identify in these wounds, which could be missed before ITB pump implantation and subsequently precipitate later wound infection (332).

2.4.6.3 Dystonia

Generalised dystonia affects 15 to 25% of people with CP (333, 334). In a recent study, Lin et al. reported secondary dystonia due to cerebral palsy in 150 of 230 patients (53.7%) (335). The presence of dystonia was found to be a predisposing factor for catheter complications and SSI in this study. These findings are consistent with previous results (174, 233, 274, 336). Albright et al. explained this observation due to the dystonic patients having less response to ITB therapy and more dystonic movements (219). These dystonic movements can place pressure on the pump and catheter insertion sites and contribute to surgical site breakdown and catheter stress (274). In addition the patients are typically undernourished due to the high metabolic needs of dystonic movements leading to increased susceptibility to infection (337).

This idea was supported by Turner et al. who presented 22 patients with intractable spasticity or dystonia who had received intra-ventricular baclofen (IVB) therapy after their experiences of multiple ITB therapy complications. The surgical revision rate\(^q\) was less in IVB patients (0.50) in comparison to

\(^q\) the average number of surgical revisions per average number of follow-up years (336).
0.84 in ITB therapy (336). Same result was presented by Haranhalli et al. who also used IVB therapy in two patients who had multiple catheter revisions due to excessive twisting from dystonic movements in the trunk (174).

Recently, Rocque et al. stated that insertion of the intraventricular catheter can often be much easier technically than inserting intrathecal catheter especially in patients with severe dystonia not responding to ITB therapy (234), or in patients with spinal fusions (337).

In this study, IVB therapy was not used however; it should be considered as an alternative to ITB especially when catheter complications are likely to be a problem.

2.4.6.4 Implantation site

Results from several studies have shown that the subfascial technique was statistically associated with fewer infections in comparison to implantation in subcutaneous tissue (173, 278, 307). It was explained by offering more coverage and protection to the pump. This may minimise the possibility of wound dehiscence and skin ulceration in very thin children (278).

Contrary to expectations, this study did not find a significant difference in infections between subfascial and subcutaneous techniques. This may be explained by small number of patients who had implantation at subcutaneous sites in comparison to the subfascial group.

Interestingly, a significant association between using subfascial technique and the decline in incidence of catheter migration in comparison to the subcutaneous technique was noted and could be related to catheter tunnelling. In the subcutaneous technique, the catheter runs in the subcutaneous layer of the skin surrounded by the fat until it connects with the pump nozzle. This slippery fatty tissue may increase migration risks. Whereas
in subfascial techniques the anterior half of the catheter’s tunnel passes between the muscles layers before it arrives in the subcutaneous tissues. This muscular surrounding of the catheter may restrict its movement and decreases the incidence of migration. In addition, nearly at the midaxillary line, where the catheter changes its plane from inter-muscular to subcutaneous tissue, the change in direction and depth may act as a natural anchor for the catheter, helping to prevent its migration. Additionally, the muscular coverage of the catheter connector could reduce the risk of catheter fracture complications (170), Figure 2-8.

The manufacturer produced a new type of two-piece catheter (The Ascenda® intrathecal catheter) (338), that has more resistance to mechanical stretch and kink, which is an improvement in a necessary part of the ITB device. It became available in last 5 years. Tiara et al. have recommend its use to minimise the complication rate of ITB therapy (304).

![Figure 2-8 Tunnelling path of the catheter from ITB pump site to intraspinal space](image-url)
Although, subfascial pump placement may be associated with a lower complication rate, the refilling of subfascially implanted pumps can be more difficult and may require fluoroscopy to locate the refilling port. Another risk of the subfascial technique is the possibility of pump migration to the peritoneal cavity as the continuous tone of the muscular abdominal wall might induce chronic pressure of the pump against the inner abdominal fascia resulting in progressive erosion (339).

2.4.6.5 Weight

In cerebral palsy patients, the weight-for-age and height-for-age often track below the 5th percentiles on growth charts for general populations, especially in patients without feeding tubes (340). These undernourished patients have a dearth of subcutaneous tissue, while ITB pumps are relatively bulky devices, leading to stretching and continuous compression of the skin against it. This impairs the blood supply, which could lead to skin necrosis and subsequent infection (309).

In our study, the multivariate analysis did not show a significant relationship between patients’ weight at time of implantation and infection events. This is possibly because the weight is a poorer indicator of malnutrition compared to for instance, the body mass index (BMI) (341, 342). However, it is not feasible to use the BMI in severely spastic quadriplegic children as their muscle contractures and spinal scoliosis make measurements of the body length inaccurate (343). Consequently, it is not consistently reliable enough to utilise the BMI in these particular patients.

Kong et al. suggested that using triceps skinfold thickness instead of weight-for-height percentile may be a more appropriate anthropometric measure of state in children with quadriplegic CP (344). Arm circumference (AC) is
another tool to measure the nutritional state however Samson-Fang et al. reported that AC is a poor screening tool in comparison to triceps skinfold thickness (342).

2.4.7 Complication rate throughout practice
Penn et al. reported that catheter complication rates and performance do not decline with the surgeon’s experience (145). This was not true in our study; as the frequency of complication has declined gradually over time throughout practice. This could be explained by multiple factors: the cumulative surgical experience that was gained from a long period of ITB practice; using the modified subfascial technique; and the use of the new SynchroMed II infusion pump device (20). The surgeon’s experience was found to significantly correlate to the survival of hardware implantation in neurosurgery practice (345-348).

In a multidisciplinary conference, the “ITB Therapy Best Practice Forum,” in March 2004, Minneapolis, Minnesota, USA a significant correlation between surgeons’ level of experience and treatment outcomes was presented. The recommendation is that neurosurgeons involved in ITB implantation are to perform 10 or more implantations per year to maintain satisfactory expertise in the procedure (171).

2.4.8 Mortality with ITB therapy
Although the adverse effects and complications are very common with the ITB therapy in children with cerebral palsy, death related to ITB therapy was not reported in the literature even in large series (173, 206, 278). The eight deaths recorded in our results were related to underlying disabilities and other comorbidities, which is in agreement with the findings of Motta el al. (278).
expectancy in children with cerebral palsy is curtailed by the presence and severity of mental retardation as well as associated physical impairments (349). Unfortunately, improvements in medical care have not clearly altered the poor prognosis for the most severely disabled children (349).

2.4.9 Practical considerations and management recommendations

2.4.9.1 Intrathecal baclofen withdrawal syndrome

Intrathecal baclofen withdrawal syndrome can be severe and sometimes life threatening, needing early and urgent management (210). It is crucial that all patients, caregivers, family members, and their family physician be educated and provided with leaflets outlining the signs of over- and under-dose, including the name and contact information of their provider in case of emergency. Patients should also have bracelets with drug dose, physician and manufacturer’s contact details (350).

Boster et al. consulted multidisciplinary groups of clinicians involved in ITB management to provide expert consensus on the best ITB practices. The panel recommends that the clinician should emphasise every at refill, regarding low reservoir alarm dates and the need to comply with pump refill schedules to avoid the potential for life-threatening withdrawal syndrome if the patient missed a refill date. Alarms should also be shown to the patients every refill to ensure that the alarms can be heard. In addition, the patients need to be familiar with the critical and noncritical alarm sounds (351).

The consensus also suggests to increase the low-reservoir alarm volume (e.g., from 2 mL to 3 mL) for patients who occasionally miss their refill appointments. So, their appointments should be few days earlier to avoid the risk of withdrawal due to low-reservoir volume (351).
Boster et al. also recommend having a structured, consistent on-call system for patients in every practice managing ITB therapy. The on-call system should include direct communication between the managing clinician, implanting surgeon, emergency department, and critical-care team. Patients should be encouraged to use the on-call system if they have any concern regarding the ITB (351). Emergency department should have a protocol to guide diagnosis and management of acute ITB withdrawal or overdose. An ITB pump programmer should be available and easily accessible to ED and critical care teams. They should be trained and familiar with its manual (205). Furthermore, ITB drug delivery teams should meet routinely to review emergency protocols, therapy outcomes, and optimization protocols (205, 350). The incidence of withdrawal syndrome in the literature is based on case reports and case series indicating the scarceness of cases encountered in ITB practice (350). The wide variety of reported complication rates is related to the lack of precise definition to ITB adverse events, therefore it is necessary to propose a consensus definition of ITB complications e.g. using the International Classification of Diseases (ICD) (352), and modifying its code according to each complication especially with acute complications such as withdrawal syndrome. This unique definition of withdrawal syndrome and its manifestation could help in planning a prospective study in multicentre or national audits, aiming to identify an accurate incidence of the syndrome.

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ICD is the international standard diagnostic tool for epidemiology, health management and clinical purposes which provides a system of diagnostic codes for classifying diseases to promote international comparability in the collection, classification, and presentation of statistics (352).
Intrathecal baclofen therapy is an advanced technology that has undergone several developments since its invention, as a result of unmet clinical needs. Physicians are an important source of medical device innovation as their knowledge and feedback about the medical devices can contribute to the shaping and development of new technology. Better communication between physicians and manufacturers of ITB pumps is recommended for improving the hardware and troubleshooting (353).

To reduce the risk of ITB complications and to prolong the survival of the ITB system, it is recommended that implantation should be limited to specialised centres where health-care staff are familiar with ITB systems and the operating surgeons are expert with ITB procedures and their complications.

2.4.9.2 Diagnosis of catheter complications

Catheter complications are usually identified when cessation of ITB effect occurs especially after steadiness of therapeutic level of ITB daily dose (210). However, the diagnosis sometimes can be difficult and be several months after onset of the complications (210). They can be due to gradual occlusion of the catheter lumen or intermittent kinking of the catheter (185). Prompt diagnosis and troubleshooting for possible ITB system complications would enhance the ITB effectiveness and decrease the expense of ITB therapy (354).

Bardutzky et al. proposed a diagnostic algorithm for defining the source of ITB errors: firstly, examine the pump programming and reservoir volume by interrogating the appropriate pump hardware and software; secondly, perform an abdominal radiographic X-ray including AP and lateral views to identify catheter displacement or disconnection; lastly, scintigraphy or injection of
intrathecal contrast material (such as Omnipaque) through the catheter access port to identify any leakage from the system (355).

Diagnosis of catheter complications, according to NUH practice, was dependent on clinical observation when the patient lost the therapeutic effects of ITB therapy and did not respond to increments of their daily dose. Our protocol for diagnosing catheter complications is supported by Dvorak’s opinion that although the plain radiography is the initial method to evaluate the suspected catheter malfunction, it is only able to detect 35.1% of all catheter malfunctions (356). Furthermore, scintigraphy has a high false-negative result and limited ability to detect catheter migrations and microscopic perforations or leaks (357).

Dvorak et al. suggested two potential developments in the ITB system that would contribute to troubleshooting: the ability to interrogate the ITB pump and obtain a precise measure of the reservoir volume which would circumvent the necessity of invasive access to the reservoir in order to check the volume of baclofen in the pump; the other is the ability to measure the pressure that ITB pump has to apply to drive the baclofen into the catheter. So, a reduction in the pressure that pump exerts to drive a given volume of baclofen would be suspicious of catheter disconnection or leakage. On the other hand, increasing the pressure would point to catheter kinking or occlusion (356).

2.4.9.3 Alternative techniques to lumbar insertion of ITB catheter

Iatrogenic failure of the catheter system after spinal surgery is a big challenge in ITB practice. Manufacturers of the ITB pump warn that shortwave diathermy can damage the ITB system and thus should be avoided within 30 cm of the pump or catheter. In this study, 7 children with previous lumbar ITB systems presented with loss of ITB effect due to iatrogenic transection of the ITB pump
catheter after corrective spinal surgery. As a result of these challenges, insertion of the intrathecal catheter via a posterior cervical approach was developed to be the standard technique in the following situations: for implantation in children who had spinal fusion surgery or metalwork that obstruct lumber spinal access; iatrogenic damage after corrective surgery for scoliosis; in cases with difficult access to the lumbar thecal sac; or if spinal instrumentation is under consideration. This technique was implemented uneventfully in 20 patients.

Recently the intraventricular approach was also suggested as a new alternative technique to overcome the difficulties with the insertion of ITB catheter in patients with spinal deformities, after multiple ITB catheter complications, or in patients with severe dystonia (336).

2.4.9.4 Recommendations to reduce the risk of infection

Wong et al. recommended some actions to reduce infection rate: the number of personnel attending during the ITB implantation procedure should be restricted to the absolutely essential staff; traffic through the operating theatre should be limited. It is also essential to inspect more carefully preoperative preparations and perioperative procedures. Double gloving is much recommended during implantation surgery (358). In addition, applying the no-touch technique to confirm that the operating surgeon is the only one to touch the pump.(359).

To decrease the risk of infection associated with gastrostomy tubes (PEG), Albright et al. recommended inserting the ITB pump on the opposite side to the PEG tube (171). Fjelstad, et al. highlighted the necessity to isolate the gastrostomy tube intra-operatively and to have vigilant care postoperatively (307).
In cases of infection events it is crucial to have continuous liaison between the ITB therapy team and the microbiologist to allow accurate diagnosis and treatment.

2.4.10 Limitation of the study
This is a retrospective study where the collected data were not designed initially for research purposes. However, the guidelines of collecting retrospective data were followed, to be minimise bias due to missing data (271, 360).

2.5 Conclusion
This study summarises the experience in a large cohort of ITB recipients at a regional tertiary referral hospital over a period of more than 13 years. Although the ITB therapy offers the option for long-term and modulated management of spasticity, it has a significant risk of complications and medical problems that could deprive the child benefiting ITB. The following conclusions can be drawn from the present study:

1. ITB therapy is associated with pharmacological and surgical (device related and SSI) adverse events.
2. Device related complications (pump and catheter malfunction) were the most prevalent. Other complications such as withdrawal syndrome was not documented which could be looked at carefully in a prospective study/audit to avoid under- or mis-diagnosis.
3. The rates of ITB complications in this cohort were similar to what had been reported in other paediatric populations treated with ITB therapy.
4. It has been proven that young age, presence of dystonia and gastrostomy tubes are significant risk factors for infection development.
While the incidence of catheter complication was significantly increased with the presence of dystonia and decreased by using subfascial technique.

5. The frequency of complications in this study showed a gradual decline with on-going practice due to cumulative surgical experience, adoption of new surgical technique and the use of new pump device.
3 Chapter Three: Use of Higher Concentration Compounded Intrathecal Baclofen
3.1 Introduction

Intrathecal baclofen (ITB) pumps require the reservoir to be refilled regularly to maintain drug infusion. The available reservoir capacities of the pumps are 10, 20 and 40ml. However, due to small size and lack of adequate soft tissue cover in children, the 20ml pump is usually the most suitable size. The frequency of refilling depends on reservoir size, concentration of baclofen in the pump and daily dosage (221, 361).

In turn, the daily dosage varies depending on diagnosis, function, and severity of symptoms (163, 167, 221). For instance, 50mcg/day is used in cases with moderate spasticity and up to 2000 mcg/day in dystonia patients (214, 362, 363).

Commercial ITB (Lioresal®) is available in two concentrations, 500 and 2000mcg/ml. These concentrations can necessitate frequent refills every 2-3 weeks, especially in patients with high daily requirements or in patients using the older 10ml pump. The frequent refills may increase the risk of infection (364, 365). Additionally, the distress of repeated punctures for access, long journeys in specially-equipped vehicles to access the refill service and the resultant incurred costs, add to the burden.

Dario et al. in a study to appraise the relationship between the patient and ITB pump, one fifth of patients have reported discomfort due to frequent pump refills although they were highly satisfied with ITB treatment (366). In a long-term follow-up study of 40 patient with ITB pump implantation, 12% of the patient have expressed dissatisfaction with the frequency of pump refills (177). The manufacturer of Lioresal® recommends renewing ITB at 6 months if not all used. Additionally, they assert that concentrations greater than 2000
mcg/ml do not meet stability requirements without the formation of precipitates. However, pharmacists create higher concentrations of baclofen at 3000-8000 mcg/ml to decrease the cost and frequency of refill (179, 367). Whilst the FDA guidelines generally tolerate a 10% deviation from labelled concentration in compounded products (368), there are no FDA studies evaluating ITB or the pharmacopoeia criteria regarding ITB quality.

Baclofen is a derivative of GABA with a molecular weight 213.661 g/mo (369). Baclofen contains an amino and a carboxylic group that are able to form zwitterion structure in neutral solutions (close to physiological pH value) (182). Stored baclofen in aqueous formulation forms the degradation product 4-(4-chlorophenyl)-2-pyrrolidone (4CPP) with molecular weight 195.65 g/mol (369). Temperature and moisture may provide a favourable enviroment for degradation as they contribute to intramolecular water loss yielding the degradation (370). Chemically, 4-Amino-3-(4-chlorophenyl)butanoic acid (213.6 g/mol) is transformed into: 4-(4-chlorophenyl)-2-pyrrolidinone (195.6 g/mol) and water (18g/mol), Figure 3-1.

![Figure 3-1 Degradation of Baclofen into 4CPP and water](image)

5 Zwitterion is a chemical compound that is electrically neutral through a net cancellation of formal positive and negative charges within the compound. Zwitterions are polar and usually have a higher solubility at acid and basic pH values where a net charge exists in the compound. However, at physiologic pH a net zero charge often reduces solubility(182).
Recently, Yue et al. have evaluated baclofen (3mg/ml) solubility, stability and its chemical and physical compatibility within programmable IT infusion pumps when subjected to multiple flow rates conditions. The study showed that 3mg/ml baclofen concentration was stable during long-term storage at 25°C and remained stable under conditions simulating those encountered in clinical practice i.e. 37°C (371).

At Nottingham University Hospital (NUH), variable concentrations of baclofen are used in pump refilling. Commercial baclofen 500 mg/ml concentration is used if the daily dosage rate is below 100mcg/24hrs; 2000 mcg/ml is used if the daily dosage rates surpass 100 mg/24hrs; and 3000 mcg/ml compounded baclofen concentration is the choice if 24 hours dosages exceed 300 mgs/24hrs. This product is manufactured by Boots Contract Manufacturing (BCM) to NUH practice based on individual prescription.

No more than 3000 mcg/ml compounded baclofen concentration were used in NUH. This is because baclofen in normal saline is stable at 3600 mcg/ml concentration at room temperature (25°C) and at 3900 mcg/ml concentration at body temperature (37°C); otherwise baclofen might be precipitated in the solution. This limits the potential of using higher concentration of injectable baclofen safely more than 3000 mcg/ml. This limitation is to avoid precipitation that could cause CNS complications and/or pump malfunctions (369).
3.1.1 Objective

In this study, high concentration compounded baclofen (3000 mcg/ml) is compared with commercial baclofen (2000mcg/ml) to assess the accuracy of concentration and the percentage of baclofen degradation product (4CPP). Additionally, the invisible particulates will be quantified and the risk of infectious contamination will be evaluated.

