PAEDIATRICS

A NATIONAL MODEL OF CARE FOR PAEDIATRIC HEALTHCARE SERVICES IN IRELAND

CHAPTER 31: PAEDIATRIC METABOLIC MEDICINE

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

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ROYAL COLLEGE OF PHYSICIANS OF IRELAND

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31.0 INTRODUCTION

Inherited Metabolic Disorders (IMDs) cover a group of over 530 individual conditions, each caused by defective activity in a single enzyme or transport protein (Blau et al., 2014). Although individually metabolic conditions are rare, the incidence being <1.5 – 4 per 10,000 births, collectively they are a considerable cause of morbidity and mortality early in life (Applegarth et al., 2000).

A diagnosis of an IMD has a profound impact on patients and their families, their communities and the health system. Many of these conditions present in the newborn period or during the first few years of life, but some may also present in adolescence or later in life. The overall public health burden of these disorders is therefore cumulative. The diverse range of conditions varies widely in presentation and management according to which body systems are affected and the severity of the underlying defect. Without early identification and/or introduction of specialist diet or drug treatments, patients face severe disruption of metabolic processes in the body such as energy production, manufacture or breakdown of proteins, and management and storage of fats/ fatty acids, carbohydrates or complex molecules. The result is that patients have either a severe deficiency of products essential to health or an accumulation of toxic products. Without treatment, many conditions can lead to neurological symptoms, severe learning or physical disability, or overwhelming illness and even death at an early age. The rarity and complex nature of IMDs requires integrated specialised clinical and laboratory services to provide satisfactory diagnosis and acute/ long-term management.

Current and proposed expanded newborn bloodspot screening programmes identify some inborn metabolic diseases, and new technologies for diagnosis and more effective treatments promote improved survival rates and quality of life for children and adolescents with IMDs. Expansion of the newborn screening programme to include other treatable metabolic conditions (in line with other developed countries) is urgently required to avoid preventable morbidity and mortality amongst affected children. With major advances in new treatments and advanced technology along with improved diagnostic efficiency (Walter, 2009), there are therapies emerging for many conditions that were previously considered to be untreatable, e.g. Lysosomal Storage Disorders. Within this context, there is increasing awareness of the urgent need to improve patient access to treatments for rare metabolic diseases across Europe. Paediatricians generally have higher exposure than many other physicians to rare disease patients (Knerr and Treacy, 2014).

The challenges of the transition from paediatric- to adult-based services, which are at an early stage of development for adult patients with IMDs in Ireland as opposed to the United Kingdom (UK) and many continental European countries, has been identified as an important area to be addressed (Knerr and Treacy, 2014).

A study in the UK itemised the demand for adult patients with IMDs, including a multidisciplinary approach, with the clinician and dietitian as the core of the team, but with the collaboration of clinical nurse specialists, social workers and other specialist services including laboratory (Martín-Hernández et al., 2009). An international study that evaluated the situation of adult and adolescent patients with metabolic diseases in Germany revealed that expertise for metabolic medicine was mainly provided by metabolic paediatricians (26 paediatric metabolic departments compared to three specialised internal medical departments in this country) but that the need for independent adult metabolic services is increasing as patients with IMDs survive longer (Hoffmann et al., 2005). Management of IMDs requires a coordinated approach from the core IMD multidisciplinary team with access to IMD laboratory expertise as well as support from many different medical specialties (Rare Disease Centres Proposal, 2012/13). An IHSAB review (2006) identified the National Centre for Inherited Metabolic Disorders (NCIMD) at Children's University Hospital, Temple Street (Temple Street) as a Centre of Excellence (CoE) for paediatric metabolic medicine.

31.1 CURRENT SERVICE PROVISION

The commencement of newborn screening in the 1960s contributed considerably to the development of paediatric metabolic services at Temple Street. There has been substantial expansion of the service since then to encompass entirely metabolic functions and delivery of care as a Centre of Expertise (CoE) for metabolic diseases. The identification of new IMDs due to advanced technology, improved diagnostics and treatment strategies, and better clinical outcomes have all contributed to the expansion of workload. There are currently 1830 metabolic patients in the NCIMD Temple Street service, of which approximately one quarter are now adults and their care needs to be addressed separately; 482 adult patients continue to receive dietetic services from Temple Street.

