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Title Page

Intrathecal baclofen therapy in paediatrics: A study protocol for an Australian multi-centre, 10 year, prospective audit

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Abstract

Introduction: Increasing clinical use of Intrathecal baclofen (ITB) in Australian tertiary paediatric hospitals, along with the need for standardised assessment and reporting of adverse events, saw the formation of the Australian Paediatric ITB Research Group (APIRG). APIRG developed a National ITB Audit tool designed to capture clinical outcomes and adverse events data for all Australian children and adolescents receiving ITB therapy.

Methods and analysis: The Australian ITB Audit is a 10 year, longitudinal, prospective, clinical audit collecting all adverse events and assessment data across body functions and structure, participation and activity level domains of the International Classification of Functioning, Disability and Health (ICF). Data will be collected at baseline, 6 and 12 months with ongoing capture of all adverse event data. This is the first Australian study that aims to capture clinical and adverse event data from a complete population of children with neurological impairment receiving a specific intervention between 2011 and 2021. This multi-centre study will inform ITB clinical practice in children and adolescents, direct patient selection, record and aid decision making regarding adverse events and investigate the impact of ITB therapy on family and patient quality of life.

Ethics and dissemination: This project was approved by the individual Human Research Ethics committees at the six Australian tertiary hospitals involved in the study. Results will be published in various peer reviewed journals and presented at national and international conferences.

Strengths and Limitations of this study

- A whole population based study on the short and long term effects of intrathecal baclofen therapy in paediatrics
- Data collection of outcomes across all domains of the International Classification of Functioning, Disability and Health (ICF)
- National registry of ITB therapy adverse events for the ongoing evaluation of safety and efficacy
- The study cohort was limited to age 16 years and younger as this enabled adequate data collection prior to transition to adult services in Australian hospitals

BACKGROUND

Disabling spasticity and secondary dystonia are common problems in chronic neurological conditions such as cerebral palsy (CP). Spasticity is the most common form of hypertonia seen in children with CP[1] and can be a significant problem for many paediatric patients with spinal cord injury and traumatic brain injury. Spasticity is a velocity-dependent resistance to muscle stretch that occurs when "resistance (to external movement) increases with increasing speed of stretch and/or resistance (to externally imposed movement) rises rapidly above a threshold speed or joint angle"[2]. This differs from dystonia which is characterised by involuntary muscle contractions cause repetitive movements and twisted postures[3]. In the clinical setting, severe spasticity and dystonia are often associated with pain, sleep disorders, feeding issues and difficulties with positioning, transfers, dressing and personal cares and reduced quality of life[4-6].

Development of Intrathecal Baclofen

Baclofen is a gamma-amino butyric acid (GABA) agonist. It acts upon the GABA-B receptors in the spinal cord to reduce abnormal muscle tone. Oral baclofen is a widely used oral medication to manage spasticity of cerebral or spinal origin. The effectiveness of oral baclofen is limited by its side effects such as sedation, confusion, and lethargy. Intrathecal baclofen (ITB) delivered by an implanted pump and catheter can work directly at the spinal cord level to reduce spastic tone through presynaptic inhibition. Because of direct delivery to the central nervous system, the required dose is less than 1% of that delivered orally.

ITB was first used in adult patients with spasticity of spinal origin[7]. Albright et al[8] demonstrated its efficacy for the management of spasticity of cerebral origin. In 2000 the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) published a systematic review of the literature on the treatment of spasticity in CP with ITB[9]. ITB is effective in the reduction of spasticity as well as dystonia and is frequently used to treat hypertonicity associated with CP. A recent Cochrane review concluded the effectiveness of intrathecal baclofen for treating spasticity in children with cerebral palsy is limited by small sample sizes and methodological issues[10].

The European consensus statement on the use of ITB therapy in paediatric spasticity recommends its use in children with CP, Gross Motor Function Classification System (GMFCS) Levels IV –V where spasticity interferes with patient's activities and/ or quality of life[11]. The authors cited Level 3-4 evidence in this population[9,12-15]. In addition to the long-term reduction of hypertonicity, authors have reported improvement in comfort, positioning, ease of care provision and motor function in select groups of individuals and a reduction in the anticipated need for orthopaedic surgery[14,16-18]. Progression of hip dislocation may be reduced with ITB, although the effect of ITB on the progression of scoliosis is controversial[19,20].

Complications of ITB Therapy

It is well recorded in the literature that ITB therapy has adverse events[21-30]. In a review of 430 consecutive patients implanted with an ITB pump at a single centre, Motta & Antonello[24] analysed the rates of major complications of ITB therapy requiring surgical intervention: CSF leakage, infection and catheter malfunction. Their results were consistent with others reported in the literature with 25% of patients experiencing major complications. The European consensus on the appropriate use

of ITB therapy in paediatric spasticity recommended procedures to reduce complications including omission of the ITB test and, particularly in young and small patients, subfascial rather than subcutaneous pump placement[11]. In addition, a key factor in improving outcomes for patients is treatment in a centre dedicated to providing ITB, by specialist physicians who have experience in this procedure.

Assessment of ITB in paediatric cohorts

Historically assessment of interventions, such as ITB in paediatric cohorts, have largely occurred at the Body Functions and Structures level of the ICF[31] and fail to address the main concerns of children and their carers[32]. A literature review of paediatric ITB studies in CP (n=19) revealed 15 studies utilised assessments at the Body Functions and Structures level of the ICF, the majority reporting Modified Ashworth scores[13,22,23,25,28-30,33-37] or dystonia scale scores[25,27,30,38-40]. Seven studies reported motor outcomes utilising the Gross Motor Function Measure[41] (GMFM)[13,25,33,35,42] or Melbourne 2[43,40] assessments and six studies reported goal outcomes using a variety of validated (n=2)[38,30] or internally designed (n=4)[13,14,22,23] goal setting instruments. Health related quality of life was addressed as an outcome measure in 13 studies but few utilised paediatric validated instruments and the majority reported on internally designed, non-validated questionnaires or parental interviews (n=13)[13,14,22,23,25,27,29,30,33,35,36,40,44].

ITB in Australia

Paediatric ITB therapy commenced in Australia in 1999 and is now an established intervention in comprehensive CP clinical management programmes at six tertiary paediatric hospitals in Australia.

In 2009 APIRG was convened with medical, nursing and allied health representatives from all the tertiary paediatric hospitals providing ITB therapy in Australia. The main purpose of APIRG was to establish an agreed national ITB assessment protocol and adverse events recording system. The comprehensive assessment protocol was based on the best available evidence regarding assessment tools across all domains of the ICF[31]. A national study was proposed as each centre implanted small numbers of ITB systems each year allowing a larger pool of information. This information would be available to guide future ITB intervention. Prospective collection of data would allow:

1. The use of a standardised assessment protocol - centres could collect more information if desired.
2. Evaluation of the safety and efficacy of ITB therapy via a centralised adverse events data collection system.
3. Collection of patient and carer satisfaction with ITB therapy.
4. Support benchmarking for individual centres against national data

METHODS AND ANALYSIS

A 10 year prospective multicentre clinical audit of all new patients commencing ITB therapy in Australia under the age of 16 years, between 2011 and 2021.

Study Population and Recruitment

All new patients, commencing ITB therapy in Australia under the age of 16 years are eligible for inclusion in the study. An upper age limit of 16 years was determined in order to allow sufficient data collection post pump implant prior to transition to adult services, which usually occurs at around age 18 in most Australian paediatric tertiary hospitals. The decision regarding suitability of

ITB therapy for individual patients is made by their families and the patient's rehabilitation and movement disorder's team following a multidisciplinary assessment process including a test dose of intrathecal baclofen. There are no specific exclusion criteria.

Participation in the study is voluntary and participants can withdraw consent without fear of their withdrawal affecting their normal care. If a patient requires ITB therapy to be ceased, no ongoing data will be collected following pump removal.

The hospitals currently participating in the Australian ITB Audit include: Princess Margaret Hospital for Children, Perth, Western Australia; The Children's Hospital at Westmead, Sydney, New South Wales; Lady Cilento Children's Hospital, Brisbane, Queensland; The Royal Children's Hospital, Melbourne, Victoria; Monash Children's Southern Health, Melbourne, Victoria and The Women's and Children's Hospital, Adelaide, South Australia.

Sample Size

It is anticipated 12 to 15 ITB pumps are implanted each year in Australian children and adolescents. Data will be collected for 10 years in order to be clinically relevant.

Classification and Outcome Measures

All participants will be classified at baseline and comprehensive data collected at baseline prior to pump implant, then at 6 and 12 months post pump implant, then annually (see Table 1 for Assessments and Protocols). The selection of assessment tools and outcome measures were guided by the ICF[31] and where possible are validated measures developed for cerebral palsy and/or paediatric use.

Table 1: ITB Therapy Assessments and Assessment Protocol

Assessments & Data collected	Baseline	6 months	12 months	Annual
Background & Demographics:				
Diagnosis, Co-morbidities, Nutrition, Height, Weight, Medications	X	X	X	X
Baclofen concentration, Number of admissions & length of stay,	X	X	X	X
ITB Dose		X	X	X
Musculoskeletal Interventions:				
Botulinum toxin injections, orthopaedic surgery	X	X	X	X
Speech & Swallow: – any changes		X	X	X
Drooling Impact Scale	X	X	X	
Classification:				
GMFCS, MACS, CFCS, FMS	X	X	X	X
Body Structure & Function:				
MAS, Mod Tardieu, BADS, Hip migration status, Spine Cobb angle	X	X	X	X
Ambulant patients: (GMFCS I, II & III or equivalent)				
Sagittal Gait Pattern, 1 minute walk test & Gillette level	X	X	X	X

PEDI	X		X	
Goals: COPM	X	X	X	
Quality of Life: CPCHILD, CP QoL, CCHQ	X	X	X	

***Key**: GMFCS: Gross Motor Function Classification System; , MACS: Manual Ability Classification System; CFCS: Communication Function Classification System; MAS: Modified Ashworth Scale; BADS: Barry Albright Dystonia Scale; FMS: Functional Mobility Scale; COPM: Canadian Occupational Performance Measure; PEDI: Pediatric Evaluation of Disability Inventory; CPCHILD: Caregiver Priorities and Child Health Index of Life with Disabilities; CP QoL: Cerebral Palsy – Quality of Life Questionnaire; CCHQ: Care and Comfort Hypertonicity Questionnaire.*

1. Background and demographic data:
   a. Patient background and demographic data including gender, date of birth, diagnosis and co-morbidities are collected. Current medications are recorded prior to implant then at each time point. Health status, as defined by the number of hospital admissions and length of stay is also collected at each time point. Table 2 describes the demographic data collected at the time of enrolment into the audit.