Specific study questions that will be addressed:

1. Do the compounded and commercial baclofen concentrations match the label?
2. Does baclofen concentration degrade after injection into the pump?
3. Does the rate of baclofen degradation correlate with the rate of baclofen fall?
4. Is the number of particles in the baclofen solution acceptable?
5. Is there any correlation between baclofen degradation product and particulate formation?
6. Is the compounded baclofen solution sterile?
7. Does the use of compounded baclofen cause baclofen pump failure e.g. pump failure or catheter obstruction?
3.2 **Material and methods**

3.2.1 **Study Design**

During the refill procedure, any residual ITB solution in the reservoir is removed before replenishing with fresh ITB (commercial 2000 mcg/ml or compounded 3000 mcg/ml). The retrieved sample is routinely sent for microbiological investigation.

In this study, fresh unused ITB (compounded and commercial) was analysed for the actual potency of concentration, degradation, precipitation of baclofen and number of particulates in the solution. A sample of the same batch of ITB retrieved during refill after staying in the pump chamber at normal body temperature for variable time intervals was also sent to the same analysis for direct comparison.

The methodology was discussed with the ethics committee, who decided that a prior approval from the committee was not required, as it was a quality control study based on a waste product i.e. the retrieved fluid from the pump reservoir at the time of its planned refill.

3.2.2 **Setting:**

The experimental work was conducted at Pharmaceutical Quality Control Laboratory, F Floor, West Block, and Queen Medical Centre Campus of Nottingham University Hospital by a professional senior chemistry technician (R.B.).

3.2.3 **Samples:**

Thirty eight retrieved samples were collected from patients while in clinic visits for routine ITB refills. On-shelf vial of baclofen batches that were used for refilling the patients’ pump had undergone the same tests and compared with
patients’ samples results. Each sample (approximately 2 ml) was placed in a capped syringe and stored at 37°C to resemble the normal body environments. Every 10 samples were analysed as one set. Forty five samples were analysed. These were 38 retrieved pump’s samples in addition to samples from their refilling vials batch (2 commercial batches and 5 compounded batches from BCM)

3.2.4 Main outcome Measures:
1. The concentration level of baclofen in different solutions
2. The concentration level of baclofen degradation product 4CPP
3. The particle number in the ITB solution (particle size ≥10 µm and ≥25 µm)
4. Sterility of baclofen solution.
3.2.5 Laboratory analysis

3.2.5.1 Concentration analysis of baclofen and its degradation

Concentrations of the baclofen and 4CPP were analysed using high-performance liquid chromatography (HPLC) method according to British Pharmacopeia protocol of assessing oral solution for baclofen preparation (372).

**Apparatus**

The HPLC used is the Agilent HP 1100 system consisting of G1310A isocratic pump with solvent cabinet, G1328A manual injector (MI), G1314A variable wavelength detector (VWD) with standard flow cell (10mm path length, 14µl volume, 40 bar maximum pressure) and G2220AA 2D-Value Solution ChemStation.

**Column**

The used column was NUCLEOSIL C18, 5µm (Macherey-Nagel).

**Chemical**

Ten grams of Sodium Dodecyl Sulfate (Fisher scientific) were dissolved in 1290 ml of water (Baxter), to which 10ml orthophosphoric acid was added (Fisher scientific). Volume was completed to 2L using acetonitrile HPLC grade (Fisher scientific).

Reference baclofen was purchased from British Pharmacopoeia Reference Standards (BPCRS).

The flow rate of the HPLC system was set to 1.50ml/min. For each sample, a volume of 50µL was loaded onto the column via an Autosampler from the sample tray. The column was re-equilibrated at initial conditions for 3 minutes
before the next analysis. Each sample was analysed twice. The data of samples was collected by an Agilent G1314A.

3.2.5.2 Counting particulate numbers in baclofen solutions

The sub-visible particles were examined according to British Pharmacopeia protocol using the light obscuration particle count test (373). Light obscuration (LO) is the compendial method of choice listed in British and European pharmacopeias (373, 374). It also referred to as Single Particle Optical Sensing (SPOS). The mechanism of light obscuration technology is based on passing a dilute stream of particles in a liquid suspension between a light source and a detector. The light source in this case is a laser diode, which illuminates the individual particles in the stream and results in a shadow or blockage on a light-sensitive detector. This light blockage is termed obscuration. The detector measures this reduction in light intensity and processes the signal to determine the size of the particle (375), Figure 3-2.

![Figure 3-2 Schematic diagram showing the mechanism of light obscuration technology used in calculation of particles’ size and number](image-url)
HIAC 9703 apparatus was used to allow automatic determination of the size and the number of particles. The apparatus was standardised by using suitable certified reference materials consisting of dispersions of spherical particles of known sizes between 10µm and 25µm\(^1\) (376). These standard particles are dispersed in particle-free water (373, 374), Figure 3-3.

![HIAC 9703 apparatus used in quality control unit to quantify the particles' size](image)

**Figure 3-3** HIAC 9703 apparatus used in quality control unit to quantify the particles' size

\(^1\) symbol: µm is referred to one micrometre also known as a micron. It is one millionth of a metre, "micro=10\(^{-6}\)" (376).
3.2.5.2.1 Steps of light obscuration technique:
1. The used glassware and filtration equipment were carefully washed, with avoidance of introduction of air bubbles into the preparation.
2. 1ml of the sample was mixed with 25ml of distilled water.
3. Gas bubbles were eliminated by standing the solution for 2 minutes.
4. Five portions of the solution, each of not less than 5 ml were aspirated by the apparatus.
5. The numbers of particles equal to or greater than 10µm and 25µm were counted.
6. The obtained result of the first solution portion was disregarded and the mean number of particles in the other four portions was calculated.
7. The preparation complies with the test if the average number of particles present in the units tested does not exceed 6000 per container equal or greater than 10µm and does not exceed 600 per container equal or greater than 25µm (the number of particles detected at 25 µm needs to be added to the number detected at 10 µm) (373).

3.2.5.3 The sterility of compounded baclofen solution
The retrieved samples were sent to the microbiology laboratory for detection of solution contamination. Gram stain and culture and sensitivity test were also performed.

3.2.6 Review of medical records
The medical records of these patients were retrospectively reviewed to determine the indication of ITB implantation, duration of ITB pump implantation, daily dose of ITB, duration of usage of compounded baclofen, refill interval and any reported complications (catheter malfunction, device error, overdose, withdrawal, or infection).
The method of extracting and verification of the clinical data from medical records was discussed in details in chapter two.

3.2.7 Statistical analysis
Statistical analyses were conducted using SPSS version 21 (SPSS Inc, Chicago, IL, USA).

1- Descriptive statistics were used to define the features of the laboratory results in the study.

2- Wilcoxon Signed Ranks test was used to compare between the mean concentrations of the baclofen vial and pump samples.

3- Simple linear regression analysis was performed to analyse associations between the difference of baclofen potency from refilling vial after a stay in the pump as dependent variable and interval refill duration as independent variable. A P value < 0.05 was considered significant.

\[
\text{Differences of baclofen potency} = \text{mean of vials concentration} - \text{mean of pump samples concentration}
\]

4- Multivariate linear regression analysis was also used to adjust the association between Baclofen degradation content (4CPP) as dependant variable, and interval refill duration and the difference in baclofen potency as independent variables. The significance level was also set at P < 0.05.

5- The correlation between baclofen degradation products and particle number in baclofen solution was tested by using Pearson correlation coefficient.
3.3 Results

Each sample was analysed twice by HPLC, and the mean value of these duplicates was used as the sample concentration value for subsequent comparison of accuracy.

3.3.1 Accuracy of sample concentrations

3.3.1.1 Compounded vial:
For samples of 5 different batches of unused compounded baclofen (off the shelf samples) with an expected concentration of 3000mcg/ml, the mean concentration was 2814.6mcg/ml (93.8% of the expected value) with a range of 2792-2840mcg/ml (SD± 17.24). On average, they missed the expected concentration by 6.2%. No samples were within 5% variance from the expected concentration.

3.3.1.2 Pump’s samples (refilled by compounded baclofen):
The mean concentration of 33 retrieved samples which were refilled by compounded baclofen (BCM) was 2785.22 mcg/mL (92.84 % of the expected value), SD± 46.58, within a range of (2711-2919 mcg/ml). The mean of retrieved samples missed the expected concentration by 7.15%. None of the samples missed 10 % variance from the labelled concentration.

The mean of decreased baclofen concentration was 29.52 mcg/ml (2814.6-2785.22 mcg/mL) (SD± 25.00, Range = 8-97). It is 0.96% reduction from the unused compounded baclofen vial (p< 0.001).

Linear regression analysis did not show any significant relation between baclofen concentration decrease and duration of baclofen stay inside the pump (p=0.76).
3.3.1.3 Commercial vials:
The mean concentration of two unused different batches of commercial baclofen was 1883.35 mcg/ml (SD ± 7.8, range 1873.4-1889.6 mcg/ml) which was 94.17% from the expected (nearly within 5% variance from the expected concentration).

3.3.1.4 Pump’s samples (refilled by Commercial baclofen):
The mean concentration of 5 retrieved baclofen samples was 1811.33 mcg/mL (SD ±17.1 range=1794-1839 mcg/ml). It was 90.6% of the expected value. The mean concentration of the commercial retrieved samples missed the expected concentration by 9.4%. None of the 5 samples missed >10% variance from the labelled concentration, Table 3-1.

Thus, an overall significant decrease of the retrieved baclofen concentrations [by 72.7mcg/ml (3.57%), Wilcoxon Signed Ranks Test p=0.043] compared with the unused original commercial vial after staying in ITB pump for different durations was observed. Importantly, this change in baclofen concentration was significantly correlated with the duration of baclofen stay inside the pump (p=0.009).
Table 3-1 Results of baclofen accuracy analysis of commercial and compounded products

<table>
<thead>
<tr>
<th></th>
<th>Commercial Baclofen (Vial)</th>
<th>Commercial baclofen (Pump)</th>
<th>Compounded baclofen (Vial)</th>
<th>Compounded baclofen (Pump)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expected concentration</strong></td>
<td>2000 µg/ml</td>
<td>2000 µg/ml</td>
<td>3000 µg/ml</td>
<td>3000 µg/ml</td>
</tr>
<tr>
<td><strong>Number of samples</strong></td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td><strong>Mean baclofen concentration µg/ml</strong></td>
<td>1883.35 µg/ml</td>
<td>1811.33 µg/ml</td>
<td>2814.72 µg/ml</td>
<td>2785.2 µg/ml</td>
</tr>
<tr>
<td><strong>Difference of mean from expected value</strong></td>
<td>116.67 (5.8%)</td>
<td>188.65 (9.4%)</td>
<td>185.3 (6.2%)</td>
<td>214.78(7.15%)</td>
</tr>
<tr>
<td><strong>Range of existing concentration µg/ml</strong></td>
<td>(1873.4-1889.6)</td>
<td>(1794.0-1839) µg/ml</td>
<td>(2792-2839) µg/ml</td>
<td>(2710-2919) µg/ml</td>
</tr>
</tbody>
</table>

3.3.2 Concentration of 4-(4-chlorophenyl)-2-pyrolidinone (4CPP)

The mean concentration of 4CPP in compounded baclofen vials was 25.6mcg/ml (0.91%) which increased to 41.33mcg/ml (1.48%) in retrieved samples.

The mean concentration of 4CPP in the commercial baclofen vials was 13.9mcg/m (0.69%) which was increased in retrieved sample by more than 4 folds to 56mcg/ml (3.09%). 4-CPP percentage changes are shown in Figure 3-4.

On multivariate liner regression analysis, there was no significant increase of 4CPP in proportion to baclofen falls of 3000 mcg/ml concentration ($p = 0.099$).
Unsurprisingly, 4CPP was significantly correlated with the longer stay of ITB in the pump ($p < 0.001$).

In regard to the commercial product, the multivariate analysis revealed that the increase of 4CPP concentration was significantly correlated to both baclofen concentration fall ($p = 0.012$) and increased duration of ITB inside the pump ($p = 0.044$).

![Figure 3-4](image)

**Figure 3-4** The percentage of baclofen degradation product to baclofen concentration
3.3.3 Subvisible particulates numbers

The results of subvisible particulates analysis showed that the particle number in compounded baclofen was five times more than the particle number in commercial baclofen. There were little changes in particle number of both products after staying in pumps for variable durations, Table 3-2 and Figure 3-5.

There was no significant correlation between baclofen degradation product (4CPP) level and the particle number in the solution after staying inside the pump (p=0.123, 0.230) for particles equal to or greater than 25 µm and 10 µm respectively).

**Table 3-2** Particle concentrations in both compounded baclofen and commercial baclofen solutions

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Mean (range) of Particle ≥ 10µm [Counts/mL]</th>
<th>Mean (range) of Particle ≥ 25 µm [Counts/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial unused vial (n=2)</td>
<td>43 (13-70)/ml</td>
<td>5 (0-10)/ml</td>
</tr>
<tr>
<td>Commercial retrieved samples (n=5)</td>
<td>41(12-82)/ml</td>
<td>4 (3-13)/ml</td>
</tr>
<tr>
<td>Compounded unused vial (n=5)</td>
<td>216 (20-243)/ml</td>
<td>14 (10-61)/ml</td>
</tr>
<tr>
<td>Compounded retrieved samples (n=33)</td>
<td>245 (28-927)/ml</td>
<td>15 (0-58)/ml</td>
</tr>
</tbody>
</table>
Figure 3-5 The difference in particle number between both products.
3.3.4 Clinical data review

In reviewing the medical records for this group of patients, spasticity was the most frequent indication for implanting the ITB pump, Table 3-3.

The mean implantation duration was 68.9 months in the compounded baclofen group in comparison to 34 months in the commercial group. The mean refill interval was 83.4 and 179 days in compounded and commercial groups, respectively. No complications were reported in both groups.

The mean of daily dose in the compounded baclofen group was 512.7 mg/ml in comparison to 172mcg/ml for commercial group.

<table>
<thead>
<tr>
<th>Table 3-3 Indications, refill interval, and daily dose of ITB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication of ITB implant</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Spasticity</td>
</tr>
<tr>
<td>Longevity of ITB implant (months)</td>
</tr>
<tr>
<td>Refill interval (days)</td>
</tr>
<tr>
<td>Daily ITB dose at time of sampling µg/ml</td>
</tr>
<tr>
<td>Complications</td>
</tr>
</tbody>
</table>
In review of previous refill data for spasticity and dystonia patients, random cases were selected to demonstrate the pattern of daily dose infusion and its relation to used concentration. It was found that the daily dose requirement was progressively increased in all patients until the therapeutic dose and titration level was achieved, Figure 3-6. As expected, the daily dose required in patients with spasticity alone was lower than those with dystonia, Figure 3-7 and Figure 3-8 respectively.

![Example of ITB daily dose escalation till titration](image)

**Figure 3-6** Examples of ITB daily dose escalation in patients
**Figure 3-7** Example of a pattern of daily doses of Baclofen in a patient with spasticity.

**Figure 3-8** Example of a pattern of daily doses of Baclofen in a patient with dystonia.
3.4 Discussion

In this study, the main indications for implantation of the ITB pump were spasticity and dystonia secondary to cerebral palsy. The pattern of daily dose escalation of ITB showed a higher daily requirement of ITB to clinically control dystonia which go in line with findings of related studies (227, 231, 266, 377). Accordingly, there is a clinical need for higher concentration aqueous solutions of baclofen with acceptable pharmaceutical properties, including stability in a variety of storage conditions and for extended periods of time. Ideal baclofen solutions must be accurate in their concentration, with no significant amounts of particulates and must stay in solution without precipitation before and after administration (179). Baclofen must also be sterile to prevent serious infectious complications (378-380). Unfortunately, baclofen has poor solubility in water and easily precipitates out of solution. Only baclofen solutions with concentrations of 2000mcg/ml which has been validated to remain stable for extended periods of time (up to six months) (182). Previous studies stated that, compounded higher ITB concentrations to an upper limit of 4300 mcg/ml have been manufactured. However, the method of drug preparation in this study may not be commercially reproducible (381, 382).

Whilst the FDA guidelines generally tolerate a 10% deviation from labelled concentration in compounded products (368), there are no FDA studies evaluating ITB. In addition, there are no specific criteria for the quality of intrathecal or injectable baclofen established by the United States Pharmacopeia (USP), European Pharmacopoeia or British Pharmacopoeia (BPC). Only the Handbook of Injectable Drugs lists baclofen for intrathecal
use and includes pH, available concentrations, and sodium content in the product description, but it does not refer to the acceptable accuracy range of concentration (383).

BPC has established standard criteria for baclofen oral solution with the following requirements: The content of baclofen should be between 95.0 to 105.0% of the stated amount, with baclofen degradation not exceeding 2% of obtained solution (372).

Several studies have investigated the stability of ITB. Alvarez et al. has tested the stability of commercial products of Baclofen-Clonidine admixture. The study has shown good stability of the admixture and compatibility with ITB pump at body temperature (384). Shields et al. compared stability of admixtures combining ziconotide with commercially formulated or compounded baclofen during simulated intrathecal infusion under laboratory conditions at 37°C. Ziconotide-baclofen admixtures were more stable with compounded baclofen rather than the commercial baclofen formulation (385).

Medtronic PLC, in cooperation with Novartis (the commercial baclofen manufacturer) published a “white paper,” describing their investigations of using higher concentrations other than those used for the commercially available baclofen. Solubility and physical stability of 3 and 4 mg/ml aqueous baclofen solutions were evaluated. The study demonstrated that precipitation occurred in a concentrations more than 2 mg/ml (182), but this study has not been successfully replicated independently.

Moberg-Wolff et al. evaluated compounded ITB obtained from several pharmacies in comparison to commercial baclofen. Twenty seven samples of compounded ITB from 6 different compounding pharmacies with labelled concentrations of 2000, 3000, 4000, 5000, and 6000 mcg/ml were compared
with 2 different batches of Lioresal ITB 2000 mcg/ml. The sample passed the accuracy test if the assay was within 5% from the expected concentration. The Lioresal® samples were reported to have no concentration deviation, whereas 11 of 27 compounded baclofen samples (41%) were not within 5% variation of the aimed concentration and 22% of samples were not within 10%. Samples from compounding pharmacies have greater variation in concentration from –35% to 12% than labelled value (179). However, this study was limited because of insufficient number of samples from each compounding pharmacy, un-reporting the concentration values of assayed samples and lack of statistical calculations.