The large paediatric cohort require a high standard of multidisciplinary care, with integration of medical and psychosocial aspects, education and access to patient organisations and clinical trials, as recommended by the European Union Committee of Experts on Rare Diseases (EUCERD) in 2011 and 2013. The National Screening and Metabolic Laboratories are based at Temple Street ensuring that metabolic patients receive a continuum of diagnostic, care and support services according to their needs. Temple Street metabolic consultants also provide a service in Our Lady's Children's Hospital Crumlin (Crumlin) and in (limited) outreach clinics providing equitable and safe access for children with IMDs. As many IMDs can be fatal early in life, there are close links with Laura Lynn House and with the liaison nurse for children with life-limiting conditions. These IMDs include severe forms of mitochondrial conditions that present with liver failure or encephalopathy for example, neuro-metabolic degenerative diseases and many others.

NCIMD is a designated CoE since 2006 and has been a national centre since 1986. As a CoE, the department provides expertise for the management and care of patients with rare metabolic diseases at national level, and at international level where necessary. Our scope is to cover all metabolic patients' needs, and to bring together and coordinate multidisciplinary competences and skills (including health and social care professionals) to serve the specific medical, rehabilitation and palliation needs of these vulnerable paediatric patients. The research component of the NCIMD at Temple Street is also very strong. We contribute to research aimed at optimising diagnosis, care and treatment, including the clinical evaluation of long-term effects of new treatments.

31.1.1 Staffing

Current staffing levels are outlined below:

Medical	**Consultant**	**Registrar**	**SHO**	
	3.9WTE	3-4WTE	1-2WTE	
Nursing	**CNM3**	**Enzyme Coordinator**	**Research Nurse**	
	1WTE	1WTE (funded by industry)	1WTE (funded by grants & industry)	
	CNS	CNM2	HCA	
	1.4WTE	1WTE	1WTE	
	St. Brigid's Ward			
	CNM2	Clinical Education Facilitator	Staff Nurses	HCA
	1WTE	1WTE	10.27WTE	1WTE

Dietetics	4.4WTE funded by Temple Street (including 0.6WTE Dietitian Manager; 3.8WTE clinical posts) 1WTE funded by industry (research & clinical) 1WTE:245 paediatric patients requiring dietetic input, service provided 365 days per year with weekend/public holiday on call		
Psychology	2WTE	Social Worker	1.5WTE
Play Specialist	0.5WTE		
Physiotherapist	0.5WTE (funded by industry)		
Genetics Counsellor	0.5WTE previously funded by industry, post expired February 2014		
Administration	4.6WTE (including 0.6WTE dietetic administrative support)		

31.1.2 New Referrals

There were 374 new paediatric referrals to the service in 2014, 330 in 2013 and 362 in 2012. New paediatric referrals are received from:

- National Newborn Screening Programme (NNSP) for IMDs – Phenylketonuria (PKU), Galactosaemia, Homocystinuria, Maple Syrup Urine Disease (MSUD). Newborns with a positive blood screening result are usually seen within 24 hours for admission to Temple Street. Babies with classical galactosaemia or MSUD will be either admitted directly to Temple Street or locally for assessment by a paediatrician and initiation of therapy. Newborns are often very sick at the time of diagnosis and need specific emergency therapy. Stabilisation at peripheral units is preferable prior to transfer to Temple Street.
- Consultant paediatrician referrals, e.g. developmental and general paediatrics, neurology, cardiology, and gastroenterology. Referral letters are screened by paediatric metabolic consultants, and are either seen in outpatients in Temple Street or are admitted directly for further investigations - this cuts out unnecessary OPD visits and reduces time to diagnosis.
- Inpatient consultation referrals within Temple Street (approx. 120 per year)
- Inpatient consultation referrals from Crumlin (approx. 180-190 per year)
- Telephone consultations from paediatric and neonatal units, ICU/HDU in Dublin and nationwide
- GP referrals – suspected metabolic disorder, and known paediatric metabolic patients moving to the Republic of Ireland.