Table 2: Demographic data collected

Gender	Male or female
Date of birth	dd/mm/yyyy
Height	Centimetres. Stevenson[45] formula was used to estimate height if lower limb contractures were present.
Weight	Kilograms
Patient location	Metropolitan: lives within 100km of hospital where managing ITB team is located Regional: lives > 100km but < 1000km of hospital where managing ITB team is located Remote: lives > 1000km of hospital where managing ITB team is located
Nutrition	Categorised as oral, enteral or oral and enteral feeding.

   b. Diagnoses and Co morbidities: Diagnoses are categorised below and co morbidities defined in Table 3.
      - Acquired Brain Injury - CNS tumour, hypoxic includes near drowning and status epilepticus, infection/inflammatory, stroke, traumatic including non-accidental injury.
      - Cerebral Palsy - either bilateral or unilateral involvement, with spastic, dystonic, spastic/dystonic, or dyskinetic tone presentation.
      - Genetic – metabolic, primary dystonia, progressive/degenerative conditions (eg Hereditary Spastic Paraplegia), other
      - Spinal Cord Conditions – from any cause (eg Multiple Sclerosis, trauma, infection)

Table 3: Comorbidities and their definition

Aspiration pneumonia	Documented episodes of aspiration of saliva and or food requiring

	admission to hospital with changes on x-ray consistent with the diagnosis
Bronchiectasis	Disease where there is permanent enlargement of parts of the airways or lungs. Clubbed (usually) with history of recurrent chest infections or chronic lung disease confirmed by respiratory physician or bronchiectasis confirmed on CT scan of chest
Dysphagia	Difficulties with swallowing associated with poor oromotor control (requires a modified diet, thickened fluids or gastrostomy feeds, pain on swallowing). May have choking on thin fluids or swallowing abnormalities confirmed on modified barium swallow
Epilepsy	Recurrent seizures requiring anticonvulsant medication prn or daily
Gastro Oesophageal Reflux (GOR)	Obvious regurgitation on observation by clinician, has had cardioplasty or fundoplication due to GOR or diagnosis made by paediatric gastroenterologist. Reflux demonstrated on pH Study or imaging study (eg barium swallow, milk scan), abnormalities on endoscopy (eg stricture or Barretts oesophagus)
Hydrocephalus shunted	Ventriculoperitoneal or ventriculoatrial shunt in situ
Hydrocephalus unshunted	Diagnosis confirmed by neurosurgeon
Intellectual Disability	Confirmed by psychometric testing or on interview with school counsellor or psychologist
Oesophagitis	Endoscopy evidence of or biopsy proven oesophagitis where direct observation is 'normal'
Osteoporosis	Low impact fracture(s) or wedged vertebrae on lateral spine x-ray plus low bone mineral density on DXA/peripheral quantitative CT.
Respiratory failure	Documented hypoxia and carbon dioxide retention/ elevated bicarbonate in the appropriate clinical setting. Polysomnography may assist in this diagnosis. Non-invasive respiratory support may be considered.

c. Additional information recorded includes:
   - Data regarding the intrathecal baclofen test dose is recorded including test dose and sedation method, dose required for response and test dose adverse events
   - Baclofen concentration and total daily dose
   - Changes in nutrition, speech, swallow and use of augmentative communication
   - Salivary control is measured using the Drooling Impact Scale[46]
   - Musculoskeletal interventions, such as Botulinum Toxin-A injections and any orthopaedic surgery are also recorded for the two years prior to entry to the study and at each successive time point

d. Following pump implant the following is recorded: implant date; age of patient at implant; pump and catheter model and serial number; catheter tip height; implant technique and antibiotic use.

2. Classification of the sample:
Classification using the Gross Motor Function Classification System Expanded and Revised (GMFCS)[47], Manual Ability Classification System (MACS)[48] and Communication Function Classification System (CFCS)[49] and Functional Mobility Scale (FMS)[50] are documented for

children with CP. Equivalent classifications are allocated to non-CP participants where relevant. These classification systems contribute to a functional performance view of daily life for individuals with CP, in accordance with the WHO ICF[31].

a. GMFCS: Functional status can be categorised with respect to gross motor function by using the five levels of the gross motor classification system for cerebral palsy[51]. The levels assigned describe a child's ability in self –initiated movements, with a focus on sitting and walking. The GMFCS is clinically relevant[52] and both reliable and valid, with high inter-rater reliability[53] and good construct validity with the GMFM (r=0.91)[54].
b. MACS: is a five-point scale corresponding to the structure of the GMFCS. This scale classifies how a child uses their hands to perform day-to-day activities that are appropriate for their age[48]. Inter-rater reliability of the MACS is reported as excellent (ICC = 0.97 (0.96 – 0.98)[48].
c. CFCS: is a tool used to classify the everyday communication of an individual with CP into one of five levels according to effectiveness of communication[49]. The CFCS demonstrates content validity and shows very good test-retest reliability (ICC=0.82), good professional interrater reliability (ICC=0.77 for classification of children older than 4 years), and moderate parent-professional interrater reliability[49].
d. The FMS allows classification of functional mobility in children 4 to 18 years, taking into account the range of assistive devices the child might use[50]. The FMS rates walking ability at 3 specific distances, 5, 50, 500 metres, representing the child's mobility in the home, school and in the community. The distances are a guide - it is the environment which is most relevant. The FMS requires rating of what the child actually does at a point in time, not what they can do or used to be able to do, to record mobility status.

3. Assessment of Body Structures and Function:
   a. Passive range of motion of the limbs will be measured with goniometry.
   b. Hypertonia, as defined by abnormally increased resistance to passive stretch while the patient is attempting to maintain a relaxed state of muscle activity[2]. This is assessed clinically using passive movements about a joint to determine muscular resistance. Hence the increased tone or hypertonia is perceived by the examiner. The hypertonia may be as result of spasticity, dystonia or rigidity. The level of passive resistance of muscles will be recorded using the Modified Ashworth Scale (MAS)[55].
   c. Spasticity will be measured and quantified using the Modified Tardieu Scale (MTS) which is a valid, reliable and sensitive abridged version of the Tardieu Scale[56,57]. The MTS is consistent with current definitions of spasticity assessing muscle response to passive movement at varying velocities, including rapid passive movement.
   d. The Barry Albright Dystonia Scale (BADS)[38] will be utilised to record dystonia severity in patients with dystonia. It is a five point ordinal scale that rates dystonia severity across eight body regions. The scale has some evidence of reliability[38,58], validity[38,58-61] and excellent responsiveness to change for patients with secondary dystonia in ITB[25,27,30,34,38,62-64] and for other dystonia related interventions[65-68].
   e. Hip migration percentage (MP) is a radiographic measure of the amount of ossified femoral head which is not covered by the ossified acetabular roof[69] when measured from a frontal view of an antero-posterior pelvic radiograph[69].

f. Spinal scolioisis will be measured from antero-posterior radiographs and will be quantified as the Cobb Angle[70,71].

g. Drooling: The Drooling Impact Scale[46] is a measure to evaluate the impact of drooling in children with neurological disorders. The tool has established reliability and validity as a subjective measure of the impact of drooling on caregivers and families, and is sensitive to changes in drooling[46]. Changes in saliva control had been anecdotally noted following ITB therapy.

4. Assessment for Ambulant participants

In ambulant patients, GMFCS levels I, II or III or equivalent, additional information is assessed and recorded including:

a. The One minute walk test is a measure of functional ability and walking endurance. Children are tested at their maximal walking speed with the distance covered in 1 minute recorded. Validity[72] and reliability[73] have been established for this measure.

b. The Gillette Functional Assessment Questionnaire (FAQ) (short version) is taken from the Skill Mastery of Typically Developing Children. The FAQ is a 10 level parent-report walking scale encompassing a range of walking abilities from non-ambulatory to ambulatory in all community settings. The FAQ is a reliable and valid scale for documenting functional change in children with chronic neuromuscular conditions. Parents or carers are asked to choose the level that best describes their child's usual or typical walking abilities[74].

c. Sagittal Gait patterns: The Winters Gage and Hicks[75] classification of hemiplegic gait describes four types of gait patterns based on the sagittal plane kinematics of the ankle, knee, hip and pelvis. Similarly classification of common gait patterns in children with spastic diplegia have also been developed by Rodda and Graham[76]. Their work draws heavily on patterns of knee involvement in spastic diplegia by Sutherland and Davids[77].

d. Pediatric Evaluation of Disability Inventory (PEDI) is a standardised assessment of how a child functions with an impairment in the context of their daily life. It has established reliability and validity to detect the presence, extent and area of a functional delay in children with physical impairment or combined physical and cognitive impairment[78]. The PEDI is designed to measure a child's ability across 3 measurement scales: functional skills, caregiver assistance, and modifications measure. Each scale is divided into 3 domains including self-care, mobility and social function.

5. Goals and Quality of Life, Ease of Care Assessment:

The collection of patient and carer satisfaction with ITB therapy is one of the primary outcomes from this study. Change in parents ratings on individualised goal performance and satisfaction with goal attainment will be obtained with the Canadian Occupational Performance Measure (COPM)[79]. In addition changes in quality of life, ease of caregiving and health status will be monitored.

a. Goal setting: ITB therapy is goal directed, either for increased function or improved comfort and ease of care. Individualised goal setting, in collaboration with families, is generally acknowledged as an integral aspect of intervention[80]. Goals are determined with the child and family using the COPM[79] an established reliable and valid measure[81]. The COPM is an

individualised goal setting measure, providing a structure for the identification of goals in the occupational performance areas of self-care, productivity and leisure. It measures outcome based on individual performance and satisfaction with performance[79]. Goals are identified with the client and family, then rated on a 10-point scale for: Performance, how well they feel they can complete the activity; and Satisfaction with Performance, how satisfied they are with their current ability to complete the activity. For the purposes of the study up to a maximum of five goals are prioritised and goal performance and satisfaction are set at baseline and reassessed at 6 then 12 months.

b. Quality of Life, Health status and Ease of Care Assessment: Quality of life can be defined as "an individuals' perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[82]. Quality of life is an important construct to consider for all children with CP as there is likely to be some impact not only on the physical but also the social and emotional well-being of the child and their family. In this study the quality of life and health status of the participants as well as the caregiver burden on families will be measured. A variety of questionnaires will be utilised due to the differing domains they cover, comparison to previous ITB studies and emerging psychometric data to support their use. Quality of life will be measured at baseline, 6 and 12 months post pump implant. The study utilises the Cerebral Palsy – Quality of Life Questionnaire (CP-QoL)[83], the Care and Comfort Hypertonicity Questionnaire (CCHQ)[84] and the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD)[85].

The CP QoL is a CP specific questionnaire designed to be used for children between the ages of 4 and 12 years. This study will utilise the parent-proxy version. The CP QoL measures seven areas of a child's life: Social Wellbeing & Acceptance; Participation & Physical Health; Emotional Wellbeing; Pain & Impact of Disability; Access to Services and Family Health.

The CCHQ questionnaire was developed to evaluate functional care needs, and to a lesser extent quality of life in children with increased tone of cerebral origin, particularly those with 'severe' CP[84]. Early work on the CCHQ has been undertaken to establish content validity and the CCHQ has also been shown to be sensitive enough to detect changes when ITB was offered or dose levels changed[84]. Formal evaluation of reliability and validity has not been finalised. It is a self-report questionnaire and requires parents or caregivers to rate how easy or difficult it is for them or their child in the last two weeks to perform a range of tasks relative to a cooperative person without a disability. The areas covered include: Personal Care; Positioning/Transferring and Comfort and Interaction/Communication.