Farid and co-workers analysed ITB from a national compounding pharmacy in the United States (AnazaoHealth) and compared it with commercial baclofen (Lioresal®) in regard to the accuracy of baclofen concentration and the content of the baclofen degradation product. The study showed that analysis of nine samples of Lioresal® was within 5% of the expected concentration. Out of 27 samples from compounding pharmacy (AnazaoHealth), 22 were more than 5% while 8 were more than 10% different from the labelled concentration. Importantly, no baclofen degradation product (4CPP) was detected in any of the compounded samples tested. All samples of Lioresal® contained 4CPP less than 1% of the baclofen concentration. The study concluded that Lioresal was more precise in concentration than compounded ITB (AnazaoHealth) (386). It is noteworthy that Farid et al. study presented the details of ITB assay of samples including statistical analysis of variation between samples (386). However, the study analysed only the ITB vials as production quality control and it did not appraise baclofen stability after administration into the pump.
In a 2010 patent, “High concentration baclofen preparations” the authors state that they prepared baclofen solutions at concentrations of 4000, 5000 and 6000mcg/ml which remained clear and free of particulates for 12 months when stored at room temperature and additionally stable for 60 days at 37° C (387). However, these samples were not analysed following administration into drug delivery systems (388).

3.4.1 Precision of compounded baclofen concentration versus commercial product

Our study demonstrates that the precision of off-shelf vial of commercial baclofen concentration is more accurate than the compounded baclofen vial that was supplied from the compounding pharmacy (BCM) in keeping with findings from similar studies (179). However, analysis from retrieved samples after administration into the pump showed that there was a statistically significant change in the accuracy of concentrations in commercial ITB compared to a minimal change of the compounded ITB concentrations. The findings of the current study are consistent with those of Yue and co-investigators who assessed physical and chemical stability of baclofen 3 mg/mL in prefilled syringes over 36 months (at 3, 6, 9, 12, 18, 24, and 36 months) with storage at 25° C where the compounded baclofen content remained unchanged and no precipitation was observed (371).

In addition, the stability of ITB 3000 mcg/ml was evaluated in simulated clinical study. Intrathecal 3mg/ml formulation was placed in SynchroMed II and Codman Medstream pumps at 37° C for study durations of 218 days, and evaluated at different flow rates (110 µl/day - 400 µl/day). The exposed pumps to baclofen 3mg/ml were then dissected and evaluated for signs of deterioration. The results showed that ITB 3mg/ml formulation was stable at
different flow rates and throughout different expected residence times for both pump models. Moreover, the components from both pumps did not reveal any noticeable deterioration after exposure to the 3 mg/ml formulation (371). Our findings bear important implications for the stability of the compounded baclofen rather than the commercial ITB after administration in the pump under normal body temperature for extended duration. However, with a small sample of the commercial ITB and its longer stay inside the pump (mean of refill duration was 179 day compared to 83.39 days for compounded samples), caution must be applied, as the findings might not be transferable to clinical practice.

3.4.2 Baclofen degradation content 4-((4-chlorophenyl)-2-pyrolidone (4CPP)

During long-term storage and upon heating, baclofen forms a poorly soluble degradation product with lactamic structure 4CPP. This degradation reduces the potency of baclofen in solution (182, 389). It is not known if 4CPP can cause the same side effects as baclofen. However The Analytical Profiles of Drug Substances suggests that 4CPP is less toxic than baclofen, given that oral toxicological testing in male rats showed the LD50 of baclofen was 228 mg/kg and 841 mg/kg for 4CPP (382). The British Pharmacopeia recommends that 4CPP should not exceed >2% of the concentration in oral baclofen solution but no exact values for ITB solution have been recommended (373). The current study showed a four times increase of baclofen degradation product in commercial ITB after being in the pump in comparison to slight

\[^u\] An LD50 is an abbreviation for "Lethal Dose, 50%" or median lethal dose. It is the amount of the substance required (usually per body weight) to kill 50% of the test population i.e. the lower the LD50 dose, the more toxic the pesticide (382).
increase in compounded product. As expected the degradation in both products was affected by long-term stay in the ITB pump. However, the degradation was not related to drop of baclofen 3000 mcg/ml concentration which was not the case in commercial baclofen 2000 mcg/ml concentration.

Yue et al. have evaluated the degradation of baclofen at 3000 mcg/ml concentration and reported that the percentage of 4CPP degradation product has steadily increased over 36 months of the study. Degradation levels started at 0.128%, then increased to 0.14% after 12 months, 0.154% after 24 months and increased to 0.17% at 36 months (371).

Our findings are in agreement with Farid et al’s study that showed more degradation in commercial ITB as compared with compounded ITB solution (386). This was attributed to the method of sterilisation of the ITB solution. Commercial ITB was sterilised using thermal methods thus being exposed to higher temperaturesvi (389) compared with compounded ITB whose sterilisation was achieved using filtration (386).

These findings suggest less stability of the commercial ITB in comparison to compounded 3000mcg/ml after stay inside the pump. However, this could be explained by the longer stay of commercial baclofen inside the pump in our study group. However, the relatively small number of samples in our study could be an additional reason.

3.4.3 Invisible particulates
Baclofen is known for poor solubility in water. Dissolved baclofen, especially at higher concentrations, is inclined to precipitate into particles in the solution

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vi Common sterilization protocol is using a heating regimen at 121.1° C. for 30 minutes. It was hypothesized that shorter heating times may lead to a solution with fewer degradation products, as the baclofen would have less time under the stress of heating to degrade (389).
over time leading to a reduced concentration of baclofen in addition to the undesirable particulate matter. It is not known if these particulates inside the pump can block the filter between the pump reservoir and catheter which potentially carries the risk of reducing or completely blocking the infusion of ITB.

The current study is the first attempt to assess the particles’ numbers and revealed significantly low particulate levels in commercial baclofen with little changes after being inside the pump. The compounded solution had higher particulate number; nearly 5 times more than the commercial solution though it was still compliant with USP and BPC requirements (373).

3.4.4 Correlation between baclofen degradation product and particulate formation

The number of particles observed in ITB solution was not correlated with the assay value of baclofen degradation product. This finding is consistent with the study of Sigg et al. which examined the nature of the particulates by filtration of the solutions. The infiltered-out particulates were re-dissolved and analysed by HPLC. Interestingly, the results confirmed that the precipitate was baclofen and the particulate formation was not related to the amount of degradation product present in the formulation (182).

3.4.5 Relationship between compounded baclofen and device related ITB complications

In the current study, review of patients’ medical records did not demonstrate that using the higher ITB concentration was associated with catheter or ITB pump malfunction, or increasing demand of daily ITB dose. In addition, no withdrawal syndrome was documented as a result of cessation of baclofen infusion. However, we did not review all patients whose pumps were refilled.
by compounded baclofen as many children received their refill service in peripheral hospitals. They might have experienced ITB pump complications that were not presented to NUH.

3.4.6 The sterility of ITB solutions
The potential threat of patient harm related to compounded sterile preparations such as ITB could also be due to possible inconsistency in sterility assurance. This risk is well recognised and has resulted in several reported outbreaks with other compounded products (378, 380, 390). Recently, a multicentre outbreak of fungal meningitis among patients, who received a compounded steroid injection into the spinal region, resulted in 64 deaths and 750 illnesses (391).

CNS infection reported after pump implantation has raised the concerns with potential contamination of the compounded formulation and noncompliance with sterile precautions during intrathecal pump refilling (365, 392, 393). In this study, all samples either commercial or compounded, underwent microbiological analysis and were confirmed to be sterile after administration into the ITB pump which indicates strict implementation of sterile precautions during pump refills.

3.4.7 Administration modes and dose tailoring
Infusion mode of ITB can be either continuous or be programmed for variable dosing. The latter allows for dose variations throughout the 24-hour period which could help in reducing the daily need ITB (167, 394). Contrasting this, simple continuous mode provides consistent delivery of drug over the time. There is some suggestion in the literature that the majority of patients are well managed with this mode of delivery (351, 395). However, the therapeutic
outcomes of ITB could be optimised by tailoring the daily dosing according to an individual child’s daily routine and needs (351). Heetla et al. indicated that intermittent boluses may result in an overall better clinical response compared to simple continuous mode of ITB delivery, and even permitting a reduction in total daily dose (394).

3.4.7.1 Flex dosing

If the patient has a predictable spasticity pattern, flex dosing would be recommended to optimise the therapeutic outcome. The flex mode adjusts the ITB dosing based on the variable spasticity pattern and daily schedule of the patient to maintain functional spasticity control (396, 397). These patients usually need moderate degree of spasticity during the day to help their transfers and mobility. However, this spasticity could interfere with evening or night sleep. Thus, an increase in dose before bedtime would be convenient to give overnight relief of spasticity and to reduce morning stiffness. Usually, the increase in dose would not exceed 10% to 15% of the baseline dose (351), Figure 3-9.

![Day/Night Flex dosing](image)

**Figure 3-9** an example of flex dose in 24 hours

3.4.7.2 Periodic Bolus Dosing

In a few cases, the response to the ITB therapy is limited despite dose
escalation to reach four to six times the screening test dose. In these cases, the patient has not yet experienced an effect similar to that of the screening test. A few studies have recommended a periodic bolus dosing mode to increase clinical response (180, 351, 396, 398). The periodic bolus mode maintains the total daily dose but the basal rate is lowered while part of the total dose (15% to 20%) is infused via periodic boluses. Boster et al. stated that the consensus of expert clinicians with ITB practice recommended to divide the periodic bolus into four separate doses to be given in equal doses every 6 hours as the elimination half-life of the ITB ranges from 0.9-5.0 hours (161), Figure 3-10.

Historically, one of the reasons for trying periodic bolus dosing was the feedback from individuals who had an improvement in their muscle tone after ITB pump implantation, but they did not feel as good as when they had received their trial bolus dose (396).

![Periodic Bolus Dosing](image)

**Figure 3-10** An example of periodic bolus dosing in 24 hour

The effectiveness of periodic bolus infusion to control the need for increasing ITB dosages could stem from better distribution of baclofen in the cerebrospinal fluid as ITB flow might be increased by adding intermittent...
boluses to simple continuous dosing (399). In addition, the pulsatile ITB bolus infusion could cause an increase in the fluctuations of ITB concentrations over time around the catheter tip. These fluctuations may induce receptor resensitisation, which could explain the reduction of the overall daily dose of ITB (178, 394).

3.4.8 Further work
Trissel et al. in a patent (2013) have reported their attempts to prepare aqueous baclofen solutions at higher concentrations up to 6000 mcg/ml by direct dissolution in 0.9% sodium chloride injection. They increased the solubility of baclofen in the solution by using either high temperature or changing the pH (by acidification or alkalisation) and back titration of the solution after producing the compound. They have claimed that a solution of baclofen at concentrations ranging from 3000mcg/ml up to 4000 mcg/ml is stable for at least 60 days at 37°C (387).

Current solution of IT baclofen utilises preservative-free normal saline as an excipient (182). However, the normal saline pH (roughly 5.5) (400) differs from that of the CSF (7.33) (401). Moreover, osmolality, concentration of inorganic salts, and the absence of glucose, protein, cholesterol, and other lipids, are other differences between saline and CSF (402, 403). This might cause potential adverse effect to the neural tissues and the subarachnoid space.(403-405). Recently, Meythaler and co-workers have attempted to develop a stable high concentration of ITB in a solution similar to the CSF. The artificial CSF solution is similar to CSF but without protein or bicarbonate, as the presence of bicarbonate (HCO3) in the artificial CSF might cause shifts in the pH of the solution as it converts to CO2. Furthermore; CO2 bubbles can
develop inside the pump can affect pumping rate unpredictably (369). Meythaler et al. were able to manufacture IT baclofen 4 mg/ml formulation that remained stable after 18 months in the artificial CSF solution (369). In addition, they claim that the artificial CSF may also be less toxic to the CNS tissue (369), in comparison to normal saline that could cause possible harmful effects on CNS cells (403-405).

In another study, the role of microspheres coated in baclofen, administered as a gel, was examined as an alternative vector of baclofen delivery. This new method may enable delivery of higher baclofen concentrations than the currently available products (183, 406).

3.4.9 Study Limitations

This is a quality control study of the refill practice in Nottingham University Hospitals. It assessed only one source of compounded baclofen that has been used for more than 10 years. We did not assess other sources of compounded IT baclofen at higher concentrations.

Thus, the results of this study are neither applicable to the quality of ITB from other compounding suppliers, nor establish the general standards for both commercial and compounded products.

The number of the commercial ITB samples is relatively small in comparison to the compounded group. In addition, other pharmaceutical features such as pH, ionic strength, osmolality, specific gravity and density of the solution were not examined.

This study is liable to selection bias as we did not retrieve and examine all samples from ITB pumps that were refilled by compounded ITB 3000mcg/ml concentration.
3.5 CONCLUSIONS

We report a quality control study on the 3000 mcg/ml concentration of ITB used at NUH for treatment of severe spasticity in children.

1. The study showed that commercial ITB concentration is more accurately matching the label in comparison to compounded baclofen. However, the compounded baclofen concentration is still in a satisfactory range.

2. We found that baclofen concentration can change inside the ITB pump especially after a long duration.

3. Commercial baclofen is more liable to degradation compared to the compounded one.

4. The number of particles in compounded solution is higher than the commercial product. However, it is still in an acceptable range.

5. There was no significant correlation between baclofen degradation, and particulate formation.

6. Both commercial and compounded products are safe regarding sterility for intrathecal injection.

7. Although we did not find any clinical or device complications related to compounded baclofen, it could have a potential risk of pump failure or catheter obstruction due to its greater number of particulates in comparison to the commercial baclofen.
4 CHAPTER FOUR: LONG TERM EFFECT OF INTRATHecal BACLOFEN ON FUNCTIONAL STATUS AND QUALITY OF LIFE
4.1 Introduction

4.1.1 Health and Quality of Life Outcomes

Health outcome was defined by Donabedian (1985) as “a change in patients' current and future health status that can be attributed to precedent health care” (407, 408). Traditional outcome measures include: symptoms and pain relief, adverse reactions, survival data, morbidity and mortality ratios, and other indicators such as laboratory and diagnostic tests’ results. These outcome measures are conventionally the main endpoints in clinical trials and they gained themselves a reputation of being objective or ‘hard data’ (409). On the other hand, clinical trials do not usually include patients’ self-reported health status as it is considered subjective or ‘soft data’ (410). However, measuring the patients’ perception of their well-being may be the most important health outcome measure especially in those diseases where there is no known cure, yet the experience of having the disease can be dramatic. Neurological diseases fall into this category. For instance, for patients with CP, the negative emotional feeling could be prevented or reduced if health related quality of life issues are considered in their management plans (411).

Over the last 20 years, there has been a rapid increase in the development and use of quality of life (QOL) evaluations in an effort to enhance patients’ health and determine the value of healthcare services (412, 413). Consequently, inclusion of QOL measurements in clinical trials has become a priority. Different clinical trial groups such as the U.K. Medical Research Council (MRC), National Cancer Institute of Canada (NCIC), and the European Organization for Research and Treatment of Cancer (EORTC),
suggested that QOL should be considered as an endpoint in all new trials (414).

In 1994, in order to organise quality of life research, the World Health Organization (WHO) proposed the following definition: “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (415). The QOL concept is shaped by five domains involving all aspects of the human condition: 1) physical status and functional abilities; 2) psychological status and well-being; 3) social interactions; 4) economic and/or vocational status and; 5) spiritual status (416).

Health related quality of life (HRQOL) is considered to be a sub-domain of the overall concept of QOL (417, 418). HRQOL has been defined as “the functional effect of an illness and its consequent therapy on a patient, as perceived by that patient” (416).

4.1.2 Relationship between quality of life and functional assessments in children with cerebral palsy

The concept of intervention outcomes was changed after the publication of a new model for specifying function and disability by the World Health Organization (WHO), known as the International Classification of Functioning, Disability and Health™ (ICF) (419). So physicians became more interested in functional outcomes than improving the motor milestones such as range of

According to the ICF, a person’s functioning is a result of dynamic interactions of three dimensions with the environment. The three dimensions are (1) impairments of body structures or body functions; (2) activity limitations such as difficulties in performing a specific task or lacking the skills required for everyday living; and (3) participation restrictions with respect to social roles. Furthermore, the ICF addresses the effect of personal and environmental contextual factors on the three dimensions. Current literature on disability research highlights the importance of addressing performance enhancement in all three dimensions of the ICF (i.e., function, activity, and participation) (419).
motion (ROM), decrease in muscle tone, or optimising other physiological measures (420). In recent studies, children’s feeling about their capability to achieve daily activities has been considered in the assessment of functional disability. Measuring how people feel about aspects of their lives directly related to health is known as health-related quality of life (HRQOL) (421). The difference between functional and HRQOL measurements can be examined by the example of children who have the same functional disabilities, who do not have the same experience of QOL. The patient’s self-assessment and perception of their personal HRQOL may be considerably different from the judgment of healthcare staff. Therefore, it is important to measure HRQOL from the patients’ perspective (412, 413, 422).

Generally, the measurement of HRQOL aims to give a more detailed picture about the patient’s status that is complementary to the conventional effort of the physician to describe specific functional assessments (421).

4.1.3 Reasons for measuring QOL in children with CP

“Measurement is the first step that leads to control and eventually to improvement. If you can’t measure something, you can’t understand it. If you can’t understand it, you can’t control it. If you can’t control it, you can’t improve it.”  

H James Harrington (423, 424).

Currently, there are a number of rationales to include HRQOL in clinical research and practice. Firstly, children with advanced CP usually undergo different health interventions to enhance their quality of life and to facilitate their caregiving. These interventions are resource-intensive. So, it is necessary to evaluate these interventions using outcome measures that are more purposeful to the children and their caregivers (425). Secondly, HRQOL
can correspondingly be used to establishing clinical guidelines, and in economic evaluations alongside clinical trials to assess the cost-effectiveness of new health technologies (426). Lastly, studying HRQOL in long-term survivors of children with CP can detect unnoticed long-term ongoing problems even after intervention especially late problems of psychosocial adaptation (427). In addition it can be utilized as an early predictor of survival in these patients (428-432) and a guide to appropriate alteration in management according to the patient’s status (433-436).

4.1.4 Challenges in Measuring HRQOL in Children with Disabilities

Measuring HRQOL in children with severe developmental disabilities is challenging due to their inability to communicate. This leads to relying on parents or caregivers to report their perception of their child’s quality of life (437).