There are close working relationships between the multidisciplinary metabolic team, the metabolic laboratories, and the national newborn screening laboratory in Temple Street. The primary purpose of the NNSP is to provide early treatment for IMDs detected by screening in order to prevent severe disability or death. The incidence of selected IMDs diagnosed on newborn screening in Ireland is:

Newborn Screening Introduced	IMD	Irish Incidence
1966	Phenylketonuria	1:4,500
1971	Homocystinuria	1:68,000
1972	Classical Galactosaemia	1:16,476
1972	Maple Syrup Urine Disease	1:125,000

The annual reports of the NNSP show actual numbers of cases diagnosed in recent years, highlighting that the majority of paediatric metabolic patients attending the metabolic service in Temple Street are not diagnosed through newborn screening:

IMD	2007	2008	2009	2010	2011	2012	2013	2014
Phenylketonuria	19	26	13	16	12	13	18	19
Classical Galactosaemia Homocystinuria	2	5	10	6	2	7	9	7
Homocystinuria	1	0	1	1	2	0	0	2
Maple Syrup Urine Disease	2	0	0	0	1	0	0	0
TOTAL	24	31	24	23	17	20	27	28

The 'top ten' metabolic diseases seen in NCIMD Temple Street are:

- PKU
- Respiratory chain defects/ mitochondrial disorders
- Classical galactosaemia
- Homocystinuria
- Fatty acid oxidation defects (all types)
- Mucopolysaccharidoses (all types)
- Glutaric aciduria (GA1)
- Urea cycle defects
- Glycogen storage disorder (all types)
- MSUD

Mucopolysaccharidosis Type 1H (MPS1H) is more common in Ireland than any other country (1:26,000 incidence) and patients with Hurler Syndrome (severe phenotype) require haematopoietic stem cell transplantation. The retirement of Dr. Anne O'Meara, consultant oncologist in Crumlin who had performed approximately 50 MPS1H transplants, has led to significant problems in the provision of care to the MPS1H patient group as there is no local transplant service currently offered to these children. Since March 2013, six children have been referred to Manchester for transplantation at an agreed cost of €200,000 per transplant. These patients require specialised haematology expertise pre-, during and post-transplant and the metabolic unit at Temple Street is unable to take on the transplant-related care of these patients. Their care pathway is complex, involving metabolic medicine and haematology teams at Crumlin and Royal Manchester Children's Hospital, as well as many other disciplines including ear, nose and throat (ENT), ophthalmology and orthopaedics split between the two main children's hospitals. A local transplant service is urgently needed, and will have the potential to reduce costs given that on average three babies are diagnosed with MPS1H annually.

31.1.3 Clinical Activity

In principle, children with IMDs who present early in life (i.e. as neonates or during infancy) suffer from a more severe form than patients with a later onset. It is therefore estimated that the management of neonatal or infant cases is much more complex than the management of patients with late onset or intermittent form. There are metabolic diseases that present as overwhelming illness in young children, e.g. Leigh's disease, urea cycle defects, organic acidurias, LARS defect (Casey et al., 2012), and patients who survive into adulthood usually have a milder phenotype. Other conditions, such as PKU, are much less detrimental in adult males and females beyond their child-bearing years than in vulnerable children and babies.

Another feature of the clinical workload is the relatively large proportion of children from the Travelling community, who are over-represented, as children from this population have a 15-fold increased prevalence of IMDs in comparison to children not from the Travelling community (Lam et al., 2013).

Current caseloads are as follows (data correct as of July 2015):

Total No. of Children	Total No. of Adults	TOTAL	New Paediatric Referrals Pending (waiting list)	No. Requiring Dietitian Input
1348 (<18 years)	482 (18 years +)	1830	107	1153 (63%)

Inpatient and outpatient activity is summarised as follows:

	2012	2013	2014
Admissions to St. Brigid's Ward Temple Street	381	449	564
Total Number of Bed Days	1217	1118	1590
OPD Clinics (Temple Street only)	2246	2100	2502

The total number of admissions is higher than reported here as sick neonates are usually admitted to Michael's B ward or ICU, or admissions may be to a general paediatric ward (e.g. for muscle biopsies) or to the day ward (e.g. for MRI or lumbar puncture). The average length of stay is three days (2014 data).