The CPCHILD evaluates function and health status, caregiver burden and health related quality of life in children with severe CP. It has been validated for use for caregivers of children with severe developmental disabilities such as those with non-ambulatory CP and traumatic brain injury, who would be categorised in level IV or V of the GMFCS[85]. Responsiveness to change has been demonstrated following hip surgery in children with CP, GMFCS levels IV and V[86]. The domains of the CPCHILD include: Personal Care; Positioning, Transferring and Mobility; Comfort and Emotions; Communication and Social Interactions and Health. It also comments on pain and the importance of QOL items to the child.

6. Adverse Events:

The Australian Therapeutic Goods Administration defines an adverse event (AE) as unintended and sometimes harmful occurrences associated with the use of a medicine, vaccine or medical device[87]. This national audit is a centralised, systematic adverse event reporting system for all children and adolescents receiving ITB therapy in Australia.

A paediatric rehabilitation specialist experienced in the use of ITB therapy at each site grades each AE according to the type, severity and causality. The date the AE occurred is recorded; for events that last several days the first date of the event is recorded. AE type are divided into: Synchromed system related, drug related and patient related (see Table 4). Severity of the AE is rated as either mild, moderate or severe (see Figure 1). For causality, events are graded as: unrelated or unlikely; possibly related or probably/definitely related to ITB therapy (defined in Figure 2). These are attributed on the basis of patient history, onset or duration of symptoms and consistency with previous literature of AE reported to be related to ITB therapy. Classification of AE in this manner is based upon the OHRP Guidance on Unanticipated Problems and Adverse Events[88]. The intervention required and outcome for ITB therapy are also recorded (see Figure 3).

Table 4: ITB Therapy Adverse Event Type

Synchromed System	Drug	Patient
Pump	Overdose	Infection
Battery expiry	Human error	Lumbar wound
Flipping of pump	System error	Dorsal wound
	Withdrawal	Pocket
	Human error	Meningitis
	System error	
Catheter	Drug sensitivities	Other
Kinking	Bladder/ bowel disturbance	CSF leak
Obstruction	Dizziness	Issue with refill
Dislodgement	Drowsiness	Pseudomenngocoele
Disconnection	Gastrointestinal upset	
Fracture	Hypotension	
	Hypotonia	
	Mood changes	
	Respiratory depression	
	Seizures	

Severity	
Mild	Awareness of signs or symptoms Observation but intervention is not indicated; signs and symptoms are transient

Moderate	Events introduce a low level of inconvenience and may interfere with daily activities Simple therapeutic measures are indicated
Severe	Events interrupt the patient's normal daily activities Systemic drug therapy or other treatment; they usually require admission to hospital.

Figure 1: Severity Ratings for ITB related Adverse Events

Causality	
Unlikely/unrelated	Temporal history not consistent with ITB therapy Other diagnoses more likely Pre-existing symptoms Inconsistent reporting of signs/symptoms
Possible	Temporal history may be consistent with ITB therapy Diagnosis may fit with ITB therapy No pre-existing symptoms Consistent reporting of signs/symptoms
Probable/ definite	Temporal history consistent with ITB therapy Known adverse event reported in the literature No pre-existing symptoms Consistent reporting of signs/symptoms

Figure 2: Definitions of causality of ITB Adverse Events

Medical Interventions	Surgical Interventions
Reprogramming	Replacement of pump
Replacement of Drug	Repositioning of pump
Antibiotic treatment (oral or IV)	Device removal and cessation of therapy
Treatment for baclofen overdose	Replacement of catheter
Treatment for baclofen withdrawal	Reposition of catheter or repair
	Blood patch, re-suture, Surgical glue

ITB Therapy Outcome

ITB therapy continued

ITB therapy ceased

Patient died related to ITB therapy

Patient died unrelated to ITB therapy

Figure 3: Adverse Event Interventions and ITB therapy outcome

Data entry

Data collected at each hospital site is de-identified and entered into the Australian ITB Audit Tool© Access database. Data are collected and entered at baseline, 6 months and 12 months and annually after ITB pump insertion. Adverse event data is collected from date of pump implant to date of termination from the study. Data collection ceases if ITB therapy ceases, the patient dies or once patients transition to adult services.

Secondary Outcome

It is anticipated that an annual report will be generated from the national study by APIRG and distributed to the participating hospitals.

DISCUSSION

This protocol paper presents the background and study design of a 10 year, longitudinal, prospective, clinical audit. It is the first Australian study aiming to capture clinical and adverse event data from a complete population of children with neurological impairment receiving ITB therapy. Combining data from the small numbers from each participating site ensures data can be used to guide ongoing clinical decision making and adverse event problem solving around ITB therapy for Australian children and adolescents. Assessment of outcomes across the domains of the ICF, utilising psychometrically robust outcome measures where possible, will ensure comparison to studies in the literature and contribute further to the accumulating literature around ITB therapy for children.

ETHICAL CONSIDERATIONS AND DISSEMINATION

All participating Australian sites obtained individual ethics approval from their Human Research Ethics committees: The Children's Hospital at Westmead, NSW HREC 10/CHW/59; Princess Margaret Hospital for Children, Perth, WA HREC Ref 1797EP; Lady Cilento Children's Hospital, QLD HREC/10/QRCH/2; The Royal Children's Hospital, VIC HREC 32052; Monash Children's Southern Health, VIC HREC 11103B and The Women's and Children's Hospital, SA, WCH HREC 388A. The study was registered with the Australian New Zealand Clinical Trials Registry with a registration number ACTRN 12610000323022. Results of this study will be published in relevant peer reviewed journals. Results will also be presented at relevant national and international conferences.

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study with an unrestricted educational grant but have provided no further ongoing funding and do not have access to any data or manuscripts.

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Intrathecal baclofen therapy in paediatrics: A study protocol for an Australian multi-centre, 10 year, prospective audit

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Title Page

Intrathecal baclofen therapy in paediatrics: A study protocol for an Australian multi-centre, 10 year, prospective audit

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Abstract

Introduction: Increasing clinical use of Intrathecal baclofen (ITB) in Australian tertiary paediatric hospitals, along with the need for standardised assessment and reporting of adverse events, saw the formation of the Australian Paediatric ITB Research Group (APIRG). APIRG developed a National ITB Audit tool designed to capture clinical outcomes and adverse events data for all Australian children and adolescents receiving ITB therapy.

Methods and analysis: The Australian ITB Audit is a 10 year, longitudinal, prospective, clinical audit collecting all adverse events and assessment data across body functions and structure, participation and activity level domains of the ICF. Data will be collected at baseline, 6 and 12 months with ongoing capture of all adverse event data. This is the first Australian study that aims to capture clinical and adverse event data from a complete population of children with neurological impairment receiving a specific intervention between 2011 and 2021. This multi-centre study will inform ITB clinical practice in children and adolescents, direct patient selection, record and aid decision making regarding adverse events and investigate the impact of ITB therapy on family and patient quality of life.

Ethics and dissemination: This project was approved by the individual Human Research Ethics committees at the six Australian tertiary hospitals involved in the study. Results will be published in various peer reviewed journals and presented at national and international conferences.

BACKGROUND

Disabling spasticity and secondary dystonia are common problems in chronic neurological conditions such as cerebral palsy (CP). Spasticity is the most common form of hypertonia seen in children with CP[1] and can be a significant problem for many paediatric patients with spinal cord injury and traumatic brain injury. Spasticity is a velocity-dependent resistance to muscle stretch that occurs when "resistance (to external movement) increases with increasing speed of stretch and/or resistance (to externally imposed movement) rises rapidly above a threshold speed or joint angle"[2]. This differs from dystonia which is characterised by involuntary muscle contractions cause repetitive movements and twisted postures[3]. In the clinical setting, severe spasticity and dystonia are often associated with pain, sleep disorders, feeding issues and difficulties with positioning, transfers, dressing and personal cares and reduced quality of life[4-6].

Development of Intrathecal Baclofen

Baclofen is a gamma-amino butyric acid (GABA) agonist. It acts upon the GABA-B receptors in the spinal cord to reduce abnormal muscle tone. Oral baclofen is a widely used oral medication to manage spasticity of cerebral or spinal origin. The effectiveness of oral baclofen is limited by its side effects such as sedation, confusion, and lethargy. Intrathecal baclofen (ITB) delivered by an implanted pump and catheter can work directly at the spinal cord level to reduce spastic tone through presynaptic inhibition. Because of direct delivery to the central nervous system, the required dose is less than 1% of that delivered orally.

ITB was first used in adult patients with spasticity of spinal origin[7]. Albright et al[8] demonstrated its efficacy for the management of spasticity of cerebral origin. In 2000 the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) published a systematic review of the literature on the treatment of spasticity in CP with ITB[9]. ITB is effective in the reduction of spasticity as well as dystonia and is frequently used to treat hypertonicity associated with CP. A recent Cochrane review concluded the effectiveness of intrathecal baclofen for treating spasticity in children with cerebral palsy is limited by small sample sizes and methodological issues[10].

The European consensus statement on the use of ITB therapy in paediatric spasticity recommends its use in children with CP, Gross Motor Function Classification System (GMFCS) Levels IV –V where spasticity interferes with patient's activities and/ or quality of life[11]. The authors cited Level 3-4 evidence in this population[9,12-15]. In addition to the long-term reduction of hypertonicity, authors have reported improvement in comfort, positioning, ease of care provision and motor function in select groups of individuals and a reduction in the anticipated need for orthopaedic surgery[14,16-18]. Progression of hip dislocation may be reduced with ITB, although the effect of ITB on the progression of scoliosis is controversial[19,20].

Complications of ITB Therapy

It is well recorded in the literature that ITB therapy has adverse events[21-30]. In a review of 430 consecutive patients implanted with an ITB pump at a single centre, Motta & Antonello[24] analysed the rates of major complications of ITB therapy requiring surgical intervention: CSF leakage, infection and catheter malfunction. Their results were consistent with others reported in the literature with 25% of patients experiencing major complications. The European consensus on the appropriate use

of ITB therapy in paediatric spasticity recommended procedures to reduce complications including omission of the ITB test and, particularly in young and small patients, subfascial rather than subcutaneous pump placement[11]. In addition, a key factor in improving outcomes for patients is treatment in a centre dedicated to providing ITB, by specialist physicians who have experience in this procedure.

Assessment of ITB in paediatric cohorts

Historically assessment of interventions, such as ITB in paediatric cohorts, have largely occurred at the Body Functions and Structures level of the ICF[31] and fail to address the main concerns of children and their carers[32]. A literature review of paediatric ITB studies in CP (n=19) revealed 15 studies utilised assessments at the Body Functions and Structures level of the ICF, the majority reporting Modified Ashworth scores[13,22,23,25,28-30,33-37] or dystonia scale scores[25,27,30,38-40]. Seven studies reported motor outcomes utilising the Gross Motor Function Measure[41] (GMFM)[13,25,33,35,42] or Melbourne 2[43,40] assessments and six studies reported goal outcomes using a variety of validated (n=2)[38,30] or internally designed (n=4)[13,14,22,23] goal setting instruments. Health related quality of life was addressed as an outcome measure in 13 studies but few utilised paediatric validated instruments and the majority reported on internally designed, non-validated questionnaires or parental interviews (n=13)[13,14,22,23,25,27,29,30,33,35,36,40,44].