4.1.5 Quality of life measuring instruments

Quality of life measuring instruments are either generic or condition-specific scales. Generic scales are designed to be applicable in general populations or through populations of people with varied conditions (438). They are not convenient to assess the effectiveness of intervention for a specific disability as they do not comprise domains that are specific to the condition. Hence, if a child with CP completed a generic HRQOL instrument, the scores might not completely capture the real quality of life because some important domains that have an influence on his or her life (such as pain, discomfort, and communication) would not be evaluated (439). For instance, the Child Health Questionnaire (CHQ) is a widely used generic instrument which has been
utilised to assess HRQOL in CP (440). However, the physical function items within the CHQ were not pertinent to children with severe CP (421).

On the other hand, condition-specific instruments are designed to be applicable to one specific disease, and they are tailored to detect subtle features of this disease. They also evaluate small changes following any intervention and determine factors associated with it (441). Caregiver Questionnaire (CQ) is a disease-specific instrument that was designed by the Rehabilitation Institute of Chicago (USA), for evaluation of quadriplegic CP children who had undergone selective dorsal rhizotomy. Neither the reliability nor the validity of the CQ has been formally examined. In addition, it does not include several items related to the quality of life of severely disabled children, such as health, emotional and behavioural aspects (442, 443).

Recently, four disease specific instruments have been designed to measure the QOL of children with CP. These include: the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD™) (443), the Paediatric Quality of Life Inventory (PedsQL) CP Module (444), the DISABKIDS CP Module (445), and the Cerebral Palsy Quality of Life Questionnaire-(CP QOL) (446). In a systematic review, Carlon et al. appraised the psychometric properties and clinical effectiveness of these new instruments. From points of reliability and validity, the ease of access, the free availability, and the time of completion, the CP QOL-Child and the CPCHILD™ were found to be the most appropriate measures to evaluate the QOL in CP children (447). Nevertheless, the validity and reliability were superior in CPCHILD™ than in CP QOL instrument (447).

The WeeFIM® Instrument and Paediatric Evaluation of Disability Inventory (PEDI) are well known and are the most commonly recommended in
published literature for standardised assessment of functional disabilities in CP children (448-450).

The PEDI was created to evaluate rehabilitation of children with disabilities between the ages of 6 months to 7.5 years. Three aspects are combined into the PEDI; functional skill level, amount of caregiver assistance and adaptive equipment used. A total of 237 items are administered by a trained individual that requires 45-60 minutes for completion (444). While the PEDI has been validated in the CP population (451), the large number of items included makes this a cumbersome instrument. Moreover, the PEDI is only valid in young children (younger than 7.5 years), and it also needs specialist training for administration (452).

WeeFIM® is an evaluative measure of rehabilitation outcomes in children with severe disability. WeeFIM® was validated for use in CP children from the age of 0 to 18 years. Although WeeFIM® is a brief and easy instrument to administer (453), it requires specialised training and accreditation, in addition to the costs associated with using a copyrighted instrument (452).

4.1.6 Measuring approaches to changes in HRQOL

HRQOL responsiveness or change following intervention can be evaluated either by direct or indirect approaches. In the direct approach; the clinicians solicit the patient’s judgment of the change directly, whether the symptoms improved, remained the same, or deteriorated (454, 455).

In clinical research, the ‘indirect’ measures of change are favoured. This is because the researchers measure the patient’s status at different time points as for instance, before intervention and after intervention (pre-test to post-test measurement), then compute the change between the two tests (456, 457).
While this method is a common approach in QOL research, the ‘test then-test’ or Quasi-experimental study (458, 459) has been designed as another indirect approach in an effort to reduce the response-shift phenomenon which sometimes happens with ordinary indirect approach (460). In the ‘then-test’ method, the patients are requested at one time point to rate their contemporary condition and also retrospectively rate their former status (455). Recall bias is a theoretical concern regarding the then-test approach. However in multi-item scales, the agreement between pre status and retrospective pre status (“then-test”) was remarkably high. Thus, recall bias did not appear to play a major role in this regard (455).

4.1.7 Quality of life in patients with intrathecal baclofen therapy
Since the introduction of ITB therapy as an effective treatment for spasticity, HRQOL has been examined as a clinical outcome of ITB intervention (460, 461).

Borowski et al. directly asked the patients or their caregiver about their satisfaction after receiving the ITB therapy. More than 85% of caregivers were satisfied and willing to recommend it to other patients (462). However, this evaluation was simple and subjective (462). In their study, Tassel et al. retrospectively assessed the effect of ITB therapy on HRQOL and showed that wheelchair comfort and nursing care improved after ITB therapy. Although this study covered several items of the activities of daily living, it used a subjective non-validated questionnaire (463). Vles et al., have prospectively evaluated HRQOL in 17 patients after implanting ITB pump, using CHQ and

\[\text{Response shift: is a subjective change of patients' perceptions due to recalibration of their internal standard and values as a result of intervention (460).}\]
Visual Analogue Scale (VAS), to assess parent satisfaction with ITB therapy. This study presented positive effects on pain, ease of care, emotional and the physical activities. Although this study was a prospective designed research, the sample was small and it did not correlate the results with other factors that might affect the outcome (440).

4.1.8 Aim of the work

This study aims to answer these questions:

1. Does the HRQOL and functional status outcomes of CP children improve after ITB pump implantation?
2. Which health related quality of life domain has good outcomes?
3. Are the HRQOL changes related to functional improvement?
4. What is the extent of responsiveness of functional status and HRQOL to ITB therapy?
5. What are the determining factors that influence ITB outcomes?
4.2 Materials and Methods

4.2.1 Patient Population
Seventy five patients who received ITB therapy in Nottingham University Hospitals between January 2008 and January 2011 were recruited to evaluate the effect of ITB therapy on their HRQOL and functional status. The children were interviewed after at least one year of ITB implantation assuming that the child had achieved the therapeutic effect after titration of ITB daily dose.

4.2.2 Study design
This is a quasi-experimental study (test then-test approach) to evaluate the HRQOL and functional status outcomes of ITB therapy. The expected outcomes were the change in the total scores of each instrument. The study was conducted as an audit for service evaluation of routine practice in Nottingham University Hospitals (registered audit number 14-338C).

4.2.3 Data collection setting
The data were gathered via direct interview with patients or their caregivers after signing written consent. The interviews were conducted in the outpatient clinic during their routine visits for ITB pump refills.

The demographic and comorbidity variables of this group of patients were collected retrospectively from their medical records. The method of data extraction and verification (including how the cases were ascertained, how the notes were retrieved, and the way of defining the comorbidities e.g. cognitive impairment and orthopaedic complications), are discussed in detail in chapter two.
4.2.4 Outcome Measurement tools

The WHO developed the “International Classification of Functioning, Disability, and Health” (ICF) which is a classification scheme of health and functional disabilities. This is done by coding a wide range of information about health in an effort to utilise a consistent mutual language facilitating global communication about health and functional status. In addition, it allows for assessment and comparison of HRQOL instruments that measure outcomes after health intervention in disabled populations (458). The ICF Child and Youth version (ICF-CY) is geared towards children and young adults and is designed to be sensitive to changes associated with growth and development (464, 465).

The ICF-CY has moved the focus of clinicians toward enabling the individual to overcome activity and participation restrictions. The most important feature of ICF-CY is that it is a classifier model instead of being hierarchical. For example, a person with limited functionality and activity might not encounter any problems in participation due to personal and environmental factors.

**ICF has two parts, each with two components:**

Part 1- Functioning and Disability which includes:

*Body functions and structures*

Body functions are the physiological functions of body systems (including psychological functions) while body structures are anatomical parts of the body such as organs, limbs and their components. Impairments are limitations in body function or structure that result in a significant deviation or loss of that organ or system (464).
Both body functions and body structures are classified in two different sections which are organised according to the body systems. These two classifications are designed for use in parallel. For example, body functions include basic human senses such as hearing and vestibular functions and their structural correlates exist in the form of ear and its structures (464).

**Activities and Participation**

Activity is defined by WHO as the execution of a task or action by an individual, and activity limitations are difficulties in executing activities (464). Participation is defined as involvement in a life situation, and participation restrictions are problems an individual encounters in a life situation. Activity limitations often lead to participation restrictions and both are associated with disability (464).

Activities and participation are given in a single section that covers the full range of life areas (from basic learning, communication and mobility to composite areas such as interpersonal interactions and social and civic life). Participation is a key construct of the ICF (464). Participation for children includes domains of learning and applying knowledge, communication, home life, school life, social life, relationships, and leisure and recreation. The ICF offers two qualifiers for activities and participation. These are: (1) capacity, which indicates the highest probable level of functioning that a child can do in a standardised environment, and (2) performance which is defined as how a child actually performs activities in everyday life situation and is measured in a person’s current environment (464). Inconsistencies between children’s capacity and performance are presumed to be due to environmental or personal ‘contextual’ factors. Hence, differences in aspects of children’s
participation have been attributed to movement, manual and intellectual abilities, and also to the environment in which they live (466).

Capacity to perform an action only partially explains children’s activity and participation. To focus on activity, rather than participation will divide people into groups based on disability type. Participation is something other than being able to perform activities. Persons, who are not capable of performing the activity (activity restrictions), can still participate, even if someone else, such as an assistant, performs the activity for them. The individual alone can determine his/her own level of participation (467).

The ICF emphasises the level of an individual’s health rather than disability level and presents participation as one of the main areas of a person’s functioning, along with body structure, function and activities. Different areas such as communication, mobility, domestic life and social relationships comprise some of the elements of participation. These activities reflect how an individual functions within his or her environment in different life roles. Focusing on how they function in their close environment will provide more information about their health and well-being than focusing on the diagnosis, degree and type of disability as characteristics for participation and health (468).

Part 2: Contextual Factors which include:

Environmental factors:

Environmental factors constitute the physical, social and attitudinal environment in which people live and conduct their lives. These factors are external to individuals and can have a positive or negative influence on the individual’s performance as a member of society.
The categories listed under environmental factors include: (i) products and technology, (ii) natural environments and human made changes to environment, (iii) support and relationships, (iv) attitudes, and (v) services, systems and policies.

**Personal factors:**

Personal factors are the particular background of an individual’s life and living, and comprise features of the individual that are not part of a health condition or health states. These factors may include gender, race, age, other health conditions, fitness, lifestyle, social background, education, profession, past and current experience (past life events and concurrent events), overall behaviour pattern and character style, individual psychological assets and other characteristics, all or any of which may play a role in disability at any level (464, 469).

The current study was based on the ICF model dimensions to identify the level of activities and participation and the level of body functions, Figure 4-1 illustrates the items to be assessed according to the ICF-model of CP. CPCHILDM™ was utilised to assess the impact of ITB therapy on HRQOL, and the Paediatric Functional Independence Measure (WeeFIM) was applied to assess the functional outcomes. Both of these instruments were selected due to their established responsiveness\(^\text{y}\) (443, 470), reliability\(^\text{z}\) (443, 471) and validity (443, 471).

\[^{y}\text{Responsiveness is sensitivity to change or ability to discover alterations over time.}\]
\[^{z}\text{Reliability is ability of the measurement to produce the same results when repeated in the same population. Validity is the ability of the measurement to assess what it intends to measure e.g. functional status.}\]
Figure 4-1 Illustration of the assumed assessment procedure according to the ICF-model
4.2.4.1 WeeFIM®

WeeFIM® is the child version of Functional Independence Measure (FIM), which was designed by the National Task Force for Medical Rehabilitation to assess functional independence of severely disabled adults. Its aim was to track the rehabilitation progress in patients with acquired disability as in spinal cord injury and traumatic brain injury patients. WeeFIM® consists of 18 items that were designed to evaluate the ability of the child to perform the main functional skills, not to evaluate the impairment, and to follow the outcome changes across health interventions. The 18 items are categorised into three main areas; self-care, mobility, and cognition. These domains comprise all developmental features. WeeFIM® assessment can be attained either by interview or by direct observation of the patient performing the tasks according to standard criteria (453).

The ‘Self-care’ domain consists of 8 items: eating, grooming, bathing, dressing the upper body, dressing lower body, toileting hygiene, and maintaining sphincter control of both bladder and bowel in two separate items (453). ‘Mobility and locomotion’ includes five items: transferring (changing position) from chairs, toilet seats and tubs, walking indoors and outdoors, self-mobility (crawl or wheelchair), and using stairs (453). ‘Cognition’ domain is includes five items: language comprehension, expression, social interaction, problem solving, and memory retention (453). The minimum score is 18 and the maximum score is 126 (453, 472).

WeeFIM® rating scale is very concise. It is seven levels of specific ordinal criterion which classifies the functional status into two categories; independent and dependent. The higher level of independence is level seven where the child does not need assistance to achieve the task without any
equipment. At level six, the child can achieve the task independently but needs aiding equipment, or there is a concern to complete it safely or in time. The dependent category lies from level 1 - 5 and the patient needs partial to full assistance to complete the task. At level five, the patient needs supervision. At level four the patient can do more than 75% of tasks but needs minimal physical contact or promotion. At level three, the child can achieve 50-74% of the task with moderate contact assistance, achieving between 25-49% with maximal contact assistance is scored level 2, and the complete dependency (effort less than 24%) with total support is level one.

WeeFIM® has several advantages, i) it is a less time consuming measure requiring 20-30 minutes to carry out, ii) its validity and reliability have been examined for use in severely disabled children with CP, and iii) the administrator needs to be trained and certified before starting to interview the patients to ensure consistency in the rating process (473).
4.2.4.2 CPCHILD™

The CPCHILD™ is a disease-specific measure that was designed to assess and trace the change of HRQOL in children with severe CP disability after health intervention from the perspective of their caregivers (443). It contains 37 items covering six domains: Personal Care; Positioning, Transferring and Mobility; Comfort and Emotions; Communication and Social Interaction; Health issues; and Overall quality of life (443). Each CPCHILD™ item is rated in two aspects: the degree of difficulty to achieve the task which is graded on a 7-point ordinal scale from zero as impossible to 6 as no problem. Then the level of assistance from the caregiver is graded on a 4-point ordinal scale rated zero as totally dependent to 3 which is completely independent. The minimum score of each item is zero and the highest score is 9. However, in the comfort and emotions domain, the rating of the level of assistance modifier aspect is omitted due to the difficulty to interpret by the caregiver and only rating is zero through 6. In the Comfort and Emotions domain, the maximum score is 8 only (474).

It is noteworthy that test re-test reliability of CPCHILD™ is high. The Intraclass Correlation Coefficient (ICC) for the overall score is 0.97 (95% CI: 0.95-0.99). The ICC range of the main 6 domains ranged from 0.88 to 0.96 (443).
4.2.5 Statistical analysis

1- Paired sample t-test was used to compare changes between pre-implantation and post-implantation scores for each instrument.

2- To compare the responsiveness of both CPCHID and WeeFIM® to ITB therapy, the effect size (Cohen’s d score) was calculated.

\[
d = \frac{\text{mean of postimplantation score} - \text{mean of preimplantation score}}{\text{pooled standard deviation (SD)}}
\]

\[
Pooled (SD) = \sqrt{\frac{\text{postimplant SD}^2 + \text{preimplant SD}^2}{2}}
\]

A Cohen’s d score of zero means that the intervention has no effect. The effect is considered small if Cohen’s d is between 0.2 and 0.5, moderate between 0.5 to 0.8, and large if more than 0.8 (475, 476).

3- Multivariate linear regression analysis was used to determine the influence of independent variables (such as cognitive state, orthopaedic deformities, age of the patient, and epilepsy) in the evolution of each outcome.

SPSS 21 for Windows was used for data analysis. Gardner’s Effect Size Illustrator (version 1.1) was used to calculate Cohen’s d scores (477).
4.3 Results

The data set includes 75 patients with ITB pump implantation performed between January 2008 and January 2011. They were interviewed by one investigator (AA) to assess the outcomes of ITB therapy on HRQOL and functional status. Participant demographic characteristics are summarised in Table 4-1.

Table 4-1 General characteristics of the subjects in this study (N=75).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at implantation</td>
<td>10.8 (3.5-18) SD± 4.325</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
</tr>
<tr>
<td>Indication of ITB pump implantation:</td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>71</td>
</tr>
<tr>
<td>Primary dystonia</td>
<td>2</td>
</tr>
<tr>
<td>Hereditary paraplegia</td>
<td>2</td>
</tr>
<tr>
<td>Cognitive status</td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>10</td>
</tr>
<tr>
<td>Fair</td>
<td>24</td>
</tr>
<tr>
<td>Impaired</td>
<td>41</td>
</tr>
<tr>
<td>Associated epilepsy</td>
<td>37/75 (49%)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>14/75 (18%)</td>
</tr>
<tr>
<td>Orthopaedic deformity</td>
<td>36/75 (48%)</td>
</tr>
<tr>
<td>VP shunt</td>
<td>7/75 (9%)</td>
</tr>
<tr>
<td>Injection of Botulism</td>
<td>27/75 (36%)</td>
</tr>
</tbody>
</table>

4.3.1 Changes in health-related quality of life outcomes (CPCHILD™)

There was an overall improvement in HRQOL measurement after implantation of ITB therapy. All aspects of CPCHILD™ instrument revealed a
significant difference between baseline and post-implantation. Radar plots\textsuperscript{aa} illustrate the changes that occurred in each subclass of the main domains of CPCHILD\textsuperscript{TM} instrument.

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{figure4_2.png}
\caption{Changes after implantation in personal care and ADL domain (CPCHILD\textsuperscript{TM}).}
\end{figure}

Figure 4-2 illustrates the difference between pre-implantation and post-implantation scores. Each spoke on the plot represents an individual subscale of personal care and ADL domain. Changing diapers, eating and dressing were the most responsive items in this domain. Total change of personal care domain was \( \approx 19\% \), representing the second most significant change after comfort and emotions domain from improvement aspect.

\textsuperscript{aa}Plots are read from the center outward along each spoke. Scores are shown on concentric circles beginning with 0 at the center and increasing toward outer line
Figure 4-3 shows the changes in mobility and transferring domains and its individual subscales after implantation. Transferring in/out of bed, transfer from a wheelchair and getting in/out of the vehicle showed the most prominent improvement after implantation. However standing was the least affected by ITB therapy. There was an overall moderate change of ≈17% in the entire domain.
Figure 4-4 Changes after implantation in comfort & emotions domain (CPCHILD™)

Figure 4-4 represents the changes in comfort and emotion domain. There was a uniform large improvement across all subscales. From the plot, it can be noticed that the comfort and emotion domain has the greatest change across all CPCHILD™ domains ≈ 22 %.
Figure 4-5 shows the changes across the communication and social interaction domain. Communication with caregiver and playing with others are the most prominent items before and after implantation. Nevertheless, there was a consistent mild change through this domain by 15%.
4.3.2 Which domain has the best outcome?