The metabolic ward has gradually been reduced from a full time ward to a five-day ward (four nights/five days, Monday to Friday). This has adversely affected the ability to admit children for planned investigations, e.g. fasting studies. The number of admissions was 500 in 2008 compared with 564 in 2014. Despite an increase in workload, available resources are being used more efficiently, through better outpatient and community services for patients with IMDs, e.g. vaccines administered locally with telephone contact and vaccine protocols, and the transfer of patients on enzyme replacement therapy (ERT) to home therapy. St. Brigid's ward was open for 228 days in 2014, and the significant rate of transfer of metabolic patients to other wards within the hospital can affect continuity of a child's ongoing treatment and care. In addition to approximately 120 inpatient consultation referrals within Temple Street, there are 180-190 in-house metabolic consultations in Crumlin each year which is an under-resourced service provided by the metabolic consultants with no secretarial or nursing support and minimal non-consultant hospital doctor support. There are seven to nine metabolic clinics held each week in Temple Street, with seven to 12 patients attending each clinic, 48 weeks per year.

All clinics are consultant-led with the exception of the PKU clinic, which is nurse- dietitian-led under the supervision of a paediatric metabolic consultant. A two-day multidisciplinary mucopolysaccharidoses clinic is held annually with a metabolic consultant and representatives from neurosurgery, dentistry, ophthalmology. There are also six dietetic-led carers clinics held each year. Outpatient clinics in Crumlin are led by the consultants from Temple Street (Dr. Ellen Crushell and Dr. Joanne Hughes) with minimal non-consultant hospital doctor support (4 hours SHO time per week). There are approximately 100-110 metabolic patient attendances in Crumlin each year.

Outreach clinics have been established to provide a better service for children with IMDs. Limerick is at the forefront (four clinics / year since January 2012) with Dr. Anne Marie Murphy acting as the local paediatrician with an interest in paediatric metabolic medicine. Eighteen children with IMDs were reviewed locally in 2014 at a consultant-led clinic with specialist nurse and dietitian support. An outreach service is also planned for Cork

and Galway. A concern for service planning is the long-term sustainability taking into account yearly increases in patient numbers and the complexity of care required. In line with international best practice, patients want to have shared care portfolios with local paediatricians and GPs where possible.

31.1.4 Education and Training

The Temple Street metabolic team provides education and training to healthcare professionals of all disciplines, as well as other groups such as teachers and personal/homecare facilitators, in Dublin and elsewhere whenever possible. However, there is a lack of paediatric specialist registrar (SpR) trainees which has been highlighted for a number of years, and enhanced education of future paediatricians and trainees in paediatric metabolic diseases is strongly recommended. A national survey of paediatricians and neonatologists undertaken in 2008 by the Health Service Executive (HSE) found that only 26% of respondents (18/70) had some training in paediatric metabolic medicine.

The nursing component of the metabolic unit is very strong, with the development of a metabolic education FETAC Level 8 course affiliated with Dublin City University run over seven non-consecutive days. This course has been adapted to include inviting other health and social care professionals to undertake the module. While the unit has clinical nurse specialists, it does not have advanced nurse practitioners, who would have a greater emphasis on research and audit.

Online access to patient/parent information and education as well as research activities is provided through the new NCIMD website (http://metabolic.ie). We launched our new website on 15 October 2015. It was accessed by over 3,000 users so far.

31.1.5 National Rare Disease Plan

The national rare disease plan was launched in July 2014 with a view to improving care of patients with rare diseases, and has gained momentum in raising awareness of rare diseases and the need to improve patient access to treatments for rare diseases. It will provide a framework for recognition of rare diseases and sharing of knowledge and expertise.