ITB in Australia

Paediatric ITB therapy commenced in Australia in 1999 and is now an established intervention in comprehensive CP clinical management programmes at six tertiary paediatric hospitals in Australia.

In 2009 APIRG was convened with medical, nursing and allied health representatives from all the tertiary paediatric hospitals providing ITB therapy in Australia. The main purpose of APIRG was to establish an agreed national ITB assessment protocol and adverse events recording system. The comprehensive assessment protocol was based on the best available evidence regarding assessment tools across all domains of the International Classification of Functioning, Disability and Health (ICF)[31]. A national study was proposed as each centre implanted small numbers of ITB systems each year allowing a larger pool of information. This information would be available to guide future ITB intervention. Prospective collection of data would allow:

1. The use of a standardised assessment protocol - centres could collect more information if desired.
2. Evaluation of the safety and efficacy of ITB therapy via a centralised adverse events data collection system.
3. Collection of patient and carer satisfaction with ITB therapy.
4. Support benchmarking for individual centres against national data

METHODS AND ANALYSIS

A 10 year prospective multicentre clinical audit of all new patients commencing ITB therapy in Australia under the age of 16 years, between 2011 and 2021.

Study Population and Recruitment

All new patients, commencing ITB therapy in Australia under the age of 16 years are eligible for inclusion in the study. An upper age limit of 16 years was determined in order to allow sufficient data collection post pump implant prior to transition to adult services, which usually occurs at

around age 18 in most Australian paediatric tertiary hospitals. The decision regarding suitability of ITB therapy for individual patients is made by their families and the patient's rehabilitation and movement disorder's team following a multidisciplinary assessment process including a test dose of intrathecal baclofen. There are no specific exclusion criteria.

Participation in the study is voluntary and participants can withdraw consent without fear of their withdrawal affecting their normal care. If a patient requires ITB therapy to be ceased, no ongoing data will be collected following pump removal.

The hospitals currently participating in the Australian ITB Audit include: Princess Margaret Hospital for Children, Perth, Western Australia; The Children's Hospital at Westmead, Sydney, New South Wales; Lady Cilento Children's Hospital, Brisbane, Queensland; The Royal Children's Hospital, Melbourne, Victoria; Monash Children's Southern Health, Melbourne, Victoria and The Women's and Children's Hospital, Adelaide, South Australia.

Sample Size

It is anticipated 12 to 15 ITB pumps are implanted each year in Australian children and adolescents. Data will be collected for 10 years in order to be clinically relevant.

Classification and Outcome Measures

All participants will be classified at baseline and comprehensive data collected at baseline prior to pump implant, then at 6 and 12 months post pump implant, then annually (see Table 1 for Assessments and Protocols). The selection of assessment tools and outcome measures were guided by the ICF[31] and where possible are validated measures developed for cerebral palsy and/or paediatric use.

Table 1: ITB Therapy Assessments and Assessment Protocol

Assessments & Data collected	Baseline	6 months	12 months	Annual
Background & Demographics:				
Diagnosis, Co-morbidities, Nutrition, Height, Weight, Medications	X	X	X	X
Baclofen concentration, Number of admissions & length of stay,	X	X	X	X
ITB Dose		X	X	X
Musculoskeletal Interventions:				
Botulinum toxin injections, orthopaedic surgery	X	X	X	X
Speech & Swallow: – any changes		X	X	X
Drooling Impact Scale	X	X	X	
Classification:				
GMFCS, MACS, CFCS, FMS	X	X	X	X
Body Structure & Function:				
MAS, Mod Tardieu, BADS, Hip migration status, Spine Cobb angle	X	X	X	X
Ambulant patients: (GMFCS I, II & III or equivalent)				

Sagittal Gait Pattern, 1 minute walk test & Gillette level PEDI	X X	X	X X	X	***Key**: GMFCS: Gross Motor Function Classification System; , MACS: Manual Ability Classification System; CFCS: Communication Function Classification System; MAS: Modified Ashworth Scale; BADS: Barry Albright Dystonia Scale; FMS: Functional Mobility Scale; COPM: Canadian Occupational Performance Measure; PEDI: Pediatric Evaluation of Disability Inventory; CPCHILD: Caregiver Priorities and Child Health Index of Life with Disabilities; CP QoL: Cerebral Palsy – Quality of Life Questionnaire; CCHQ: Care and Comfort Hypertonicity Questionnaire.*
<u>Goals:</u> COPM	X	X	X		
<u>Quality of Life:</u> CPCHILD, CP QoL, CCHQ	X	X	X		

1. <u>Background and demographic data</u>:
   a. Patient background and demographic data including gender, date of birth, diagnosis and co-morbidities are collected. Current medications are recorded prior to implant then at each time point. Health status, as defined by the number of hospital admissions and length of stay is also collected at each time point. Table 2 describes the demographic data collected at the time of enrolment into the audit.

Table 2: Demographic data collected

Gender	Male or female
Date of birth	dd/mm/yyyy
Height	Centimetres. Stevenson[45] formula was used to estimate height if lower limb contractures were present.
Weight	Kilograms
Patient location	Metropolitan: lives within 100km of hospital where managing ITB team is located Regional: lives > 100km but < 1000km of hospital where managing ITB team is located Remote: lives > 1000km of hospital where managing ITB team is located
Nutrition	Categorised as oral, enteral or oral and enteral feeding.

   b. Diagnoses and Co morbidities: Diagnoses are categorised below and co morbidities defined in Table 3.
      - Acquired Brain Injury - CNS tumour, hypoxic includes near drowning and status epilepticus, infection/inflammatory, stroke, traumatic including non-accidental injury.
      - Cerebral Palsy - either bilateral or unilateral involvement, with spastic, dystonic, spastic/dystonic, or dyskinetic tone presentation.
      - Genetic – metabolic, primary dystonia, progressive/degenerative conditions (eg Hereditary Spastic Paraplegia), other
      - Spinal Cord Conditions – from any cause (eg Multiple Sclerosis, trauma, infection)

Table 3: Comorbidities and their definition

Aspiration pneumonia	Documented episodes of aspiration of saliva and or food requiring admission to hospital with changes on x-ray consistent with the diagnosis
Bronchiectasis	Disease where there is permanent enlargement of parts of the airways or lungs. Clubbed (usually) with history of recurrent chest infections or chronic lung disease confirmed by respiratory physician or bronchiectasis confirmed on CT scan of chest
Dysphagia	Difficulties with swallowing associated with poor oromotor control (requires a modified diet, thickened fluids or gastrostomy feeds, pain on swallowing). May have choking on thin fluids or swallowing abnormalities confirmed on modified barium swallow
Epilepsy	Recurrent seizures requiring anticonvulsant medication prn or daily
Gastro Oesophageal Reflux (GOR)	Obvious regurgitation on observation by clinician, has had cardioplasty or fundoplication due to GOR or diagnosis made by paediatric gastroenterologist. Reflux demonstrated on pH Study or imaging study (eg barium swallow, milk scan), abnormalities on endoscopy (eg stricture or Barretts oesophagus)
Hydrocephalus shunted	Ventriculoperitoneal or ventriculoatrial shunt in situ
Hydrocephalus unshunted	Diagnosis confirmed by neurosurgeon
Intellectual Disability	Confirmed by psychometric testing or on interview with school counsellor or psychologist
Oesophagitis	Endoscopy evidence of or biopsy proven oesophagitis where direct observation is 'normal'
Osteoporosis	Low impact fracture(s) or wedged vertebrae on lateral spine x-ray plus low bone mineral density on DXA/peripheral quantitative CT.
Respiratory failure	Documented hypoxia and carbon dioxide retention/ elevated bicarbonate in the appropriate clinical setting. Polysomnography may assist in this diagnosis. Non-invasive respiratory support may be considered.

c. Additional information recorded includes:
- Data regarding the intrathecal baclofen test dose is recorded including test dose and sedation method, dose required for response and test dose adverse events
- Baclofen concentration and total daily dose
- Changes in nutrition, speech, swallow and use of augmentative communication
- Salivary control is measured using the Drooling Impact Scale[46]
- Musculoskeletal interventions, such as Botulinum Toxin-A injections and any orthopaedic surgery are also recorded for the two years prior to entry to the study and at each successive time point

d. Following pump implant the following is recorded: implant date; age of patient at implant; pump and catheter model and serial number; catheter tip height; implant technique and antibiotic use.

2. Classification of the sample:
Classification using the Gross Motor Function Classification System Expanded and Revised (GMFCS)[47], Manual Ability Classification System (MACS)[48] and Communication Function

Classification System (CFCS)[49] and Functional Mobility Scale (FMS)[50] are documented for children with CP. Equivalent classifications are allocated to non-CP participants where relevant. These classification systems contribute to a functional performance view of daily life for individuals with CP, in accordance with the WHO ICF[31].

a. GMFCS: Functional status can be categorised with respect to gross motor function by using the five levels of the gross motor classification system for cerebral palsy[51]. The levels assigned describe a child's ability in self –initiated movements, with a focus on sitting and walking. The GMFCS is clinically relevant[52] and both reliable and valid, with high inter-rater reliability[53] and good construct validity with the GMFM (r=0.91)[54].
b. MACS: is a five-point scale corresponding to the structure of the GMFCS. This scale classifies how a child uses their hands to perform day-to-day activities that are appropriate for their age[48]. Inter-rater reliability of the MACS is reported as excellent (ICC = 0.97 (0.96 – 0.98)[48].
c. CFCS: is a tool used to classify the everyday communication of an individual with CP into one of five levels according to effectiveness of communication[49]. The CFCS demonstrates content validity and shows very good test-retest reliability (ICC=0.82), good professional interrater reliability (ICC=0.77 for classification of children older than 4 years), and moderate parent-professional interrater reliability[49].
d. The FMS allows classification of functional mobility in children 4 to 18 years, taking into account the range of assistive devices the child might use[50]. The FMS rates walking ability at 3 specific distances, 5, 50, 500 metres, representing the child's mobility in the home, school and in the community. The distances are a guide - it is the environment which is most relevant. The FMS requires rating of what the child actually does at a point in time, not what they can do or used to be able to do, to record mobility status.