The radar plot in Figure 4-6 revealed the changes throughout all CPCHILD™ domains. From the graph, the ITB response was maximal in the comfort and emotions domain 22%, followed by self-care ≈19%, mobility ≈17%, communication ≈12%, while the least change was observed in the overall health domains 10%. Similar score gains were detected in the quality of life domain. The overall change in CPCHILD™ was 16%.
Generally, the pre-implanting and post-implanting scores were around 40 and 60% of normative value, and the changes were approximately 20%, Figure 4-7.

**Figure 4-7** Graph comparing the CPCHILD™ scores in each domain, pre and post implantation and compared with normative values of the CPCHILD™ instrument
4.3.2.1 Student's t-test for changes in CPCHILD™ scores

The paired sample Student's t-test revealed a significant difference between pre-implantation and post-implantation measures in all CPCHILD™ domains. Post-implantation score represents the change in total CPCHILD™ (mean 59.5: SD 14.7) from pre-implantation score (Mean: 42.9 SD ± 14.4), t(74): 20.5 and p<0.05, Table 4-2.

**Table 4-2** CPCHILD™ mean of pre and post implantation measures and results of Student's paired t-test between the two scores

<table>
<thead>
<tr>
<th></th>
<th>Pre-implantation mean ±SD</th>
<th>Post-implantation mean ±SD</th>
<th>Difference of mean 95% CI</th>
<th>t-value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal care and ADL</td>
<td>35.25±14</td>
<td>54.78±15</td>
<td>19.8 (15.1 - 24.5)</td>
<td>16.896</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positioning, transferring, locomotion</td>
<td>31.50±15.7</td>
<td>48.45±16.7</td>
<td>16.9 (7.7 - 18.2)</td>
<td>12.746</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comfort and emotions</td>
<td>43.24±16.14</td>
<td>65.51±13.14</td>
<td>22.3 (17.5 - 26.9)</td>
<td>16.945</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Communication and participation</td>
<td>44.53±20.9</td>
<td>59.36±25.15</td>
<td>15.2 (4.3 - 40.4)</td>
<td>11.984</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Health status</td>
<td>56.45±18.27</td>
<td>67.46±16.5</td>
<td>11.01 (-20.3 - 16.6)</td>
<td>10.115</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life</td>
<td>43.73±17.18</td>
<td>60.26±19.7</td>
<td>16.5 (10.1 - 21.9)</td>
<td>10.723</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total CPCHILD™ score</td>
<td>42.9±14.43</td>
<td>59.49±14.7</td>
<td>16.53 (0.5 - 43.3)</td>
<td>20.500</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
4.3.3 Functional status outcome (changes in WeeFIM® score)

WeeFIM® measurements showed improvement after ITB implantation. Figures (4-8 to 4-10) represent the results of the three main WeeFIM ® domain and their sub-items.

4.3.3.1 Self-care Domain

![Figure 4-8 Changes in Self-care domain (WeeFIM ®).](image)

Figure 4-8 shows a radar plot of changes in the self-care domain after implantation. The mean score increased from 16.98 SD± 1.45 preoperatively to 20.73 SD± 1.32 postoperatively (3.75 points improving is equivalent to a 5.7% compared to normative value). All subscales showed uniform improvements, 5 points in eating, 4 points in grooming, bathing, dressing the upper limbs, toileting and bowel management, and lastly 3 points in dressing lower limbs and bladder management.
4.3.3.2 Change in mobility domain

![Graph showing changes in mobility domain (WeeFIM II®).](image)

**Figure 4-9** Changes in mobility domain (WeeFIM II®).

The pre-operative WeeFIM II® score increased from 10.2, SD±0.75 to 12.4, SD±0.98 postoperatively (2.12 points equivalent to 6% from normative value). Transferring from chairs, toilet and tub or shower represented the biggest improvement in this domain by 3 points, then walking and climbing stairs by 1 and 2 points respectively, Figure 4-9.
4.3.3.3 Changes in cognition domain

![Radar plot showing changes in cognition domain after implantation.](image)

**Figure 4-10** Change in cognition domain (WeeFIM II®)

The radar plot in Figure 4-10 represents changes in cognitive function after implantation. The total mean score increased from 14.4 SD±1.4 preoperatively to 17.2 SD±1.7 postoperatively (2.8 point improvement that equivalent to 7.7% of normative value=35). Social interaction subscale revealed the best improvement by increasing 4 points, and the remaining subscales increased by 3 points.

In general, the value of WeeFIM scores (pre- and post-implantation), were low in comparison to normative value, Figure 4-11.
4.3.3.4 Student’s $t$-test for changes in WeeFIM scores.

The overall average of WeeFIM II® score increased from 42.01 SD±21.07 preoperatively to 50.5 SD±28.46 postoperatively. The paired sample $t$-test result was significant ($p<0.001$), Table 4-3.

**Table 4-3** WeeFIM mean of pre and post implantation measures and results of Student’s paired $t$-test between the two scores

<table>
<thead>
<tr>
<th></th>
<th>Pre-implantation mean ±SD</th>
<th>Post-implantation mean ±SD</th>
<th>Difference in mean 95%CI</th>
<th>$t$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-care</td>
<td>16.75±1.3</td>
<td>20.75±1.2</td>
<td>3.70 (0.05 - 6.13)</td>
<td>6.534</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Locomotion and transferring</td>
<td>10.38±5.61</td>
<td>12.51±7.80</td>
<td>2.12 (-0.243 - 4.103)</td>
<td>5.786</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>14.46±8.13</td>
<td>17.27±9.23</td>
<td>2.81 (0.15 - 5.41)</td>
<td>9.300</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total Score</td>
<td>42. ±21.07</td>
<td>50.5±28.46</td>
<td>8.62 (0.17 - 16.20)</td>
<td>8.900</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
4.3.4 Responsiveness extent (effect size measurement) of health related quality of life (CPCHILD™) and functional status (WeeFIM II®)

Measuring the effect size, between pre- and post-implantation scores to distinguish the response effect of CPCHILD™ and WeeFIM II® instruments, revealed:

4.3.4.1 CPCHILD™

The responsiveness of the CPCHILD™ instrument was moderate to large in CPCHILD™ individual domains (Cohen’s d range 0.5-1.5). The largest response effects were in self-care and comfort domains (>1.3), followed by the total CPCHILD™ score (Cohen’s d: 1.14). The lowest effect was in the communication domain, Table 4-4.

<table>
<thead>
<tr>
<th>CPCHILD™ domain</th>
<th>Cohen’s d (effect size)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-care</td>
<td>1.36</td>
<td>0.001</td>
</tr>
<tr>
<td>Positioning</td>
<td>1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comfort</td>
<td>1.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Communication</td>
<td>0.50</td>
<td>0.002</td>
</tr>
<tr>
<td>health</td>
<td>0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life</td>
<td>0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total score of CPCHILD™</td>
<td>1.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
4.3.4.2 WeeFIM®

The response effect of ITB on functional status (as measured by effect size of change in WeeFIM®) shows a small effect in all domains (Cohen’s d range 0.28-0.32) and in the total score (Cohen’s d: 0.32.), Table 4-5.

An interesting observation driven from the aforementioned results is that the ITB effect on HRQOL is larger than its effect on functional status.

<table>
<thead>
<tr>
<th>WeeFIM II® domains</th>
<th>Cohen’s d (effect size)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-care</td>
<td>0.339</td>
<td>p = 0.039</td>
</tr>
<tr>
<td>Mobility and transferring</td>
<td>0.316</td>
<td>p = 0.055</td>
</tr>
<tr>
<td>cognition</td>
<td>0.326</td>
<td>p = 0.065</td>
</tr>
<tr>
<td>Total Score of WeeFIM II®</td>
<td>0.371</td>
<td>p = 0.049</td>
</tr>
</tbody>
</table>
4.3.5 The relation between HRQOL and functional status

Significant correlations were found between pre-implantation status of CPCHILD™ and WeeFIM scores ($r=0.829 \ p<0.001$), as well as their post implantation scores ($r=0.785 \ p<0.001$). However, no significant correlation ($r =0.217 \ p=0.061$) was found between the changes of HRQOL (total gained score of CPCHID) and functional state (total gained score of WeeFIM), Table 4-6.

Table 4-6 The Spearman's rank correlation coefficients between CPCHILD™ and WeeFIM® instruments

<table>
<thead>
<tr>
<th>Parameters tested</th>
<th>Pearson Correlation</th>
<th>Significance (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation between Pre-implant WeeFIM score and Pre CHCHILD scores</td>
<td>0.829**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Correlation between Post Implant WeeFIM and Post implant CPCHILD™ scores</td>
<td>0.785**</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Correlation between the gained WeeFIM and gained CPCHILD™ score</td>
<td>0.217</td>
<td>0.061</td>
</tr>
</tbody>
</table>

4.3.6 The relationship between functional baseline and changes in HRQOL aspects

The correlation between the gained scores$^{bb}$ of individual CPCHILD™ domains and the pre-implant WeeFIM individual scores (a baseline of functional state) revealed a significant positive correlation between cognitive domain and the change in communication and social participation domain in CPCHILD™ ($r=0.416 \ p=<0.001$), personal care domain ($r=0.337 \ p=0.003$), and locomotion and transferring ($r=0.319 \ p=0.005$).

$^{bb}$ Gained score= postimplant score – preimplant score
Moreover, a significant positive correlation was found between mobility domain (in WeeFIM score) before implantation and changes in personal care domain, and locomotion and transferring domain in CPCHILD™ instrument (r=0.31 p 0.007) and (r=0.253 p=0.023), respectively, Table 4-7.

**Table 4-7** Spearman’s rank correlation coefficients between CPCHILD™ gained scores and pre WeeFIM II® instruments

<table>
<thead>
<tr>
<th>Gained score of CPCHILD™ domains</th>
<th>Pre self-care function WeeFIM</th>
<th>Pre Mobility function WeeFIM</th>
<th>Pre Cognitive function WeeFIM</th>
<th>Pre WeeFIM Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal care</td>
<td>r value</td>
<td>0.226</td>
<td>0.310**</td>
<td>0.337**</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.051</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td>Locomotion and transferring</td>
<td>r value</td>
<td>0.249*</td>
<td>0.253*</td>
<td>0.319**</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.031</td>
<td>0.028</td>
<td>0.005</td>
</tr>
<tr>
<td>Comfort and emotion</td>
<td>r value</td>
<td>-0.195</td>
<td>-0.255*</td>
<td>-0.311**</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.093</td>
<td>0.027</td>
<td>0.007</td>
</tr>
<tr>
<td>Communication and participation</td>
<td>r value</td>
<td>0.307</td>
<td>0.334</td>
<td>0.416</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.007</td>
<td>0.003</td>
<td>0.000</td>
</tr>
<tr>
<td>health</td>
<td>r value</td>
<td>-0.146</td>
<td>-0.132</td>
<td>-0.213</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.211</td>
<td>0.258</td>
<td>0.066</td>
</tr>
<tr>
<td>Overall QOL</td>
<td>r value</td>
<td>0.198</td>
<td>0.211</td>
<td>0.092</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.088</td>
<td>0.069</td>
<td>0.430</td>
</tr>
<tr>
<td>Total score of CHCHILD</td>
<td>r value</td>
<td>0.153</td>
<td>0.173</td>
<td>0.147</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.189</td>
<td>0.138</td>
<td>0.208</td>
</tr>
</tbody>
</table>

*r: correlation coefficient

**significant at 0.01
4.3.7 Predicting factors of HRQOL and functional status

4.3.7.1 HRQL predicting factors (CPCHILD™ changes)

Multivariate linear regression analysis for CPCHILD™ model revealed that epilepsy is a negative predictive factor for HRQOL improvement. Interestingly, the total functional state before implantation (pre-implant WEEFIM score) was not significantly related to change in CPCHILD™ Score, Table 4-8.

Table 4-8 Multivariate linear regression analysis of post-implantation changes in CPCHILD™ total score

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardised Coefficients</th>
<th>Standardised Coefficients</th>
<th>t</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>Std. Error</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>orthopaedic complications</td>
<td>-0.894</td>
<td>2.416</td>
<td>-0.051</td>
<td>-0.30</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>-8.783</td>
<td>3.826</td>
<td>-0.499</td>
<td>-2.29</td>
</tr>
<tr>
<td>FIM Pre-cognition</td>
<td>-0.511</td>
<td>0.374</td>
<td>-0.474</td>
<td>-1.46</td>
</tr>
<tr>
<td>FIM pretotal 1</td>
<td>0.076</td>
<td>0.124</td>
<td>0.182</td>
<td>0.60</td>
</tr>
<tr>
<td>implant age/m</td>
<td>0.012</td>
<td>0.020</td>
<td>0.071</td>
<td>0.61</td>
</tr>
<tr>
<td>V-P shunt</td>
<td>-0.472</td>
<td>3.489</td>
<td>-0.016</td>
<td>-0.13</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>-0.339</td>
<td>2.404</td>
<td>-0.018</td>
<td>-0.141</td>
</tr>
<tr>
<td>Sex</td>
<td>-4.010</td>
<td>2.145</td>
<td>-0.214</td>
<td>-1.83</td>
</tr>
</tbody>
</table>

a. Dependent Variable: Difference in CP child score
4.3.7.2 Functional status predicting factors (WeeFIM change)

Multivariate linear regression analysis showed that good cognitive state and absence of orthopaedic complications were significant predicting factors of WeeFIM score gains (p=0.006 and 0.004, respectively), Table 4-9.

**Table 4-9** Multivariate linear regression analysis of post-implantation changes in WeeFIM total score

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardised Coefficients</th>
<th>Standardised Coefficients</th>
<th>t</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>Beta</td>
<td>Std. Error</td>
<td>Beta</td>
<td>t</td>
</tr>
<tr>
<td>Sex</td>
<td>-1.868</td>
<td>1.538</td>
<td>-0.099</td>
<td>-1.214</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>-0.667</td>
<td>1.709</td>
<td>-0.034</td>
<td>-0.390</td>
</tr>
<tr>
<td>V-P shunt</td>
<td>-0.054</td>
<td>2.497</td>
<td>-0.002</td>
<td>-0.022</td>
</tr>
<tr>
<td>botox injection</td>
<td>0.708</td>
<td>1.403</td>
<td>0.041</td>
<td>0.504</td>
</tr>
<tr>
<td>epilepsy</td>
<td>-0.574</td>
<td>1.663</td>
<td>-0.032</td>
<td>-0.0345</td>
</tr>
<tr>
<td>Presence of orthopaedic complication</td>
<td>-7.533</td>
<td>2.505</td>
<td>-0.415</td>
<td>-3.0</td>
</tr>
<tr>
<td>WeeFIM Pre-cognition</td>
<td>0.440</td>
<td>0.154</td>
<td>0.405</td>
<td>2.851</td>
</tr>
<tr>
<td>implant age/m</td>
<td>-0.004</td>
<td>0.014</td>
<td>-0.020</td>
<td>-0.251</td>
</tr>
</tbody>
</table>

a. Dependent Variable: total Difference

a. Dependent Variable: WeeFIM change
4.4 Discussion

Evaluating outcomes is the sole method of assessing the effectiveness of health interventions and quality of services. HRQOL measurement in CP research is more informative than other clinical measures, which do not express the wellbeing of children and their caregivers. This chapter has focussed upon the impact of ITB on the patients’ HRQOL and functional status. These were assessed by using two standardised measures (WeeFIM and CPCHILD™) of evaluating quality of life for children with CP. We have shown that using WeeFIM and CPCHILD™ described the positive impact of ITB upon different domains of quality of life.

The baseline (pre-implantation score) scores of CPCHILD™ and WeeFIM (42.3 and 41, respectively) were slightly less than the expected values reported in the instruments’ manuals. The CPCHILD’s manual reported the total scores of severely disabled CP patients lie between 44.4 ±8.1- 56.3±12. In this cohort the baseline score was 42.3. WeeFIM total score in quadriplegic CP patients was reported as 43 ± 23 in a pilot study by Marshall et al. (453). However, in the current study the WeeFIM baseline scores was 41. This difference possibly indicates the higher severity of CP in this cohort.

4.4.1 Effectiveness of ITB on HRQOL and functional status
Intrathecal baclofen therapy showed significant improvement in HRQOL through increasing all domains of CPCHILD™ as well as its total scores. The best improvement was shown in the comfort and emotional domain which correspond with the previous findings reported by Gooch et al. However, they used a non-validated questionnaire to score the comfort and pain relief (225). Hoving et al. used generic instrument (CHQ-PF50) in a randomised controlled
study to report the ITB therapy effects. They stated that relief of pain and discomfort was the most responsive items in CHQ-PF50 questionnaire to ITB therapy in comparison to the control group (457).

This improvement in comfort and relief of pain is critical in these patients as more than 60% of them usually experiences pain and discomfort, particularly during sleep. In addition, patients also sit for extended periods of time in the same position (478, 479).

The next significant improvement after ITB therapy was observed in the self-care and mobility domain which matches previous findings. Awaad et al. described ITB therapy benefits in self-care and mobility domains of the PEDI instrument especially in patients with high pre-implantation scores (285). This also correlates with another study by Ward et al, using the Canadian Occupational Performance Measure (COPM) and goal attainment scaling (GAS), who showed the improvement in these domains especially positioning and transfers (266). In contrast to these findings, Hoving et al. in an RCT found no significant change in either the PEDI or GMFM scores that evaluated self-care and mobility (457). Similarly, Campbell et al. showed no GMFM improvement after ITB therapy and the PEDI only showed small changes in patients’ mobility (209).

The health domain is unique for CPCHILD™ questionnaire, and is the most objective domain in this instrument as its score depends on frequency of hospital visits and number of medications. In the current study, the

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C The Child Health Questionnaire™ (CHQ) is a family of general quality of life surveys that have been designed and normed for children from 5-to-18 years of age. The parent form is available in 2 lengths - the CHQ-PF50 and the CHQ-PF28 (457).
improvement in health domain after ITB therapy could be related to omitting or reducing some of the routine medications used in CP such as oral baclofen and diazepam (480). Furthermore, the hospital visits may have declined due to improvement in other consequences of spasticity as for instance orthopaedic deformities and correction operations (47).

Communication ability is frequently compromised in CP children (481), which affects their social integration (482). The current study showed significant change in perception of communication and social interaction. This has been reported in other studies. Awaad et al demonstrated improvement of the social domain in the PEDI scale (285).

In the current study a significant positive correlation was found between gained score in communication and social interaction domains in CPCHILD™ and pre-implantation scores of cognitive function on WeeFIM scale. This is in accordance with previous studies that linked the communication disabilities to the cognitive state (481).

Cognition domain scores in WeeFIM showed mild improvement after ITB implantation. This result supports previous findings of positive changes in the cognition domain of FIM instrument (adult version of WeeFIM) after implanting the ITB pump in traumatic brain injury (TBI) patients (483). Furthermore, recovery of vegetative patients with TBI after ITB pump implantation has also been reported (484, 485). This observation could support the idea of a positive effect of ITB on cognition. In acquired brain injury, the brain and function were already established (486). However, in CP the brain injury occurred very early in life and so the brain did not have the opportunity for natural development of its function (28, 30). Powell et al stated
that executive function\textsuperscript{dd} is the latest cognitive area to develop until reaching adolescence (487). Nevertheless, a recent study examined the efficacy of ITB therapy in improving mobility and cognition on a rat model of CP showed only a significant effect on mobility but not on the cognition (486).

Further neuroscience research should focus on exploring the effect of ITB on cognitive function. Natale et al. have commenced an experimental study to measure cortical activity by functional magnetic resonance imaging (fMRI) in patients with severe spasticity to compare these results after ITB therapy aiming at finding new motor and sensory activities (397).

4.4.2 Measuring the effect size of ITB therapy on HRQOL and functional status

Null hypothesis significant testing (NHST) is deemed to be a core of statistical method that verifies an established null hypothesis according to the given significance level. Using of NHST only indicates if an effect exists but does not inform of the size of that effect (488).

In this study, the effect size of CPCHILD™ changes was large, in contrast to small effect size of the functional changes in WeeFIM scores.

Effect size (ES) is a simple method to quantify the effect of an intervention. It is easy to calculate, readily understood and can be applied to the HRQOL outcome. It allows us to move beyond the simplistic, 'Does it work or not?' to the far more sophisticated, 'How well does it work in a range of contexts?' (489).

\textsuperscript{dd} Executive function in CP is impaired due to early damage of the white matter tracts, which connect the prefrontal and posterior brain regions (487).
It is noteworthy that ES measuring was pioneered by Jacob Cohen\textsuperscript{ee}. However, Cohen did not create anything which was not already in statistics, but rather gave a means to spread the concept of statistical power and size of an effect among non-statisticians. He derived Cohen’s $d$ score directly from the already known statistical test such as Students t-test (490).

Cohen’s $d$ is an estimate measure of ES in terms of number of standard deviations that mean scores shifted above or below the population mean stated by the null hypothesis. The larger the value of $d$, the larger the effect in the population (491). It estimates the size of a shift in the population as a number of standard deviations that scores shifted. The numerator is the sample mean difference between pre- and post-intervention scores. The denominator is the pooled standard deviation for two scores (491).

The limitation of ES is that the characteristics of the distribution, particularly at baseline, may strongly influence the ES. Accordingly, the same amount of individual change produces different effect sizes depending upon heterogeneity of the sample at baseline. Therefore, the larger the baseline SD, the smaller would be the resultant effect. Therefore, when using ES for an individual or group to determine clinically meaningful change, we should be aware that the conclusion might be influenced by sample heterogeneity (492, 493).

4.4.3 The relationship between changes in HRQOL and functional status

Using the CPCHILD™ and WeeFIM measures permitted a correlation between the different domains in the two instruments. This in particular

\textsuperscript{ee} Jacob Cohen was a United States statistician and psychologist. He laid the foundations for current statistical meta-analysis and the methods of estimation statistics(490).
highlighted a surprising lack of correlation between changes in physical functioning and perception of HRQOL.

In the current study, there was a significant correlation between both baselines of CPCHILD™ and WeeFIM scores and also between the post-implantation scores of both instruments that may give an impression of a reciprocal relationship between HRQOL and functional status. Nevertheless, the correlation between gained scores of both instruments was not statistically significant which means improving quality of life is not dependant on the functional improvement of patients.

This discrepancy of improvement between HRQOL and functional status could be explained by the nature of WeeFIM instrument as an evaluation tool of disability, focusing objectively on the ability to perform certain tasks against predetermined criterion (494). In contrast, CPCHILD™ is a proxy tool measuring caregivers’ perceptions of the HRQOL of their children, which is based on their feelings about functioning, participation, social, and emotional well-being (443). Another possible explanation is the disability paradox phenomenon where patients reported better QOL that did not correspond to their disability. This phenomenon could occur because: firstly, patients or their caregivers understand and accept the functional disabilities (495); secondly, overcoming the functional disabilities by adapting external factors and modifying environmental factors to improve the social interaction of the patients, can lead to intensification and improvement in QOL feeling (496).

4.4.4 The relationship between functional independence and quality of life
Reduced activity levels and participation restrictions due to multiple impairments in children with CP may lead to a reduced QOL (497). In this
study, the baseline functional status (especially pre-implantation cognitive and mobility status) is positively correlated with some domains in CPCHILD™ in particular communication and participation, and locomotion and transferring domains. These findings suggest that children with CP who are more independent in performing basic activities of daily living before implantation will feel better about their social life, community interaction, transferring and mobility. This finding corroborates the ideas of Chulliyil et al. who concluded that children with CP children who were more functionally dependent were found to have worse QOL (497).

Parkes et al. also stated that children with CP and severe impairments participated significantly less in most activities of daily living (498). The neural lesions and subsequent cognitive impairments of children with CP can impact their ability to develop the mental skills needed to engage in unrestricted social interaction. This dynamic is reciprocal, as restrictions in social participation can negatively impact the development of cognitive functioning (30).

4.4.4.1 Overlap between WeeFIM and CPCHILD™

Functional status and QOL are important health outcomes. Functional outcomes were used to measure objective dimensions such as mobility and activities of daily living (ADL). However, HRQOL outcomes have gained their popularity from evaluation of both objective and subjective dimensions. The subjective component tends to be more valued by children and their parents, while the objective component is classically more informative for the service provider’s needs (499).
The International Classification of Functioning Disability and Health for Children and Youth (ICF-CY), provides a universal language to measure health, education, and social activities of children and youth. All the components of the ICF-CY are linked to each other in bi-directional relationship (469). WeeFIM as functional status instrument and CPCHILD™ as HRQOL instrument seem to be overlapping in measuring different categories in ICF-CY model. In self-care domain, both instruments share assessment of eating (ICF code: d550) and drinking (d560); washing (d5100); oral hygiene (d5210); toileting activities (d530), and wearing upper (d5400) and lower limbs (d5401).

The cognitive domain of WeeFIM assesses these categories in ICF framework: comprehension (Communicating-receiving d310-d329), expression (Communicating-producing 330-d349) and social interaction (d710-d729). CPCHILD™ also covers these items in communication & social interaction domain i.e. understanding; understood; and playing alone and with others.

CPCHILD™ is designed to evaluate HRQOL, and covers a broader concept of health. It measures caregivers’ perspectives of the health status, comfort, wellbeing, functional abilities and ease of caregiving of children with severe developmental disabilities (443). Unlike the CPCHILD™, the WeeFIM was designed only to measure the functional performance and identify what the child can actually do within a specific environment. However, it was not designed to measure well-being (500). Given the fact that individuals with similar functional disabilities may show a range of different scores for HRQOL (421, 499), therefore, the CPCHILD™ can be used as a complementary
measure to the WeeFIM to provide a more comprehensive description of the child’s well being, more than the functional measure offers (443, 501).

4.4.5 Factors affecting functional status and HRQOL outcomes

In this study, multivariate linear regression (MLR) revealed that good cognitive status and absence of orthopaedic complications are significant predictors of improving the functional status. The relationship between cognitive state and improving the functional status after ITB therapy was reported previously by Scheinberg et al. who noted the significant improvement in upper limb function in cognitive intact patients (502). Similarly, Groden et al. reported the associations between cognitive state and functional activity (279). Furthermore, Wong et al. studied risk factors affecting functional independence in children with CP by using the WeeFIM instrument. Their result showed that epilepsy and cognitive state are the factors that influence the functional status (503). Moreover, Chiang-Soon Song et al. reported the positive correlation between cognitive functioning in children with CP and activities of daily living in children with CP (326).

However, the effect of baclofen on cognitive function is poorly understood. Some studies suggested GABAβ receptor agonists, e.g. baclofen, can elevate the hippocampal content of the brain-derived neurotrophic factor (BDNF) which is essential for cognitive function (415, 418). Furthermore, baclofen was suggested to have neuronal neuroprotective effects (504).

Song et al. recommended that the significant correlation between physical and cognitive function should be considered during setting of goals of ITB therapy before implantation. This is because rehabilitation exercises for
cognitively intact children, like standing and active movement are different from the goals for less active child with cognitive impairment (326).

In the current study, orthopaedic complications of spasticity, for instance deformity and muscle contraction, were found to have a negative effect on the functional outcome of ITB therapy. Previous studies stated that correction of orthopaedic complications improve the functional state in children with CP (505, 506). Furthermore, the presence of epilepsy was a negative predicting factor of HRQOL outcomes in CPCHILD™ score. Epilepsy occurred in more than one third of children with CP (507). This group of patients need long-term antiepileptic mono or polytherapy. Moreover, they have a tendency for frequent hospital admissions due to status epilepticus and refractory seizures (407), which subsequently has a negative effect on health related QOL. This highlighted the importance of good seizure control to enhance the efficacy of health interventions in optimising the quality of life (503).

Arnaud et al. suggested that multiple comorbidities in children are obstacles to participation in school or to engagement in social activities. Consequently, they lead to a decline in children’s QOL (508). However, in this study, comorbidities such as visual impairment and hydrocephalus did not significantly influence changes in HRQOL or functional status after implantation.

The conclusion emerging from these findings is that children with intact cognition and without orthopaedic deformity or refractory epilepsy would have the best functional and HRQOL prognosis after ITB therapy. Therefore, to optimise the HRQOL after ITB therapy, efforts should be directed to modify these comorbidities by controlling intractable epilepsy (509) and correction of
musculoskeletal deformities (510). New therapies such as pantocalcin and erythropoiesis-stimulating agents (ESAs) have been suggested for improving cognitive function (327, 332).

4.4.6 Novelty of this study
The strength of this study was its single centre cohort studied over a prolonged period using standardised measures and different method of collecting the data. This study is a quasi-experimental (test then-test) design that has several advantages: 1) the interview is implemented at only one point to assess two points in time which is time and cost saving, 2) the test then-test is not prone to response shift bias as the patients’ standard about their state and changes after the interventions become consistent (455, 495), 3) the then-test studies are less prone to have missing data which could affect the power of statistical analysis (511).

This study attempted to find the relationship between HRQOL on functional status. This was achieved by using CPCHILD™ and WeeFIM instruments which are validated, reliable and sensitive to changes after health intervention(443).

4.4.7 Limitations and future considerations
The present study is subject to a number of limitations. Firstly, this study depends mainly on proxy report (parent-report data) whereas the WHO and the International Association for Child Psychology and Psychiatry stated that children should address their own QOL (512, 513). Nevertheless, it was suggested that if the children have obstacles like young age, cognitive impairments, or disabilities, then the proxy-report is the only method to assess their QOL using their caregivers in assuming they have intimate
knowledge of the children (514). The CPCHILD™ instrument used in this study was designed and validated as a proxy reporting instrument for severely disabled children.

Secondly, the retrospective design of this study might be prone to recall bias. However, Hassan et al. reported that recall bias was not such a burden in parent-reported data as has often been suggested (515). Interviewing techniques and choosing the validated and specific questionnaire should reduce the recall bias (516).

However, a prospective QOL study might be considered to measure outcome over time, and to capture the impact of long-term outcomes. It can be considered as an alternative to the conventional randomised clinical trial that may provide results more generalisable to clinical practice (518).

The major advantage of using a prospective cohort study is the accuracy of data collection and its resistance to patient recall bias as data are collected during the progress of the study rather than after the patient has developed the outcomes. Due to the longitudinal nature of the prospective cohort study, it also has the advantage of documenting a clear timeline of progression from intervention to outcomes (519). In addition, Prospective, longitudinal data collection may reveal time-dependent evolution of HRQOL domains. Patients may then serve as their own controls (518).

Thirdly, the impact of ITB therapy on caregivers’ stress was not evaluated despite that having a severely disabled child with CP can affect caregivers’

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**f** The prospective quality of life study is longitudinal survey that takes place over the forward passage of time. The data are collected at baseline of study before any intervention then the subjects are followed into the future in order to record the development of any of the outcomes of interest (517).
QOL and mental health (520, 521). Caregivers of children with CP may be under more physical, psychological, and financial burdens compared with those who provide care for children who develop in a typical manner because their greater responsibilities (522, 523).

Care and Comfort Caregiver Questionnaire (CareQ), was developed to measure difficulty of care experienced by caregivers of children with moderate to severe functional limitations due to CP. The CareQ also eases the communication between the caregiver and the clinician in setting therapeutic goals for the child (524).

The Coping Health Inventory for Parents (CHIP) is a well-recognised measure of coping among parents of chronically ill children (525). It is an appraisal of caregivers' cognitive and behavioural efforts to manage the demands of a stressful situation and coping responses to management of family life (525).

The Measure of Processes of Care (MPOC) is a well validated and reliable self-report measure of parents' perceptions of the extent to which the health services they and their children receive from children's rehabilitation treatment centres. It is a way to assess family-centred behaviours of health care provider (526).

Lastly, WeeFIM instrument and CPCHILD™ cover most aspects of ICF model for CP except the personal aspect. Other disease specific instruments for CP such as CP QOL cover all domains so should be considered in further studies.
4.5 Conclusions

This study defines the health related quality of life and functional outcomes for a cohort of 75 patients with CP who have received intrathecal baclofen. Four main findings emerge from this study:

Firstly, intrathecal baclofen can change and enhance health related quality of life and functional status, even though the former has a greater responsiveness than the later.

Secondly, the pre-implantation cognitive state and absence of orthopaedic deformity are predictors of functional response to ITB therapy.

Thirdly, controlling comorbidities such as epilepsy would enhance the impact of the ITB therapy on HRQOL.

Fourthly, the pre-operative functional state is correlated with improved communication and social participation in disabled children, which could facilitate their integration in society.

In future investigations, it might be possible to examine more closely the effect of ITB therapy on cognitive states and also the relationship between cognition and physical function. Large randomised controlled trials using the tools applied in this study could provide more definitive evidence and this data could be used to calculate the power of such studies.
5 Chapter Five: General Discussion and Further Work
5.1 Introduction

This thesis addresses the results of studying one of the largest cohorts of children who received intrathecal baclofen (ITB) therapy for spasticity and dystonia, mainly as a consequence of cerebral palsy (CP), but also for some other indications. This patient group was characterised by being consecutive as it included all children presenting to Nottingham University Hospitals (NUH) between 1998 and 2011. All the patients were from a single tertiary centre, more than 90% of them had CP as the indication for ITB therapy, and lastly all of the patients were screened, operated on, and followed up by one neurosurgeon (MHV).

I retrospectively studied the safety and efficacy of the ITB therapy aiming firstly, to audit ITB service performance at NUH, and secondly to determine the effect of using ITB therapy.

5.1.1 ITB therapy and impact on NHS practice

This thesis was conducted as an audit. A Cochrane review stated that an audit can develop the practice of health care professionals (527, 528). Furthermore, it helps the physicians to implement evidence based medicine and optimise health care interventions regularly in the face of increasing pressure to justify treatment costs (260, 527).

The main aim of this study was to evaluate our selection criteria and complication rates against standards. The standard criteria were driven from NICE guidelines and Cochrane Database of Systematic Reviews.

In this cohort, the compliance with NICE guidelines selection criteria was 96%. In Only nine patients the age was below the recommended age of 4 years. NICE guidelines recommended that the child would need to be physically big
enough for implanting the ITB pump to be comfortably accommodated. However, the guidelines did not give a precise age at which an infusion pump should first be implanted. Rather, it pointed out that prescribers will use the drug’s summary of product characteristics (SPC) to inform decisions made with individual patients (113). According to SPCs of ITB, it is indicated in paediatic population aged ≥ 4 years with severe chronic spasticity of cerebral origin or of spinal origin (11, 529). Furthermore, the pump manufacturer (Medtronic Inc.) advised that safety and effectiveness in paediatric patients below the age of 4 years of age have not been established and children should have adequate body mass to accommodate the implantable pump for chronic infusion (324).

The aim of ITB implant in this young group (<4 years) was to prevent the progression of spasticity and its long-term consequences such as muscle contracture and fixed deformity. In this young group, deep infection was reported in two patients that required explanting the ITB device. One of them had experienced infection twice. The rate of infection in this group was 22% in comparison to 9.4% in the whole study cohort. In multivariate analysis, the lower age was found as a risk factor for ITB infection. Early implantation of ITB in children below the age of 4 years had been reported in previous studies (5, 6). Albright et al. have implanted ITB pump into few children younger than 4 years of age including a 9-month-old, 18-lb infant who suffered from severe spasticity (164). Although the ITB procedure should not be the standard modality in children below the age of 4 years, the decision to do otherwise should come ideally from a multidisciplinary team with expertise in all of the various treatment modalities. This decision should take in consideration the child size and the suitability to other treatment options. A re-audit to evaluate
the compliance with the selection criteria is therefore advised to make sure that this recommendation is implemented in routine practice.

Secondly the complication rate associated with ITB therapy in NUH was in accordance with the published figures in Cochrane Database of Systematic Reviews. This study was the first to audit ITB practice at NUH and the complication rate is considered as benchmarking for future evaluation in monitoring of the service. It is also a quality assurance tool that indicates that the outcome is similar to other ITB service providers.

5.1.2 Usefulness of long-term follow-up of this cohort

This study presented outcome data associated with a median follow-up of 4.02 years. A longer follow-up period will help in evaluating the sustainable effect of ITB therapy and compare the outcomes of ITB treatment over variable lengths of time.

Other advantages of a longer follow-up may include:

- It could provide detailed understanding and evaluation of the relationship between risk factors and the development of adverse events of ITB treatments over different lengths of time (1).
- The effect of ITB on the overall survival of children with CP can only be evaluated through a lifelong follow up of this cohort. Furthermore, such follow-up data would allow a comparison between the prognostic effect of ITB treatment and other therapeutic modalities in CP (530).
- It might demonstrate if the ITB intervention affects the natural history of the disease e.g. evaluating scoliosis progression in quadriplegic spastic CP after long-term insertion of ITB pumps (240, 242, 243).
It would demonstrate the long-term durability and safety of ITB therapy, in addition to long-term patient satisfaction (531).

It would allow more a realistic estimation of the relative costs and benefits of ITB intervention (532). Saulino et al. evaluated the long-term economic effects of intrathecal baclofen (ITB) based on costs of care before and after implantation and concluded that patients receiving ITB would expect to experience a reduction in cumulative future medical costs relative to anticipated costs in the absence of a pump implant (533).

Certain outcomes could be related to other variables over time such as changes in body composition and body weight (323, 534, 535).