3. Assessment of Body Structures and Function:
   a. Passive range of motion of the limbs will be measured with goniometry.
   b. Hypertonia, as defined by abnormally increased resistance to passive stretch while the patient is attempting to maintain a relaxed state of muscle activity[2]. This is assessed clinically using passive movements about a joint to determine muscular resistance. Hence the increased tone or hypertonia is perceived by the examiner. The hypertonia may be as result of spasticity, dystonia or rigidity. The level of passive resistance of muscles will be recorded using the Modified Ashworth Scale (MAS)[55].
   c. Spasticity will be measured and quantified using the Modified Tardieu Scale (MTS) which is a valid, reliable and sensitive abridged version of the Tardieu Scale[56,57]. The MTS is consistent with current definitions of spasticity assessing muscle response to passive movement at varying velocities, including rapid passive movement.
   d. The Barry Albright Dystonia Scale (BADS)[38] will be utilised to record dystonia severity in patients with dystonia. It is a five point ordinal scale that rates dystonia severity across eight body regions. The scale has some evidence of reliability[38,58], validity[38,58-61] and excellent responsiveness to change for patients with secondary dystonia in ITB[25,27,30,34,38,62-64] and for other dystonia related interventions[65-68].

e. Hip migration percentage (MP) is a radiographic measure of the amount of ossified femoral head which is not covered by the ossified acetabular roof[69] when measured from a frontal view of an antero-posterior pelvic radiograph[69].

f. Spinal scolioisis will be measured from antero-posterior radiographs and will be quantified as the Cobb Angle[70,71].

g. Drooling: The Drooling Impact Scale[46] is a measure to evaluate the impact of drooling in children with neurological disorders. The tool has established reliability and validity as a subjective measure of the impact of drooling on caregivers and families, and is sensitive to changes in drooling[46]. Changes in saliva control had been anecdotally noted following ITB therapy.

4. Assessment for Ambulant participants

In ambulant patients, GMFCS levels I, II or III or equivalent, additional information is assessed and recorded including:

a. The One minute walk test is a measure of functional ability and walking endurance. Children are tested at their maximal walking speed with the distance covered in 1 minute recorded. Validity[72] and reliability[73] have been established for this measure.

b. The Gillette Functional Assessment Questionnaire (FAQ) (short version) is taken from the Skill Mastery of Typically Developing Children. The FAQ is a 10 level parent-report walking scale encompassing a range of walking abilities from non-ambulatory to ambulatory in all community settings. The FAQ is a reliable and valid scale for documenting functional change in children with chronic neuromuscular conditions. Parents or carers are asked to choose the level that best describes their child's usual or typical walking abilities[74].

c. Sagittal Gait patterns: The Winters Gage and Hicks[75] classification of hemiplegic gait describes four types of gait patterns based on the sagittal plane kinematics of the ankle, knee, hip and pelvis. Similarly classification of common gait patterns in children with spastic diplegia have also been developed by Rodda and Graham[76]. Their work draws heavily on patterns of knee involvement in spastic diplegia by Sutherland and Davids[77].

d. Pediatric Evaluation of Disability Inventory (PEDI) is a standardised assessment of how a child functions with an impairment in the context of their daily life. It has established reliability and validity to detect the presence, extent and area of a functional delay in children with physical impairment or combined physical and cognitive impairment[78]. The PEDI is designed to measure a child's ability across 3 measurement scales: functional skills, caregiver assistance, and modifications measure. Each scale is divided into 3 domains including self-care, mobility and social function.

5. Goals and Quality of Life, Ease of Care Assessment:

The collection of patient and carer satisfaction with ITB therapy is one of the primary outcomes from this study. Change in parents ratings on individualised goal performance and satisfaction with goal attainment will be obtained with the Canadian Occupational Performance Measure (COPM)[79]. In addition changes in quality of life, ease of caregiving and health status will be monitored.

a. Goal setting: ITB therapy is goal directed, either for increased function or improved comfort and ease of care. Individualised goal setting, in collaboration with families, is generally acknowledged as an integral aspect of intervention[80]. Goals are determined with the child and family using the COPM[79] an established reliable and valid measure[81]. The COPM is an individualised goal setting measure, providing a structure for the identification of goals in the occupational performance areas of self-care, productivity and leisure. It measures outcome based on individual performance and satisfaction with performance[79]. Goals are identified with the client and family, then rated on a 10-point scale for: Performance, how well they feel they can complete the activity; and Satisfaction with Performance, how satisfied they are with their current ability to complete the activity. For the purposes of the study up to a maximum of five goals are prioritised and goal performance and satisfaction are set at baseline and reassessed at 6 then 12 months.

b. Quality of Life, Health status and Ease of Care Assessment: Quality of life can be defined as "an individuals' perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[82]. Quality of life is an important construct to consider for all children with CP as there is likely to be some impact not only on the physical but also the social and emotional well-being of the child and their family. In this study the quality of life and health status of the participants as well as the caregiver burden on families will be measured. A variety of questionnaires will be utilised due to the differing domains they cover, comparison to previous ITB studies and emerging psychometric data to support their use. Quality of life will be measured at baseline, 6 and 12 months post pump implant. The study utilises the Cerebral Palsy – Quality of Life Questionnaire (CP-QoL)[83], the Care and Comfort Hypertonicity Questionnaire (CCHQ)[84] and the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD)[85].

The CP QoL is a CP specific questionnaire designed to be used for children between the ages of 4 and 12 years. This study will utilise the parent-proxy version. The CP QoL measures seven areas of a child's life: Social Wellbeing & Acceptance; Participation & Physical Health; Emotional Wellbeing; Pain & Impact of Disability; Access to Services and Family Health.

The CCHQ questionnaire was developed to evaluate functional care needs, and to a lesser extent quality of life in children with increased tone of cerebral origin, particularly those with 'severe' CP[84]. Early work on the CCHQ has been undertaken to establish content validity and the CCHQ has also been shown to be sensitive enough to detect changes when ITB was offered or dose levels changed[84]. Formal evaluation of reliability and validity has not been finalised. It is a self-report questionnaire and requires parents or caregivers to rate how easy or difficult it is for them or their child in the last two weeks to perform a range of tasks relative to a cooperative person without a disability. The areas covered include: Personal Care; Positioning/Transferring and Comfort and Interaction/Communication.

The CPCHILD evaluates function and health status, caregiver burden and health related quality of life in children with severe CP. It has been validated for use for caregivers of children with severe developmental disabilities such as those with non-ambulatory CP and traumatic brain injury, who would be categorised in level IV or V of the GMFCS[85].

Responsiveness to change has been demonstrated following hip surgery in children with CP, GMFCS levels IV and V[86]. The domains of the CPCHILD include: Personal Care; Positioning, Transferring and Mobility; Comfort and Emotions; Communication and Social Interactions and Health. It also comments on pain and the importance of QOL items to the child.

6. Adverse Events:

The Australian Therapeutic Goods Administration (TGA) defines an adverse event (AE) as unintended and sometimes harmful occurrences associated with the use of a medicine, vaccine or medical device[87]. The TGA has adopted the Good Clinical Practice guidelines for the conduct of clinical trials from the International Conference on Harmonisation[88]. This national audit is a centralised, systematic adverse event reporting system for all children and adolescents receiving ITB therapy in Australia.

A paediatric rehabilitation specialist experienced in the use of ITB therapy at each site grades each AE according to the type, severity and causality. The date the AE occurred is recorded; for events that last several days the first date of the event is recorded. AE type are divided into: Synchromed system related, drug related and patient related (see Table 4). Severity of the AE is rated as mild, moderate or severe (see Table 5). For causality, events are graded as: unrelated or unlikely; possibly related or probably/definitely related to ITB therapy (defined in Table 6). These are attributed on the basis of patient history, onset or duration of symptoms and consistency with previous literature of AE reported to be related to ITB therapy. Classification of AE in this manner is based upon the OHRP Guidance on Unanticipated Problems and Adverse Events[89]. The intervention required and outcome for ITB therapy are also recorded (see Figure 1).

Table 4: ITB Therapy Adverse Event Type

Synchromed System	Drug	Patient
Pump	Overdose	Infection
Battery expiry	Human error	Lumbar wound
Flipping of pump	System error	Dorsal wound
	Withdrawal	Pocket
	Human error	Meningitis
	System error	
Catheter	Drug sensitivities	Other
Kinking	Bladder/ bowel disturbance	CSF leak
Obstruction	Dizziness	Issue with refill
Dislodgement	Drowsiness	Pseudomeningocele
Disconnection	Gastrointestinal upset	
Fracture	Hypotension	
	Hypotonia	
	Mood changes	
	Respiratory depression	
	Seizures	

Table 5: Severity Ratings for ITB related Adverse Events

Severity	
Mild	Awareness of signs or symptoms Observation but intervention is not indicated; signs and symptoms are transient
Moderate	Events introduce a low level of inconvenience and may interfere with daily activities Simple therapeutic measures are indicated
Severe	Events interrupt the patient's normal daily activities Systemic drug therapy or other treatment; they usually require admission to hospital.

Table 6: Definitions of causality of ITB Adverse Events

Causality	
Unlikely/unrelated	Temporal history not consistent with ITB therapy Other diagnoses more likely Pre-existing symptoms Inconsistent reporting of signs/symptoms
Possible	Temporal history may be consistent with ITB therapy Diagnosis may fit with ITB therapy No pre-existing symptoms Consistent reporting of signs/symptoms
Probable/ definite	Temporal history consistent with ITB therapy Known adverse event reported in the literature No pre-existing symptoms Consistent reporting of signs/symptoms

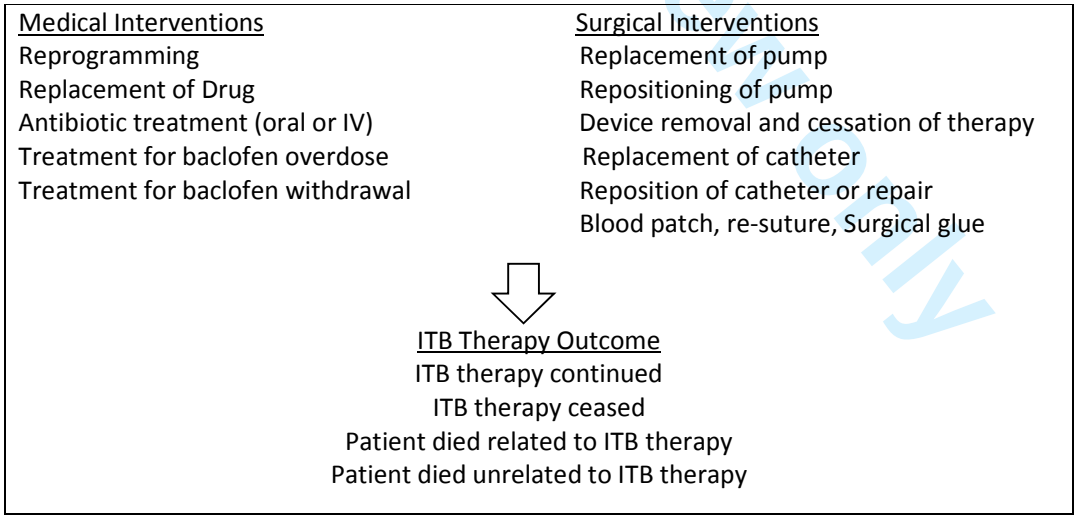

Figure 1: Adverse Event Interventions and ITB therapy outcome

Data entry

Data collected at each hospital site is de-identified and entered into the Australian ITB Audit Tool© Access database. Data are collected and entered at baseline, 6 months and 12 months and annually

after ITB pump insertion. Adverse event data is collected from date of pump implant to date of termination from the study. Data collection ceases if ITB therapy ceases, the patient dies or once patients transition to adult services.