5.1.3 ITB and selective dorsal rhizotomy for treating spasticity in children

ITB therapy is an expensive intervention, however many studies have shown its cost effectiveness. In a study from the UK about the cost-benefit ratio of ITB in severe spasticity, the authors concluded that the cost per QALY lies in the range of £6900 to £12800; which was considered to be acceptable in the context of other NHS funded interventions (245).

Nevertheless, there has been a re-introduction of selective dorsal rhizotomy as another modality for treating spasticity. Few studies tried to compare the effectiveness of both modalities (536, 537). However, these comparative studies have been performed before the release of NICE guidelines of indications and contraindication of both modalities. NICE guidelines produced in July 2012 clearly recommend considering ITB therapy for children and young people who typically have: moderate or severe motor function problems (GMFCS level III, IV or V) and bilateral spasticity affecting upper and
lower limbs (quadriplegic child) (11). On the other hand, they consider selective dorsal rhizotomy to improve walking ability in children and young people with spasticity at GMFCS level II or III with pure spasticity in lower limbs. NICE guidelines give predominant dystonia, athetosis, ataxia, and severe cognitive delay, severe scoliosis or hip dislocation, as exclusion criteria for SDR surgery (113).

5.1.4 Clinical distinction between dystonic cerebral palsy and primary dystonia
The motor dysfunction in children with CP is not simply attributable to spasticity or corticospinal tract dysfunction but also, it might include disruption of the complex integration of multiple areas of the brain such as the cortex, cerebellum, basal ganglia, and brainstem. Thus, a child with CP may manifest other kinds of hypertonia and movement disorders such as dystonia and ataxia. It is becoming increasingly apparent that mixed movement disorders are more common than isolated pure spasticity or dystonia (538). Once one type of movement or tone abnormality is treated, another underlying movement may become more apparent (539). Therefore, selecting and evaluating appropriate treatments for children with CP has been challenging, due to difficulty in identifying the presence and importance of coexisting motor disorders e.g. dystonia, athetosis, and ataxia (540). Albright et al. stated that dystonia is frequently misdiagnosed to the extent that it is common for a child to be referred after a selective lumbar rhizotomy with a diagnosis of “recurrent spasticity” when, in fact, the child has undiagnosed dystonia (541).

Dystonia is defined as “a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements,
abnormal postures, or both ”(542, 543). Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation (544).

Types of dystonia
There are numerous systems for the classification of dystonia. Considering the underlying pathological process, dystonia may be defined as:

(i) Primary dystonia which occurs in patients who have no signs of structural abnormality in the CNS. Tremor may or may not be present.

(ii) Dystonia plus syndrome which occurs when dystonia is combined with other pathological changes (these include dopa-responsive dystonia and myoclonic dystonia) (545).

(iii) Secondary dystonia is seen when there is a demonstrable structural or metabolic disorder e.g. dystonic CP.

Dystonia, like other movement disorders in children, are more often secondary than primary, and more often associated with lesions of the brain such as those of CP (541).

Lin et al. systematically reviewed the characteristics of the dystonia in 279 children who were referred for possible DBS or ITB neurosurgical intervention. The results showed that 230/279 (77.4%) of the patients were referred due to secondary dystonia, 30/279 (10.7%) were primary dystonia, and 19/279 (6.8%) were dystonia-plus syndrome. The dystonic CP was the main cause of secondary dystonias (150/230) 65%, and spasticity coexists with dystonia in one third of this group (79/230) 34.3% (335).

Dystonic CP is the second most common type of CP after purely spastic forms (546), affecting 15%-20% of patients with CP (547). It is usually bilateral, and abnormal movements and postures, mostly begin after the first year of life, and progress slowly over several years. In children with severe CP, dystonia
may be so profound and sustained that it manifests as hypertonia rather than abnormal involuntary movements (548). Although the brain insult that causes secondary dystonia does not progress in CP, it is clear that dystonia can worsen as the brain matures (549, 550).

Age of onset of dystonic postures in CP varies between 2 and 6 years. It is usually preceded by a period of developmental motor delay (544), and associated with impairments such as learning disability and epilepsy (32). Brain MRI demonstrates abnormal findings in about 80% of individuals with CP (551), which include abnormalities of the basal ganglia or thalamus abnormalities or both\(^99\) (546, 552).

On neurological examination of individuals with CP, dystonia is characterised by the presence of fluctuating hypertonia and/or involuntary postures and movements triggered by arousal, such as wakening from sleep, tiredness, and lack of sleep, cognitive tasks, emotional state; and physiological phenomena, such as hunger and temperature, tactile stimulation, or voluntary movement (553).

Primary dystonia is rare. The incidence of early-onset primary dystonia was estimated to range between 2 and 50 per million (554). Primary dystonia is not associated with other neurologic abnormalities apart from tremor and occasionally myoclonus (555). Primary dystonias are often attributable to a genetic mutation in the *DYT1* gene on chromosome 9q34 (556). This is characterised by: (a) a normal perinatal and developmental history, (b) no precipitating illnesses or exposure to drugs known to cause dystonia, (c) no

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\(^{99}\) The basal ganglia and thalamic lesions can be associated with the higher vulnerability of these regions because of high metabolic demand during the late third trimester of pregnancy or the perinatal period (546, 552).
evidence of intellectual, pyramidal, cerebellar, or sensory deficits, and (d) negative results of investigation for secondary causes of dystonia (especially Wilson Disease) (557).

Primary dystonia often begins in children 6 to 12 years old. It starts in one lower extremity as an involuntary foot deviation (usually plantar flexion and inversion) during walking but not at rest. It progresses slowly to affect the entire leg, then the other leg, and ultimately becomes generalised in 60-70% of patients. One tenth of patients develop segmental dystonia and only 25% remain focal. The early onset of dystonia, especially if it started in the legs, has more inclination to progress into generalised and severe dystonia (557-559). Importantly, Conventional or structural MRI studies in primary dystonia are normal (560).

The primary-plus dystonia category includes individuals with dopa-responsive dystonia (Segawa’s disease) and myoclonus-dystonia syndrome (561). The biotinidase and homovanillic acid levels are often low and the dopa decarboxylation may be disordered (562). Dystonia plus has a diurnal variation in 75% that worsens by the end of the day (563).

Dopa-responsive dystonia begins at 1 to 12 years of age, with a median onset at 6.5 years, presents most often with dystonia in a foot with gait changes, and then progresses to involve the entire body over the next few years (541).

Primary-plus dystonia may be associated with spasticity and may be misdiagnosed as cerebral palsy, although it is not associated with prematurity. In the series reported by Nygaard et al., 24% of patients with dopa-responsive dystonia had been misdiagnosed as having cerebral palsy (564). Dopa-responsive dystonia should be considered in any child who presents with dystonia or even spasticity of unknown aetiology as it responds dramatically to
L-dopa (541). Every child with dystonia or even spasticity who does not have a history consistent with CP (e.g., prematurity, intraventricular hemorrhage, perinatal hypoxia) should be given a trial of oral levodopa for 2 to 3 months to exclude the possibility of dopa-responsive dystonia (541, 565).

Other significant differences between primary and secondary dystonia:

Patients with secondary dystonia often have more dystonic posturing (that is, fixed dystonic postures), and the appearance of slow athetoid movements. However, those with primary dystonia have more frequently jerky clonic contractions. Also, dystonic tremor was observed in 60% of patients with primary and in only 24% of those with secondary dystonia (566).

Spontaneous remissions and the ability to suppress dystonic movement by sensory tricks can also help differentiate primary from secondary dystonias. Both phenomena were more frequently recorded in primary dystonia, confirming the suggestion that they are typical for its clinical course (566).

The presence of dystonia at rest suggests a secondary form of the disease (566).

Intelligence and cognitive functions are preserved in primary dystonia. In contrast, patients with secondary dystonia caused by focal lesions may have serious cognitive impairments and intellectual deficits (567).

Recommendations:

It is important not to dismiss dystonia in a child with CP without appropriate investigation. To make a diagnosis of primary dystonia, known causes of dystonia must be excluded. Clues to the diagnosis of a secondary dystonia can be revealed with a thorough history and physical examination, neuropsychology assessment, imaging, and laboratory testing (557).
Structural brain imaging (MRI) is recommended as good practice for identifying secondary forms of dystonia, in addition to predicting the functional outcome of any neurosurgical intervention such as ITB or selective dorsal rhizotomy (SDR) in children with spasticity (560, 568, 569). Grunt et al. stated that the improvements after SDR are good in patients with no MRI abnormalities (569).

Genetic analysis is also suggested in those cases where no specific cause can be determined as several monogenetic diseases present with clinical features similar to CP (550).

Assessing the cognitive function in patients with childhood dystonia, by using standardised neuropsychological tools, is essential for establishing the diagnosis and selecting the appropriate intervention to the specific needs of individual patient (567).

Selective dorsal rhizotomy is not considered appropriate for children younger than 2 years of age because CP cannot be diagnosed with certainty in young children. In addition dystonia that is concomitant with spasticity becomes clinically apparent by the age of 5 years (118).

Clinicians may choose ITB and DBS for treating severe generalised dystonia in children with CP. ITB is often considered over DBS in the presence of severe hypertonia where the tonal patterns are mixed with the presence of both dystonia and spasticity. Further studies are required to evaluate the choice of ITB versus DBS in individuals with CP and severe generalised dystonia (553).

The topic would benefit from building consensus similar to the one completed through the National Institute for Health and Care Excellence (NICE), in order to establish a pathway for spasticity for children and young people (553).
5.1.5 Screening stage

The ITB practice in NUH includes a screening stage. In this cohort more than 90% had a positive response to a test dose. Recently, some experts in the ITB therapy raised a question about the benefits from ITB screening. Albright and Ferson reported that they no longer screen the patients before ITB therapy as practically all the patients respond well to a test dose (570).

At NUH, we advocate continuing with screening patients before implantation for the following reasons: firstly, it gives the children and their caregivers an idea about what to expect from ITB therapy. Secondly, the degree of response to the ITB test dose gives us an idea about the initial ITB daily effective dose required. Lastly, ITB therapy will require a long-term relationship between the patient and health service provider more than implantation of a pump and catheter system. It will include long-term follow-up and regular pump refills. Accordingly, the test dose, the child’s response, and parents’ opinion are important components of the selection for this expensive drug delivery system.

5.1.6 Future clinical audit of baclofen withdrawal

While intrathecal baclofen therapy (ITB) is an established treatment for spasticity, complications can lead to loss of delivery and, accordingly, baclofen withdrawal. Since untreated withdrawal syndrome can be painful, or even fatal, prompt diagnosis and management of ITB withdrawal is essential (571). There is no established consensus on the definition of ITB withdrawal, representing an unmet need in the field of ITB practice. Moreover, identification of withdrawal syndrome is very difficult in patients with cerebral palsy (207), especially if they present to a clinician who is unfamiliar with ITB therapy (206).
Loss of efficacy usually presents either by: a) return of pathologic tone following adequate spasticity control on stable ITB dosing, or b) inability to optimise ITB therapy despite adequate dose escalation (571).

Medtronic, Inc emphasised the importance of observing the warning signs of ITB under-dose as it can be a result of ITB device malfunction. These warning signs include increase or return of spasticity, itching, low blood pressure, lightheadedness, and tingling sensation. These symptoms are often early signs of baclofen withdrawal (572).

Baclofen withdrawal syndrome covers a wide spectrum of signs and symptoms with a variable degree of intensity (205, 571). Future audit is required to establish the actual incidence of intrathecal baclofen withdrawal. A consensus; standardised definition of withdrawal syndrome and its manifestations, is required to help in planning a prospective study in multicentre or national clinical audit of outcomes.

This audit should aim to evaluate the ITB patients by on-going and consistent clinical assessment to optimise the patient’s response to ITB therapy and to early detect recurrence of spasticity early. An expert panel, who were managing more than 3,200 ITB patients, suggested subjective, objective, and goal achievement assessments during routine refill visits (351).

- Subjective assessments: by asking the patient about variations in spasticity control, ease of care, comfort, and potential adverse effects. Various scales, such as the Care and Comfort Caregiver Questionnaire (442) or the Spasticity Visual Analog Scale (351, 573) can be used to quantify patients subjective opinion (351).
- Objective assessments: by regular and consistent clinical evaluation of spasticity (using Ashworth Scale), muscle stretch reflexes, clonus, muscle strength, range of motion, quality of gait, and transfer abilities (351).

- Goal Attainment: by using measures such as the Canadian Occupational Performance Measure and Goal Attainment Scale (351, 574, 575).

Such regular assessment should be able to detect any suboptimal ITB therapy in patients who were previously had well-controlled spasticity. These patients should be examined carefully (205). The examination should start in an approach similar to all medical assessments: a targeted medical history, a focused physical examination, and use of radiologic/laboratory testing, as well as telemetry data derived from the pump programmer (205).

Saulino et al. categorised the wide spectrum of baclofen withdrawal symptoms into three levels: mild, moderate and severe (205).

Mild ITB withdrawal (incipient withdrawal), presents with increased muscle tone following adequate spasticity control on stable ITB dosing, pruritus without rash, and irritability (205). As pruritus is a frequent symptom after ITB withdrawal, it can be considered as an early predictor of a malfunctioning pump system, and can differentiate between increased spasticity resulting from drug tolerance or irritating factors (pressure ulcers or urinary tract infection) (576).

Moderate withdrawal syndrome includes return of pathologic tone, altered mental state, mild dysphoria, elevated creatine phosphokinase level, hypotension, paraesthesia and fever (205).
Severe or established withdrawal presents with severe increase in muscle tone, stupor and coma, rhabomyolysis, elevated creatine phosphokinase level, and seizures (205).

ITB withdrawal should be also differentiated from other syndromes with similar symptoms such as autonomic dysreflexia, malignant hyperthermia (MH), and neuroleptic-malignant syndrome (NMS) (207).

Autonomic dysreflexia\(^{hh}\) occurs in patients with spinal cord injury (SCI) above the level of the major splanchnic outflow (T6 level or higher). It presents with paradoxical bradycardia with hypertension, absence of fever, lack of exaggerated rebound spasticity, and a normal level of consciousness (577). Signs of Piloerection and cutaneous vasoconstriction are present below the level of injury, whereas vasodilation and perspiration appear above the level of injury (578). Autonomic dysreflexia could overlap with ITB withdrawal. The cessation of oral or ITB in such individuals causes a return of spasticity that can provoke an episode of autonomic dysreflexia (579). However, the patient’s vital signs (tachycardia and hypotension), mental state (delirium), and severe degree of spasticity is the characteristic of the withdrawal syndrome and differentiate it from autonomic dysreflexia (579).

Malignant hyperthermia (MH) is a familial disorder caused by a mutation in ryanodine receptor gene causing a defective in calcium-release channel of the sarcoplasmic reticulum (SR) membrane (580). Certain anaesthetics, especially halothane, cause calcium leakage from the sarcoplasmic reticulum

\(^{hh}\) Autonomic dysreflexia is caused by loss of supraspinal sympathetic control. Any non-specific stimuli below the level of injury (for example, bladder distension, rectal manipulation, painful stimuli to the skin) can induce excessive sympathetic spinal outflow below the level of lesion, which causes the cardiovascular changes (Bradycardia, sometimes followed by tachycardia Hypertension) (577).
in affected individuals resulting in sustained, rigorous muscle contraction associated with high fever. If not treated promptly with dantrolene, MH can progress to rhabdomyolysis, multiple organ failure, and death. Laboratory evidence of disordered calcium metabolism and the occurrence of previous episodes in family members strongly suggest MH. A muscle biopsy can sometimes establish the diagnosis and differentiate it from Baclofen withdrawal (581).

Neuroleptic-malignant syndrome (NMS) consists of high fever, muscular rigidity, and potentially life-threatening autonomic hyperactivity. It is precipitated by the commencement of dopaminergic antagonist drugs (e.g. haloperidol) or the withdrawal of dopaminergic agonists (e.g. levodopa, bromocriptine) (582). Treatment consists of administering a dopaminergic agonist (bromocriptine, amantadine, levodopa) in combination with intravenous dantrolene (207).

5.1.7 Future study of care givers quality of life
Looking after a child with disability is challenging both physically and psychosocially given that such disability usually spans the course of a child’s life, exceeding typical child development needs and parents, as well as families are not at all prepared for it (525).

Caregivers of children with CP may be under more physical, psychological, and financial burdens compared with those who provide care for children who develop in a typical manner because their responsibilities are greater. In addition to providing direct daily care and support, the caregivers of children with CP invest time and effort in assisting with interventions such as physical, occupational, and speech therapy (524). These burdens can be associated
with an impairment of caregivers’ physical and psychological health. A considerable research has been published on high levels of caregiver burden which show that caregivers of children with disabilities are more likely to experience depression and distress (583), poorer general emotional health and feel pessimistic about the future (584). They also feel that their caregiving prevents them from taking time for themselves (33, 34, 585, 586).

Onses et al. evaluated the quality of life and psychological aspect in mothers of children with CP, and concluded that their quality of life is significantly lower than their peers (521). This result was also supported by Eker and Tuzun who demonstrated that mothers of children with CP have poorer QOL than mothers of children who had a minor health problem (587).

Children with CP have more sleep problems than typically developing children. Recent studies have shown that mothers of children with CP also experience impaired sleep because they may encounter more frequent night disruptions related to their child’s sleep (588). In addition, poor sleep quality in mothers of children with CP is commonly reported and has been significantly associated with high levels of maternal stress difficulties (588), depressive symptoms (589), and poor psychological well-being (590).

The ICF framework emphasises the environment as critical to health and well-being. This framework highlights the important relationship between the health of the caregiver and the health of the child (34). In addition, there has been a shift in health care service delivery away from child-centred models that focus primarily on treating the disability toward family-centred services and family-centred well-being. This shift recognises the primary role of the family in child development (591, 592).
Physicians and other health care professionals should be aware of the significant association between child disability and caregiver health and QOL. Future work should address the extent to determine whether intrathecal baclofen therapy among children with CP is effective in reducing caregiver burden in parallel to its effects on their children, in order to clarify if there is an association between parents' QOL and children's well-being. This work will also assess the impact of ITB intervention on caregiver's work productivity, and to evaluate if it decreases the healthcare costs for the caregiver (34).

Several quality of life instruments could be used to assess the caregivers' QOL which include:

1-Care and Comfort Caregiver Questionnaire (CareQ)
CareQ was developed to measure difficulty of care experienced by caregivers of children with moderate to severe functional limitations due to CP. The CareQ also eases the communication between the caregiver and the clinician in setting therapeutic goals for the child (524).

2-The Coping Health Inventory for Parents (CHIP) is a well-recognised measure of coping among parents of chronically ill children (525). It is an appraisal of caregivers’ cognitive and behavioural efforts to manage the demands of a stressful situation and coping responses to management of family life (525).