Secondary Outcome

It is anticipated that an annual report will be generated from the national study by APIRG and distributed to the participating hospitals.

DISCUSSION

This protocol paper presents the background and study design of a 10 year, longitudinal, prospective, clinical audit. It is the first Australian study aiming to capture ongoing clinical and adverse event data from a complete population of children with neurological impairment receiving ITB therapy. The study ensures standardisation of ITB assessment across all Australian ITB centres and collection of a minimum data set for every child receiving ITB therapy.

Assessment of outcomes across the domains of the ICF, utilising psychometrically robust outcome measures where possible, will ensure comparison to studies in the literature and contribute further to the accumulating literature around ITB therapy for children. Collection of individualised goal performance and satisfaction with performance as well as quality of life data enables assessment of the impact of ITB upon personal cares, patient satisfaction and burden of care. Standardisation of AE classification and reporting provides the opportunity to further our understanding and management. Combing data across sites allows the association between certain AE and hypertonia types (spastic versus dystonic) and different diagnoses to be further explored. Data collected will also help identify the timing of certain complications, their management and outcomes and enable cross centre collaboration regarding expected and unexpected complications. This information is important to inform future recommendations of this intervention in paediatric populations.

Combining data from the small numbers from each participating site will provide insight into the specific diagnostic groups most likely to have the greatest benefit and carer satisfaction from ITB and ensures data can be used to guide ongoing clinical decision making and adverse event problem solving around ITB therapy for Australian children and adolescents.

ETHICAL CONSIDERATIONS AND DISSEMINATION

All participating Australian sites obtained individual ethics approval from their Human Research Ethics committees: The Children's Hospital at Westmead, NSW HREC 10/CHW/59; Princess Margaret Hospital for Children, Perth, WA HREC Ref 1797EP; Lady Cilento Children's Hospital, QLD HREC/10/QRCH/2; The Royal Children's Hospital, VIC HREC 32052; Monash Children's Southern Health, VIC HREC 11103B and The Women's and Children's Hospital, SA, WCH HREC 388A. The study was registered with the Australian New Zealand Clinical Trials Registry with a registration number ACTRN 12610000323022. Results of this study will be published in relevant peer reviewed journals. Results will also be presented at relevant national and international conferences.

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Intrathecal baclofen therapy in paediatrics: A study protocol for an Australian multi-centre, 10 year, prospective audit

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Title Page

Intrathecal baclofen therapy in paediatrics: A study protocol for an Australian multi-centre, 10 year, prospective audit

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Abstract

Introduction: Increasing clinical use of Intrathecal baclofen (ITB) in Australian tertiary paediatric hospitals, along with the need for standardised assessment and reporting of adverse events, saw the formation of the Australian Paediatric ITB Research Group (APIRG). APIRG developed a National ITB Audit tool designed to capture clinical outcomes and adverse events data for all Australian children and adolescents receiving ITB therapy.

Methods and analysis: The Australian ITB Audit is a 10 year, longitudinal, prospective, clinical audit collecting all adverse events and assessment data across body functions and structure, participation and activity level domains of the ICF. Data will be collected at baseline, 6 and 12 months with ongoing capture of all adverse event data. This is the first Australian study that aims to capture clinical and adverse event data from a complete population of children with neurological impairment receiving a specific intervention between 2011 and 2021. This multi-centre study will inform ITB clinical practice in children and adolescents, direct patient selection, record and aid decision making regarding adverse events and investigate the impact of ITB therapy on family and patient quality of life.

Ethics and dissemination: This project was approved by the individual Human Research Ethics committees at the six Australian tertiary hospitals involved in the study. Results will be published in various peer reviewed journals and presented at national and international conferences.

Strengths and Limitations of this study

- A whole population based study on the short and long term effects of intrathecal baclofen therapy in paediatrics
- Data collection of outcomes across all domains of the International Classification of Functioning, Disability and Health (ICF)
- National registry of ITB therapy adverse events for the ongoing evaluation of safety and efficacy
- The study cohort was limited to age 16 years and younger as this enabled adequate data collection prior to transition to adult services in Australian hospitals

BACKGROUND

Disabling spasticity and secondary dystonia are common problems in chronic neurological conditions such as cerebral palsy (CP). Spasticity is the most common form of hypertonia seen in children with CP[1] and can be a significant problem for many paediatric patients with spinal cord injury and traumatic brain injury. Spasticity is a velocity-dependent resistance to muscle stretch that occurs when "resistance (to external movement) increases with increasing speed of stretch and/or resistance (to externally imposed movement) rises rapidly above a threshold speed or joint angle"[2]. This differs from dystonia which is characterised by involuntary muscle contractions cause repetitive movements and twisted postures[3]. In the clinical setting, severe spasticity and dystonia are often associated with pain, sleep disorders, feeding issues and difficulties with positioning, transfers, dressing and personal cares and reduced quality of life[4-6].

Development of Intrathecal Baclofen

Baclofen is a gamma-amino butyric acid (GABA) agonist. It acts upon the GABA-B receptors in the spinal cord to reduce abnormal muscle tone. Oral baclofen is a widely used oral medication to manage spasticity of cerebral or spinal origin. The effectiveness of oral baclofen is limited by its side effects such as sedation, confusion, and lethargy. Intrathecal baclofen (ITB) delivered by an implanted pump and catheter can work directly at the spinal cord level to reduce spastic tone through presynaptic inhibition. Because of direct delivery to the central nervous system, the required dose is less than 1% of that delivered orally.

ITB was first used in adult patients with spasticity of spinal origin[7]. Albright et al[8] demonstrated its efficacy for the management of spasticity of cerebral origin. In 2000 the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) published a systematic review of the literature on the treatment of spasticity in CP with ITB[9]. ITB is effective in the reduction of spasticity as well as dystonia and is frequently used to treat hypertonicity associated with CP. A recent Cochrane review concluded the effectiveness of intrathecal baclofen for treating spasticity in children with cerebral palsy is limited by small sample sizes and methodological issues[10].

The European consensus statement on the use of ITB therapy in paediatric spasticity recommends its use in children with CP, Gross Motor Function Classification System (GMFCS) Levels IV –V where spasticity interferes with patient's activities and/ or quality of life[11]. The authors cited Level 3-4 evidence in this population[9,12-15]. In addition to the long-term reduction of hypertonicity, authors have reported improvement in comfort, positioning, ease of care provision and motor function in select groups of individuals and a reduction in the anticipated need for orthopaedic surgery[14,16-18]. Progression of hip dislocation may be reduced with ITB, although the effect of ITB on the progression of scoliosis is controversial[19,20].

Complications of ITB Therapy

It is well recorded in the literature that ITB therapy has adverse events[21-30]. In a review of 430 consecutive patients implanted with an ITB pump at a single centre, Motta & Antonello[24] analysed the rates of major complications of ITB therapy requiring surgical intervention: CSF leakage, infection and catheter malfunction. Their results were consistent with others reported in the literature with 25% of patients experiencing major complications. The European consensus on the appropriate use

of ITB therapy in paediatric spasticity recommended procedures to reduce complications including omission of the ITB test and, particularly in young and small patients, subfascial rather than subcutaneous pump placement[11]. In addition, a key factor in improving outcomes for patients is treatment in a centre dedicated to providing ITB, by specialist physicians who have experience in this procedure.

Assessment of ITB in paediatric cohorts

Historically assessment of interventions, such as ITB in paediatric cohorts, have largely occurred at the Body Functions and Structures level of the ICF[31] and fail to address the main concerns of children and their carers[32]. A literature review of paediatric ITB studies in CP (n=19) revealed 15 studies utilised assessments at the Body Functions and Structures level of the ICF, the majority reporting Modified Ashworth scores[13,22,23,25,28-30,33-37] or dystonia scale scores[25,27,30,38-40]. Seven studies reported motor outcomes utilising the Gross Motor Function Measure[41] (GMFM)[13,25,33,35,42] or Melbourne 2[43,40] assessments and six studies reported goal outcomes using a variety of validated (n=2)[38,30] or internally designed (n=4)[13,14,22,23] goal setting instruments. Health related quality of life was addressed as an outcome measure in 13 studies but few utilised paediatric validated instruments and the majority reported on internally designed, non-validated questionnaires or parental interviews (n=13)[13,14,22,23,25,27,29,30,33,35,36,40,44].

ITB in Australia

Paediatric ITB therapy commenced in Australia in 1999 and is now an established intervention in comprehensive CP clinical management programmes at six tertiary paediatric hospitals in Australia.

In 2009 APIRG was convened with medical, nursing and allied health representatives from all the tertiary paediatric hospitals providing ITB therapy in Australia. The main purpose of APIRG was to establish an agreed national ITB assessment protocol and adverse events recording system. The comprehensive assessment protocol was based on the best available evidence regarding assessment tools across all domains of the International Classification of Functioning, Disability and Health (ICF)[31]. A national study was proposed as each centre implanted small numbers of ITB systems each year allowing a larger pool of information. This information would be available to guide future ITB intervention. Prospective collection of data would allow:

1. The use of a standardised assessment protocol - centres could collect more information if desired.
2. Evaluation of the safety and efficacy of ITB therapy via a centralised adverse events data collection system.
3. Collection of patient and carer satisfaction with ITB therapy.
4. Support benchmarking for individual centres against national data

METHODS AND ANALYSIS

A 10 year prospective multicentre clinical audit of all new patients commencing ITB therapy in Australia under the age of 16 years, between 2011 and 2021.

Study Population and Recruitment

All new patients, commencing ITB therapy in Australia under the age of 16 years are eligible for inclusion in the study. An upper age limit of 16 years was determined in order to allow sufficient data collection post pump implant prior to transition to adult services, which usually occurs at

around age 18 in most Australian paediatric tertiary hospitals. The decision regarding suitability of ITB therapy for individual patients is made by their families and the patient's rehabilitation and movement disorder's team following a multidisciplinary assessment process including a test dose of intrathecal baclofen. There are no specific exclusion criteria.

Participation in the study is voluntary and participants can withdraw consent without fear of their withdrawal affecting their normal care. If a patient requires ITB therapy to be ceased, no ongoing data will be collected following pump removal.

The hospitals currently participating in the Australian ITB Audit include: Princess Margaret Hospital for Children, Perth, Western Australia; The Children's Hospital at Westmead, Sydney, New South Wales; Lady Cilento Children's Hospital, Brisbane, Queensland; The Royal Children's Hospital, Melbourne, Victoria; Monash Children's Southern Health, Melbourne, Victoria and The Women's and Children's Hospital, Adelaide, South Australia.

Sample Size

It is anticipated 12 to 15 ITB pumps are implanted each year in Australian children and adolescents. Data will be collected for 10 years in order to be clinically relevant.

Classification and Outcome Measures

All participants will be classified at baseline and comprehensive data collected at baseline prior to pump implant, then at 6 and 12 months post pump implant, then annually (see Table 1 for Assessments and Protocols). The selection of assessment tools and outcome measures were guided by the ICF[31] and where possible are validated measures developed for cerebral palsy and/or paediatric use.

Table 1: ITB Therapy Assessments and Assessment Protocol

Assessments & Data collected	Baseline	6 months	12 months	Annual
Background & Demographics:				
Diagnosis, Co-morbidities, Nutrition, Height, Weight, Medications	X	X	X	X
Baclofen concentration, Number of admissions & length of stay,	X	X	X	X
ITB Dose		X	X	X
Musculoskeletal Interventions:				
Botulinum toxin injections, orthopaedic surgery	X	X	X	X
Speech & Swallow: – any changes		X	X	X
Drooling Impact Scale	X	X	X	
Classification:				
GMFCS, MACS, CFCS, FMS	X	X	X	X
Body Structure & Function:				
MAS, Mod Tardieu, BADS, Hip migration status, Spine Cobb angle	X	X	X	X

Ambulant patients: (GMFCS I, II & III or equivalent) Sagittal Gait Pattern, 1 minute walk test & Gillette level PEDI	 X X	 X	 X X	 X
Goals: COPM	 X	 X	 X	
Quality of Life: CPCHILD, CP QoL, CCHQ	 X	 X	 X	

***Key**: GMFCS: Gross Motor Function Classification System; , MACS: Manual Ability Classification System; CFCS: Communication Function Classification System; MAS: Modified Ashworth Scale; BADS: Barry Albright Dystonia Scale; FMS: Functional Mobility Scale; COPM: Canadian Occupational Performance Measure; PEDI: Pediatric Evaluation of Disability Inventory; CPCHILD: Caregiver Priorities and Child Health Index of Life with Disabilities; CP QoL: Cerebral Palsy – Quality of Life Questionnaire; CCHQ: Care and Comfort Hypertonicity Questionnaire.*

1. Background and demographic data:
   a. Patient background and demographic data including gender, date of birth, diagnosis and co-morbidities are collected. Current medications are recorded prior to implant then at each time point. Health status, as defined by the number of hospital admissions and length of stay is also collected at each time point. Table 2 describes the demographic data collected at the time of enrolment into the audit.

Table 2: Demographic data collected

Gender	Male or female
Date of birth	dd/mm/yyyy
Height	Centimetres. Stevenson[45] formula was used to estimate height if lower limb contractures were present.
Weight	Kilograms
Patient location	Metropolitan: lives within 100km of hospital where managing ITB team is located Regional: lives > 100km but < 1000km of hospital where managing ITB team is located Remote: lives > 1000km of hospital where managing ITB team is located
Nutrition	Categorised as oral, enteral or oral and enteral feeding.

   b. Diagnoses and Co morbidities: Diagnoses are categorised below and co morbidities defined in Table 3.
      - Acquired Brain Injury - CNS tumour, hypoxic includes near drowning and status epilepticus, infection/inflammatory, stroke, traumatic including non-accidental injury.
      - Cerebral Palsy - either bilateral or unilateral involvement, with spastic, dystonic, spastic/dystonic, or dyskinetic tone presentation.
      - Genetic – metabolic, primary dystonia, progressive/degenerative conditions (eg Hereditary Spastic Paraplegia), other
      - Spinal Cord Conditions – from any cause (eg Multiple Sclerosis, trauma, infection)

Table 3: Comorbidities and their definition

Aspiration pneumonia	Documented episodes of aspiration of saliva and or food requiring admission to hospital with changes on x-ray consistent with the diagnosis
Bronchiectasis	Disease where there is permanent enlargement of parts of the airways or lungs. Clubbed (usually) with history of recurrent chest infections or chronic lung disease confirmed by respiratory physician or bronchiectasis confirmed on CT scan of chest
Dysphagia	Difficulties with swallowing associated with poor oromotor control (requires a modified diet, thickened fluids or gastrostomy feeds, pain on swallowing). May have choking on thin fluids or swallowing abnormalities confirmed on modified barium swallow
Epilepsy	Recurrent seizures requiring anticonvulsant medication prn or daily
Gastro Oesophageal Reflux (GOR)	Obvious regurgitation on observation by clinician, has had cardioplasty or fundoplication due to GOR or diagnosis made by paediatric gastroenterologist. Reflux demonstrated on pH Study or imaging study (eg barium swallow, milk scan), abnormalities on endoscopy (eg stricture or Barretts oesophagus)
Hydrocephalus shunted	Ventriculoperitoneal or ventriculoatrial shunt in situ
Hydrocephalus unshunted	Diagnosis confirmed by neurosurgeon
Intellectual Disability	Confirmed by psychometric testing or on interview with school counsellor or psychologist
Oesophagitis	Endoscopy evidence of or biopsy proven oesophagitis where direct observation is 'normal'
Osteoporosis	Low impact fracture(s) or wedged vertebrae on lateral spine x-ray plus low bone mineral density on DXA/peripheral quantitative CT.
Respiratory failure	Documented hypoxia and carbon dioxide retention/ elevated bicarbonate in the appropriate clinical setting. Polysomnography may assist in this diagnosis. Non-invasive respiratory support may be considered.

c. Additional information recorded includes:
   - Data regarding the intrathecal baclofen test dose is recorded including test dose and sedation method, dose required for response and test dose adverse events
   - Baclofen concentration and total daily dose
   - Changes in nutrition, speech, swallow and use of augmentative communication
   - Salivary control is measured using the Drooling Impact Scale[46]
   - Musculoskeletal interventions, such as Botulinum Toxin-A injections and any orthopaedic surgery are also recorded for the two years prior to entry to the study and at each successive time point

d. Following pump implant the following is recorded: implant date; age of patient at implant; pump and catheter model and serial number; catheter tip height; implant technique and antibiotic use.

2. Classification of the sample:
Classification using the Gross Motor Function Classification System Expanded and Revised (GMFCS)[47], Manual Ability Classification System (MACS)[48] and Communication Function Classification System (CFCS)[49] and Functional Mobility Scale (FMS)[50] are documented for children with CP. Equivalent classifications are allocated to non-CP participants where relevant. These classification systems contribute to a functional performance view of daily life for individuals with CP, in accordance with the WHO ICF[31].

   a. GMFCS: Functional status can be categorised with respect to gross motor function by using the five levels of the gross motor classification system for cerebral palsy[51]. The levels assigned describe a child's ability in self –initiated movements, with a focus on sitting and walking. The GMFCS is clinically relevant[52] and both reliable and valid, with high inter-rater reliability[53] and good construct validity with the GMFM (r=0.91)[54].
   b. MACS: is a five-point scale corresponding to the structure of the GMFCS. This scale classifies how a child uses their hands to perform day-to-day activities that are appropriate for their age[48]. Inter-rater reliability of the MACS is reported as excellent (ICC = 0.97 (0.96 – 0.98)[48].
   c. CFCS: is a tool used to classify the everyday communication of an individual with CP into one of five levels according to effectiveness of communication[49]. The CFCS demonstrates content validity and shows very good test-retest reliability (ICC=0.82), good professional interrater reliability (ICC=0.77 for classification of children older than 4 years), and moderate parent-professional interrater reliability[49].
   d. The FMS allows classification of functional mobility in children 4 to 18 years, taking into account the range of assistive devices the child might use[50]. The FMS rates walking ability at 3 specific distances, 5, 50, 500 metres, representing the child's mobility in the home, school and in the community. The distances are a guide - it is the environment which is most relevant. The FMS requires rating of what the child actually does at a point in time, not what they can do or used to be able to do, to record mobility status.

3. Assessment of Body Structures and Function:
   a. Passive range of motion of the limbs will be measured with goniometry.
   b. Hypertonia, as defined by abnormally increased resistance to passive stretch while the patient is attempting to maintain a relaxed state of muscle activity[2]. This is assessed clinically using passive movements about a joint to determine muscular resistance. Hence the increased tone or hypertonia is perceived by the examiner. The hypertonia may be as result of spasticity, dystonia or rigidity. The level of passive resistance of muscles will be recorded using the Modified Ashworth Scale (MAS)[55].
   c. Spasticity will be measured and quantified using the Modified Tardieu Scale (MTS) which is a valid, reliable and sensitive abridged version of the Tardieu Scale[56,57]. The MTS is consistent with current definitions of spasticity assessing muscle response to passive movement at varying velocities, including rapid passive movement.
   d. The Barry Albright Dystonia Scale (BADS)[38] will be utilised to record dystonia severity in patients with dystonia. It is a five point ordinal scale that rates dystonia severity across eight body regions. The scale has some evidence of reliability[38,58], validity[38,58-61] and

excellent responsiveness to change for patients with secondary dystonia in ITB[25,27,30,34,38,62-64] and for other dystonia related interventions[65-68].

e. Hip migration percentage (MP) is a radiographic measure of the amount of ossified femoral head which is not covered by the ossified acetabular roof[69] when measured from a frontal view of an antero-posterior pelvic radiograph[69].

f. Spinal scolioisis will be measured from antero-posterior radiographs and will be quantified as the Cobb Angle[70,71].

g. Drooling: The Drooling Impact Scale[46] is a measure to evaluate the impact of drooling in children with neurological disorders. The tool has established reliability and validity as a subjective measure of the impact of drooling on caregivers and families, and is sensitive to changes in drooling[46]. Changes in saliva control had been anecdotally noted following ITB therapy.

4. Assessment for Ambulant participants

In ambulant patients, GMFCS levels I, II or III or equivalent, additional information is assessed and recorded including:

a. The One minute walk test is a measure of functional ability and walking endurance. Children are tested at their maximal walking speed with the distance covered in 1 minute recorded. Validity[72] and reliability[73] have been established for this measure.

b. The Gillette Functional Assessment Questionnaire (FAQ) (short version) is taken from the Skill Mastery of Typically Developing Children. The FAQ is a 10 level parent-report walking scale encompassing a range of walking abilities from non-ambulatory to ambulatory in all community settings. The FAQ is a reliable and valid scale for documenting functional change in children with chronic neuromuscular conditions. Parents or carers are asked to choose the level that best describes their child's usual or typical walking abilities[74].

c. Sagittal Gait patterns: The Winters Gage and Hicks[75] classification of hemiplegic gait describes four types of gait patterns based on the sagittal plane kinematics of the ankle, knee, hip and pelvis. Similarly classification of common gait patterns in children with spastic diplegia have also been developed by Rodda and Graham[76]. Their work draws heavily on patterns of knee involvement in spastic diplegia by Sutherland and Davids[77].

d. Pediatric Evaluation of Disability Inventory (PEDI) is a standardised assessment of how a child functions with an impairment in the context of their daily life. It has established reliability and validity to detect the presence, extent and area of a functional delay in children with physical impairment or combined physical and cognitive impairment[78]. The PEDI is designed to measure a child's ability across 3 measurement scales: functional skills, caregiver assistance, and modifications measure. Each scale is divided into 3 domains including self-care, mobility and social function.