3-The Measure of Processes of Care (MPOC) is a well-validated and reliable self-report measure of parents' perceptions of the health services they receive along with their children from children's rehabilitation treatment centres. It is a way to assess family-centred behaviours of health care providers (526).
4-Pittsburgh Sleep Quality Index (PSQI) provides caregiver ratings of their own sleep. It is a self-report questionnaire that assesses sleep quality over a 1-month time interval (593).

5-The modified caregiver strain index (MCSI-13) is an ordinal scale, used to identify families with potential care-giving strain (594).

5.1.8 Intrathecal therapy uses and future prospects

There is still a major challenge for the treatment of several central nervous system (CNS) disorders such as recurrent brain tumour, multiple sclerosis and Hunter syndrome\(^\text{ii}\) (595). This challenge is related to the absence of convenient and effective methods of delivering the required medications. The two main routes of direct drug delivery to the CNS are intrathecal and direct intra-ventricular (IV) injection. These methods of drug delivery allow direct drug administration to the CSF by circumventing the blood-brain barrier, therefore allowing delivery of smaller drug doses. This consequently reduces the occurrence of side effects compared with systemic routes of drug administration, e.g. oral, intravenous and epidural. Continuous intrathecal infusion therapy is established in the treatment of intractable spasticity and chronic pain by implanting programmable infusion pumps (166, 596). IV therapy has also been tried unsuccessfully to deliver the glial cell line-derived neurotrophic factor (GDNF) for treatment of Parkinson’s disease (597). However, intraventricular baclofen was found effective and safe treatment for intractable dystonia (337).

Intrathecal injection of chemotherapy agents like methotrexate, cytosine-arabinoside and thio-TEPA were introduced as treatment options for brain

\(^{ii}\) Hunter syndrome is a rare inherited lysosomal storage disorder resulting from a deficiency of iduronate-2-sulfatase (I2S) (595).
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tumours including lymphoma (598), leptomeningeal medulloblastoma relapse(599), and leptomeningeal metastases (LM) (600). The intrathecal chemotherapy could be infused either by Ommaya reservoir or, if only a few injections are necessary, it can be injected via a lumbar puncture (601). However, continuous intrathecal programmable pumps are not currently used for chemotherapy, possibly due to the short treatment duration or due to poor prognosis of this patient group.

Prager et al. suggested using external infusion pumps to be connected with subcutaneous tunnelled catheters to the intrathecal sac for the delivery of pain control medication. They stated that external infusion pumps are cost-effective when life expectancy is a matter of weeks to months, but a fully implanted pump is economical if life expectancy is longer than 3 months (602). The value of using continuous infusion pumps for treating CNS disorders is a topical issue for future research.

5.1.9 Introduction of a new clinical procedure, intervention or technique. The clinical care of patients evolves continually through developments in equipment, investigation and procedures. This development will necessitate clinicians to introduce new approaches of treatment and new interventional procedures. Patients and their families need to be assured that their treatment is up to date and effective. Professional self-regulation gives health professionals the ability to set their own standards of professional practice, conduct and discipline. However to justify this freedom and maintain the trust of patients and their families, the professionals must be openly accountable for the standards they set and the way these are enforced.
The NICE has been given the responsibility for managing the UK “National Interventional Procedures Programme (NIPP)” which assesses the safety and efficacy of new interventional procedures. The programme’s aims are to protect the safety of patients and to support doctors, other clinicians, Clinical Governance Committees (CGC), healthcare organisations and the NHS as a whole in managing clinical innovation responsibly (603).

From 13\textsuperscript{th} November 2003, medical practitioners planning to undertake new\textsuperscript{ii} interventional procedures\textsuperscript{kk} should seek approval from their NHS Trust and CGC before doing so. The Chair of the CGC should notify the new procedure to the NIPP at the NICE unless it is already listed there. In case where the procedure has to be used as an emergency, the procedure should be notified to the trust CGC within 72 hours. The committee will consider approval of the procedure for future use as above. The only exception to the process is when the procedure is being used only within a protocol approved by a Research Ethics Committee (REC) (603, 604).

If there no available guidance from NICE on the procedure, the Committee should only approve its use if:

1. The doctor has met externally set standards of training.

2. All patients offered the procedure are made aware of the special status of the procedure and the lack of experience of its use. Patients also need to recognise that the procedure’s safety and efficacy is uncertain and be

\textsuperscript{ii} An interventional procedure should be considered new if a doctor no longer in a training post is using it for the first time in his or her NHS clinical practice (603, 604).

\textsuperscript{kk} HSC2003/011 defines an interventional procedure as one used for diagnosis or treatment that involves incision, puncture, entry into a body cavity (beyond the oropharynx), electromagnetic or acoustic energy (603, 604).
informed about the anticipated benefits and potential adverse effects of the procedure, and any other alternatives, including no treatment.

3. The Committee is satisfied that the proposed arrangements for clinical audit are sound and will capture data on clinical outcomes that will be used to review continued use of the procedure.

When NICE is collecting data under this Programme, doctors should supply the information requested on every patient undergoing the procedure. NHS Trusts are encouraged to support this to enable the NHS to have access more speedily to guidance on the procedure’s safety and efficacy. The collection of data from patients will be governed by the Data Protection Act (603, 604).

If an adverse incident occurs in association with a new interventional procedure, this should be reported to the National Patient Safety Agency via the national reporting and learning system for adverse events to be implemented across the NHS (603, 604).

Duties and Responsibilities

Individual clinicians have the responsibility to determine if there is existing NICE guidance for the proposed procedure. If there is an existing guidance, then the proposal should comply with this guidance. They should also provide information on the intended new interventional procedure including the rationale for the development, intended benefits, and potential risks. Further, resource implications, information that will be provided to patients, and methodology to audit clinical outcome should also be provided. In addition, it is imperative to provide information on how the clinician will be trained and assessed as competent in the new interventional procedure including information on the external standards for training (603, 604).
Clinical lead and responsible managers have the responsibility to review the
information provided by the clinician about the proposed new interventional
procedure, to clarify if the proposal complies with NICE guidance if this exists
for the procedure in question. Moreover, they have to assess the requirement
for the proposed procedure and also evaluate any resource implications within
the health organisation or the Trust e.g. any impact on other services such as
diagnostic or imaging services.

If the Clinical lead and responsible managers support the proposed new
interventional procedure, the proposal should be forwarded to the Medical
Director for support prior to consideration by the Clinical Governance
Committee (603, 604). The Clinical Governance Committee will have
responsibility for the formal approval of any proposed new interventional
procedure before it is introduced. If the procedure is entirely novel, the Clinical
Governance Committee should notify the procedure to the Interventional
procedures Programme at the NICE website (603, 604). If the interventional
procedure is approved by the Clinical Governance Committee then the
clinician must register and undertake an audit of the effectiveness and
outcomes of the new interventional procedure. Auditing the new procedure is
to collect and report outcome data on all patients who undergo the procedure.
The Clinical lead must ensure that an audit programme is in place to obtain
information on clinical outcomes, to continually review the procedure and to
obtain information on any adverse outcomes (603, 604).

Importantly, NICE will collect data on the procedure via the Interventional
Procedures Programme. Clinicians should supply the information requested
on every patient undergoing the procedure. The collection of data on patients
will be governed by the Data Protection Act (603, 604).
5.1.10 ITB tolerance

Although ITB is safe and effective in the majority of patients, tolerance has been reported in approximately 10% of patients during long-term treatment (303, 605). Tolerance is defined as the condition requiring gradual dose escalation of the ITB to obtain the same therapeutic effect. This physiological tolerance usually occurs in the first few months of ITB delivery and normally stabilises within the first year following pump implantation. However, in some cases of long-term baclofen infusion, a decreasing effect is seen, which persists even with progressive dose increment (606).

There is insufficient experience to establish clear guidelines for the management of baclofen tolerance. However, “a drug holiday” has been used to treat ITB tolerance. During this holiday, the baclofen infusion is gradually reduced and stopped over a two-week period, substituting it with an alternative method of spasticity management. After the drug holiday, the sensitivity to baclofen may be resumed and ITB may be restarted at the initial continuous infusion dose (607, 608).

Tolerance to ITB could be due to continuous persistent binding of GABAβ receptors by baclofen leading to down regulation of the GABAβ receptors (202, 609). However, the precise mechanism by which tolerance develops remains unexplained. It may be due to genetic variation in GABAβ receptor isoforms or variation in the processes of baclofen metabolism (321). This area could be a valuable focus for future experimental investigations.

Heetla et al. successfully treated four patients with ITB tolerance by switching the infusion mode to a six times bolus regimen per day instead of continuous infusion (394).
Considerably more research will need to be performed to establish the effects of bolus infusions of ITB. It would be interesting to compare bolus infusions with continuous infusion in a randomised controlled trial, looking for differences in the incidence of tolerance between these two infusion modes.

5.1.11 The relationship between cognition and ITB

Over the last two decades, prior studies have indicated that GABAβ receptor agonist (baclofen) might impair learning and memory in animals, whilst GABAβ antagonist improves cognitive processes (610, 611). In contrast to these earlier findings, recent studies have reported the baclofen effects to mediate neuroprotection and neuroplasticity (612, 613). Li et al. demonstrated that activation of GABAβ receptors ameliorates cognitive impairment in rats with chronic cerebral hypo-perfusion (614). They also showed the regulative effects of GABAβ receptor activation by baclofen, to reverse the neuronal damage and cognitive impairment induced by chronic cerebral hypo-perfusion, via mediating neuroprotection on hippocampal CA1 neurons (612).

Cognitive impairments in children with CP make evaluation of cognition difficult in this population. They are often misinterpreted as being impaired even when they may have typically developing cognition. Therefore, it is important that any spasticity treatment should not induce nor worsen existing cognitive impairments (616). Ayyangar et al. examined the cognitive effects of ITB in 14 children with CP in a prospective pilot study. They used three

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Il The CA1 Pyramidal Neuron is found in the CA1 region of the mammalian hippocampus in the medial temporal lobe. "CA" refers to cornu Ammon, latin for Ammon's horn (so named for the shape of the hippocampus). The neurons in the CA1 region provide a significant output pathway from the hippocampus, which plays an important role in long-term memory and spatially related tasks. CA1 pyramidal neurons, in particular, are thought to be critical to object differentiation in long-term memory (615).
different cognitive measures to cover a wide range of cognitive functions. They reported that cognitive function remained stable from baseline to implantation state with some improvement being noted in cognitive function such as choice reaction time \(^{mm}\) (616, 617). A presumed mechanism of enhancing the cognition in children with CP after treatment with ITB could be related to the reciprocal relationships between sleep, pain and cognition (618-621).

Sleep disturbances, is a common problem in children with CP (21). These disturbances include: difficulty in initiating and maintaining sleep, sleep wake transition, sleep breathing disorders, sleep bruxism\(^{nn}\) (622), excessive daytime sleeping, nightmares and sleep talking (21, 623-627). Needless to say, sleep is a necessary element of human life, and is essential for good mental health development (628). Many studies reported the crucial role of sleep in brain maturation and in the development of important cognitive functions, such as memory consolidation and learning (629). Kurdziel and co-workers reported that classroom naps consolidate learning in preschool children by improving memories acquired earlier in the day (630).

It is optimal for infants to get 14 to 15 hours of sleep a night, for toddlers to receive 12 to 14 hours, for pre-schoolers to obtain 11 to 13 hours a night, and school-aged children to get 10 to 11 hours per night (631, 632). Sleep deprivation has been reported to have a negative impact on cognitive functions such as cognitive speed, executive attention, working memory, and

\(^{mm}\) Choice Reaction Time evaluates general alertness and motor speed. It is the time elapsed between presentation of several possible stimuli and the beginning of one of several possible responses (617).

\(^{nn}\) Sleep bruxism (SB) is defined as a parafunctional behaviour of the mandible, characterized by clenching and/or grinding of the teeth (622).
social development (628, 633). Reciprocally, other studies have found that the degree of cognitive impairment could be a risk of increased sleep disturbances in children with CP (634, 635). The neurophysiological basis of the association between sleep and cognition is poorly understood. However, functional MRI studies have demonstrated that neural systems involved in executive function (i.e. prefrontal cortex) are more susceptible to sleep deprivation (636, 637).

While there are many factors related to CP that can interfere with sleep such as spasticity, dystonia, epilepsy and seizures. However, pain is reported to be the strongest contributing factor to sleep disturbances in children with physical disabilities (618, 638). Similarly, sleep deprivation was found to increase pain experience (639). Chronic pain has psycho-social implications for children with CP such as interference with the sleep (640), negative effects on their social participation (641, 642), and less quality of life in comparison to their peers who are not suffering from pain (643). Interestingly, cognitive performance has been frequently report to be decreased in chronic pain and to be improved after pain relief (644-646).

Chronic pain affects cognitive areas such as attention, learning and memory, speed of processing the information psychomotor ability and executive function (645-648).

Pain is an intrinsically attention demanding sensory process. Dick and colleagues reported a significant disruption of attention associated with impaired working memory by chronic pain (646). It was proposed that a high level of pain interferes with attentional processes during the completion of demanding tasks (649), and also interferes with information processing and retention of information (650). Brain areas constituting the network for
perception of pain include: primary and secondary somatosensory, insular cortex, anterior cingulate cortex, thalamus, and prefrontal cortex. The periaqueductal area, basal ganglia, cerebellum, amygdala and hippocampus were also found involved during pain process (651). This pain perception network has also critical role in cognitive process. (621, 652).

Other studies found a decrease of grey matter volume in pain-processing structures in chronic pain patients in comparison to healthy subjects (653-655). A grey matter loss could be a feature of cognitive status decline especially in speed of information processing and executive functions (621, 656).

Previous research has established that ITB reduces pain in children with CP, in addition to significantly reducing muscle tone which consequently improves the quality of life and facilitates ease of care (225, 461, 463, 657, 658). Moreover, Ramstad et al. reported a significant improvement in the frequency of night-time awakening along with objective severity of pain within 6 months following the implantation of an ITB pump (659). Similar results have been reported by Jan et al. who noticed an improvement in sleep quality and quantity after treating spasticity with ITB (660).

Baker et al. reported improvement in the comfort in children with CP after implanting ITB pump (661). In a randomised controlled trial by Hoving and co-investigators, reported a significant improvement in the domains of pain and discomfort; mental health; and psychosocial status after six months of ITB administration compared with the control group (259). These results are consistent with the finding of our study, which shows the most significant improvement after treatment with ITB was in the comfort and emotions domain. This domain assesses the pain and discomfort during day and night.
activities e.g. during sleep, in bed, while seated or transferring; sadness and agitation (443). Previous studies have recommended that more comfort and painless times could enhance the cognition (649, 650). Accordingly, more research is warranted for better understanding the cognitive effect of ITB.

5.1.12 The role of neuropsychologists and occupational therapists (OT) in future ITB clinical practise

The intellectual disability (ID) is defined as impairment in “general mental abilities such as reasoning, problem solving, abstract thinking, judgment, planning, and learning from experience,” with a guideline of an IQ score of ≤ 70 (662).

IQ is critical for independent participation in core activities such as education, self-care, and living independently (663). Patients with intellectual disability are characterised by a decline of socialisation functions; and difficulty in adaptation to the environment (664).

It has been reported that between 34% and 64% of children with CP have an intellectual disability (intelligence quotient, IQ < 70) (665). These data were based on different methods such as :(a) presumptions from clinical observation, from cognitive description provided by parents; (b) application of developmental scales; or (c) through formal IQ evaluations which are based on psychometric tests (666).

However, the paediatric IQ assessments are generally evolved for, and standardised with, typically developing children who do not have any physical impairments. As IQ scales require both verbal and manipulative responses, it will be difficult to apply them to children with CP (663). This lack of an
established objective assessment for people with CP may lead to over- or underestimation of their real intellectual ability.

In this study, the cognitive function was divided into three categories according to the assessment provided by the referring paediatrician. Importantly, a neuropsychologist involvement, in pre and post implantation assessment, is recommended to provide an objective quantification of the children’s cognitive function to establish a pre-implantation baseline of neurocognitive status. This benchmark will help tracing any changes in cognitive function through post-implantation follow-up and to disentangle which factors may account for post-implantation outcomes.

Neuropsychologists could help in selecting tests, modifying test administration to accommodate disability, and interpreting results from non-standard test administration. The most widely used tests by neuropsychologists in the field of CP are the Raven’s Coloured Progressive Matrices (RCPM) and the Peabody Picture Vocabulary Test (PPVT). A more thorough and detailed assessment of cognitive function by a neuropsychologist, will not only clarify efficacy of ITB on the cognitive function but also will help to identify the most suitable instruments for creating an individual learning programme. The inappropriate evaluation of the child's competence, may lead to inappropriate goals being set. Similarly, there is a risk of under evaluating a child's performance without checking basic abilities and without using suitable aids to compensate for the motor and communicative deficit. Thus, the importance of knowing a child's real abilities in the various cognitive areas is imperative in order to plan an adequate
rehabilitation programme that identifies objectives which can be attained (666-668).

Occupational therapists (OT) focus on assessing and developing an individual’s ability to function day-to-day to their highest level in normal daily activities at home, in school, out in public, and at work. The goal is to encourage the development of independence, productivity, and self-care. OT will help a person improve strength, dexterity, and coordination while performing tasks. Moreover, they will also help in decision-making, abstract reasoning, problem solving, perception, memory, and sequencing (669).

For children with CP, occupational therapy can help with muscle and joint coordination problems that can make everyday tasks difficult. Some of these tasks include eating, brushing teeth and bathing. OT can help to improve physical, cognitive and social abilities, as well as fine motor skills and posture. This therapy can also help address difficulties with processing sensory information (670, 671).

Parents and caregivers spend extended periods of time helping children with cerebral palsy in performing basic day-to-day activities. OT can help parents and care givers through reducing the demand on them, providing a sense of security and enhancing their quality of life by improving the CP child is independence (671-673).

Each child’s occupational therapy treatment plan is highly individualised and tailored to their individual physical, intellectual and social-emotional abilities (671). Occupational therapist should be involved in ITB assessment process, where he/she could perform a complete evaluation before ITB implantation.
This includes testing the child’s fine motor, perceptual and oral-motor development, and observing how the child responds to touch and movement. The occupational therapist will also interview the parents to find out about the child’s strengths and weaknesses while performing daily activities in order to set a postoperative learning and rehabilitation plan based on each child needs and abilities (669, 671-673).

OT could also evaluate the child post-ITB implantation and periodically during the follow-up period to modify the OT treatment plan based on progress and response to ITB therapy (669, 671-673).
6 References

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