5. Goals and Quality of Life, Ease of Care Assessment:

The collection of patient and carer satisfaction with ITB therapy is one of the primary outcomes from this study. Change in parents ratings on individualised goal performance and satisfaction with goal attainment will be obtained with the Canadian Occupational Performance Measure (COPM)[79]. In addition changes in quality of life, ease of caregiving and health status will be monitored.

a. Goal setting: ITB therapy is goal directed, either for increased function or improved comfort and ease of care. Individualised goal setting, in collaboration with families, is generally acknowledged as an integral aspect of intervention[80]. Goals are determined with the child and family using the COPM[79] an established reliable and valid measure[81]. The COPM is an individualised goal setting measure, providing a structure for the identification of goals in the occupational performance areas of self-care, productivity and leisure. It measures outcome based on individual performance and satisfaction with performance[79]. Goals are identified with the client and family, then rated on a 10-point scale for: Performance, how well they feel they can complete the activity; and Satisfaction with Performance, how satisfied they are with their current ability to complete the activity. For the purposes of the study up to a maximum of five goals are prioritised and goal performance and satisfaction are set at baseline and reassessed at 6 then 12 months.

b. Quality of Life, Health status and Ease of Care Assessment: Quality of life can be defined as "an individuals' perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[82]. Quality of life is an important construct to consider for all children with CP as there is likely to be some impact not only on the physical but also the social and emotional well-being of the child and their family. In this study the quality of life and health status of the participants as well as the caregiver burden on families will be measured. A variety of questionnaires will be utilised due to the differing domains they cover, comparison to previous ITB studies and emerging psychometric data to support their use. Quality of life will be measured at baseline, 6 and 12 months post pump implant. The study utilises the Cerebral Palsy – Quality of Life Questionnaire (CP-QoL)[83], the Care and Comfort Hypertonicity Questionnaire (CCHQ)[84] and the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD)[85].

The CP QoL is a CP specific questionnaire designed to be used for children between the ages of 4 and 12 years. This study will utilise the parent-proxy version. The CP QoL measures seven areas of a child's life: Social Wellbeing & Acceptance; Participation & Physical Health; Emotional Wellbeing; Pain & Impact of Disability; Access to Services and Family Health.

The CCHQ questionnaire was developed to evaluate functional care needs, and to a lesser extent quality of life in children with increased tone of cerebral origin, particularly those with 'severe' CP[84]. Early work on the CCHQ has been undertaken to establish content validity and the CCHQ has also been shown to be sensitive enough to detect changes when ITB was offered or dose levels changed[84]. Formal evaluation of reliability and validity has not been finalised. It is a self-report questionnaire and requires parents or caregivers to rate how easy or difficult it is for them or their child in the last two weeks to perform a range of tasks relative to a cooperative person without a disability. The areas covered include: Personal Care; Positioning/Transferring and Comfort and Interaction/Communication.

The CPCHILD evaluates function and health status, caregiver burden and health related quality of life in children with severe CP. It has been validated for use for caregivers of children with severe developmental disabilities such as those with non-ambulatory CP and

traumatic brain injury, who would be categorised in level IV or V of the GMFCS[85]. Responsiveness to change has been demonstrated following hip surgery in children with CP, GMFCS levels IV and V[86]. The domains of the CPCHILD include: Personal Care; Positioning, Transferring and Mobility; Comfort and Emotions; Communication and Social Interactions and Health. It also comments on pain and the importance of QOL items to the child.

6. Adverse Events:

The Australian Therapeutic Goods Administration (TGA) defines an adverse event (AE) as unintended and sometimes harmful occurrences associated with the use of a medicine, vaccine or medical device[87]. The TGA has adopted the Good Clinical Practice guidelines for the conduct of clinical trials from the International Conference on Harmonisation[88]. This national audit is a centralised, systematic adverse event reporting system for all children and adolescents receiving ITB therapy in Australia.

A paediatric rehabilitation specialist experienced in the use of ITB therapy at each site grades each AE according to the type, severity and causality. The date the AE occurred is recorded; for events that last several days the first date of the event is recorded. AE type are divided into: Synchromed system related, drug related and patient related (see Table 4). Severity of the AE is rated as mild, moderate or severe (see Table 5). For causality, events are graded as: unrelated or unlikely; possibly related or probably/definitely related to ITB therapy (defined in Table 6). These are attributed on the basis of patient history, onset or duration of symptoms and consistency with previous literature of AE reported to be related to ITB therapy. Classification of AE in this manner is based upon the OHRP Guidance on Unanticipated Problems and Adverse Events[89]. The intervention required and outcome for ITB therapy are also recorded (see Figure 1).

Table 4: ITB Therapy Adverse Event Type

Synchromed System	Drug	Patient
Pump	Overdose	Infection
Battery expiry	Human error	Lumbar wound
Flipping of pump	System error	Dorsal wound
	Withdrawal	Pocket
	Human error	Meningitis
	System error	
Catheter	Drug sensitivities	Other
Kinking	Bladder/ bowel disturbance	CSF leak
Obstruction	Dizziness	Issue with refill
Dislodgement	Drowsiness	Pseudomeningocele
Disconnection	Gastrointestinal upset	
Fracture	Hypotension	
	Hypotonia	
	Mood changes	
	Respiratory depression	
	Seizures	

Table 5: Severity Ratings for ITB related Adverse Events

Severity	
Mild	Awareness of signs or symptoms Observation but intervention is not indicated; signs and symptoms are transient
Moderate	Events introduce a low level of inconvenience and may interfere with daily activities Simple therapeutic measures are indicated
Severe	Events interrupt the patient's normal daily activities Systemic drug therapy or other treatment; they usually require admission to hospital.

Table 6: Definitions of causality of ITB Adverse Events

Causality	
Unlikely/unrelated	Temporal history not consistent with ITB therapy Other diagnoses more likely Pre-existing symptoms Inconsistent reporting of signs/symptoms
Possible	Temporal history may be consistent with ITB therapy Diagnosis may fit with ITB therapy No pre-existing symptoms Consistent reporting of signs/symptoms
Probable/ definite	Temporal history consistent with ITB therapy Known adverse event reported in the literature No pre-existing symptoms Consistent reporting of signs/symptoms

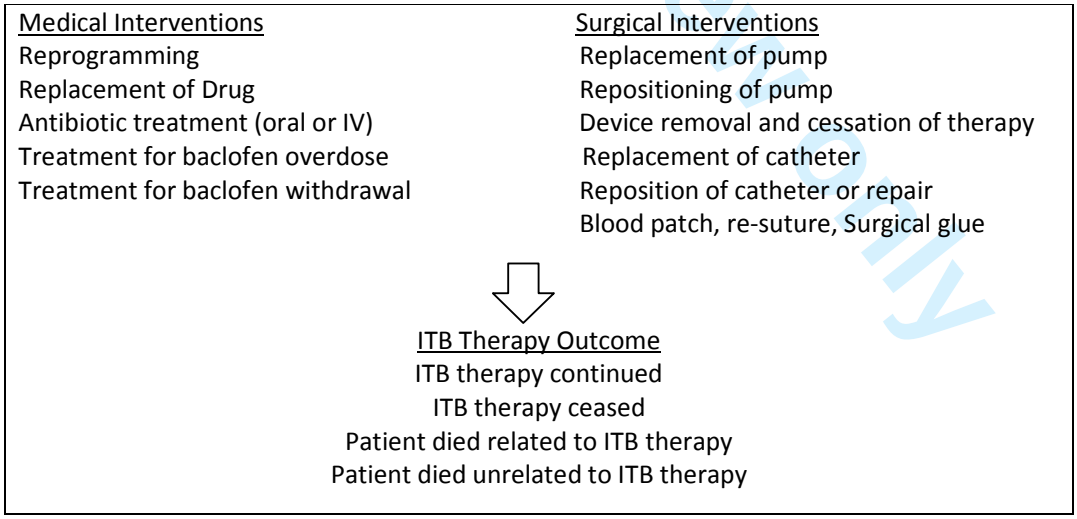

Figure 1: Adverse Event Interventions and ITB therapy outcome

Data entry

Data collected at each hospital site is de-identified and entered into the Australian ITB Audit Tool© Access database. Data are collected and entered at baseline, 6 months and 12 months and annually

after ITB pump insertion. Adverse event data is collected from date of pump implant to date of termination from the study. Data collection ceases if ITB therapy ceases, the patient dies or once patients transition to adult services.

Secondary Outcome

It is anticipated that an annual report will be generated from the national study by APIRG and distributed to the participating hospitals.

DISCUSSION

This protocol paper presents the background and study design of a 10 year, longitudinal, prospective, clinical audit. It is the first Australian study aiming to capture ongoing clinical and adverse event data from a complete population of children with neurological impairment receiving ITB therapy. The study ensures standardisation of ITB assessment across all Australian ITB centres and collection of a minimum data set for every child receiving ITB therapy.

Assessment of outcomes across the domains of the ICF, utilising psychometrically robust outcome measures where possible, will ensure comparison to studies in the literature and contribute further to the accumulating literature around ITB therapy for children. Collection of individualised goal performance and satisfaction with performance as well as quality of life data enables assessment of the impact of ITB upon personal cares, patient satisfaction and burden of care. Standardisation of AE classification and reporting provides the opportunity to further our understanding and management. Combing data across sites allows the association between certain AE and hypertonia types (spastic versus dystonic) and different diagnoses to be further explored. Data collected will also help identify the timing of certain complications, their management and outcomes and enable cross centre collaboration regarding expected and unexpected complications. This information is important to inform future recommendations of this intervention in paediatric populations.

Combining data from the small numbers from each participating site will provide insight into the specific diagnostic groups most likely to have the greatest benefit and carer satisfaction from ITB and ensures data can be used to guide ongoing clinical decision making and adverse event problem solving around ITB therapy for Australian children and adolescents.

ETHICAL CONSIDERATIONS AND DISSEMINATION

All participating Australian sites obtained individual ethics approval from their Human Research Ethics committees: The Children's Hospital at Westmead, NSW HREC 10/CHW/59; Princess Margaret Hospital for Children, Perth, WA HREC Ref 1797EP; Lady Cilento Children's Hospital, QLD HREC/10/QRCH/2; The Royal Children's Hospital, VIC HREC 32052; Monash Children's Southern Health, VIC HREC 11103B and The Women's and Children's Hospital, SA, WCH HREC 388A.
All eligible participants and their families/caregivers are provided with a Child and a Parent Information Sheet regarding the study and signed consent is obtained from the participant's parents and/or caregivers, and the participant if they are able. When patients are from culturally and linguistically diverse (CALD) backgrounds, health interpreter services available at each study site are utilised to explain the study and gain signed consent.

The study was registered with the Australian New Zealand Clinical Trials Registry with a registration number ACTRN 12610000323022.
Results of this study will be published in relevant peer reviewed journals. Results will also be presented at relevant national and international conferences.

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Competing Interests: None declared

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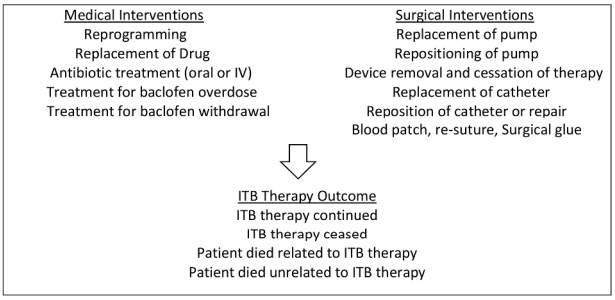

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