31.2 PROPOSED MODEL OF CARE

In the future, the national paediatric IMD centre will:

- Accept 24/7 referrals for paediatric patients with suspected IMDs
- Provide access to inpatient/ neonatal/ critical care facilities where appropriate
- Provide dedicated IMD inpatient and outpatient facilities
- Provide timely diagnosis with appropriate counselling and psychological support for the patient and their family/carers
- Work closely with general paediatricians and neonatologists to ensure the best holistic medical care for patients, particularly in the inpatient setting
- Provide access to other specialised paediatric services, e.g. hepatology, cardiology, etc. as appropriate
- Perform regular patient reviews as per national guidelines or clinical practice, with written or electronic records of current treatment and patient response
- Provide high quality clinical expertise in accordance with national policy and guidance where available, or in accordance with accepted clinical practice

- Provide 24/7 access to clinical advice in conjunction with other paediatric and adult centres in a formally agreed service provider network
- Provide appropriate pharmaceutical drug treatment, dietary therapy and care
- Perform regular laboratory and other diagnostic tests as appropriate to monitor patient response to dietary therapy and/or medication
- Provide patient-centred services, sensitive to the individual's physical, psychological and emotional needs and supported through the provision of patient-appropriate information
- Develop and implement protocols for appropriate transition of metabolic patients at Temple Street
- Initiate appropriate and safe transfer of adult IMD patients to the adult metabolic service under formal arrangements between both hospitals
- Perform a minimum annual multidisciplinary review of all patients of core IMDs
- Agree care pathways and treatment protocols, and monitor compliance
- Provide access to appropriate and agreed shared care arrangements with other primary and/or secondary care providers, 'hub-and-spoke model of care'
- Provide options for home therapy where appropriate, supported by regular clinical monitoring, e.g. for children with lysosomal storage disorders
- Provide a telephone helpline for patients' families and carers, healthcare professionals, and non-healthcare and voluntary sector professionals. Online access to patient/parent information and education as well as research activities is provided through the new NCIMD website (http://metabolic.ie).

The fundamental requirements at NCIMD Temple Street comprise increased multidisciplinary staffing levels at NCIMD Temple Street in order to provide safe, accessible, and efficient services for our expanding cohort of children and adolescents with complex IMDs. This is of particular importance for the development and implementation of an appropriate, safe and effective transition process and transfer of (adult) metabolic patients to the appropriate adult services, and for future care standards, including expanded outreach clinics in line with the 'hub-and-spoke model of care'.

31.2.1 Outreach Services

Clinicians will work together to promote appropriate outreach facilities and local support structures (for children and adolescents with general IMDs and PKU patients). Outreach clinics should be extended to encompass Cork, Limerick, Galway and others. Support is provided to the Northern Ireland metabolic service through monthly cross border meetings at the National Centre for Inherited Metabolic Disorders in Temple Street with the Belfast-based metabolic paediatrician and clinical pathologist, to discuss complex cases, diagnostic pathways and clinical management.

31.2.2 Transition from Paediatric to Adult Services

Paediatric and adult IMD centres will develop appropriate working relationships under formal arrangements at hospital level, with the centres working together to ensure smooth and efficient transition of adult patients to appropriate facilities in line with best practice. In the proposed Model of Care the paediatric IMD centre will:

- offer adult patients and their families/carers an agreed period of assessment by the joint paediatric/adult team to ensure seamless transfer to adult services
- agree and provide a formalised operational transition policy at hospital level
- provide a clinical transfer record with all relevant clinical information
- provide age-appropriate written and/or electronic information to patients and their families/carers
- Develop and implement protocols for appropriate transition of metabolic patients at Temple Street

- Initiate appropriate and safe transfer of adult IMD patients to the adult metabolic service under formal arrangements between both hospitals. Transfer/transition of metabolic patients from NCIMD to the Adult Metabolic Service at The Mater has to incorporate the complex needs of these patients and their risk of acute metabolic decompensations.

31.2.3 Patient Education Programmes

Patient and parent education programmes, development of patient/family information material, active involvement and close collaboration with parent support groups are essential and well-established components of the metabolic service at Temple Street. A range of educational material has been developed by multidisciplinary team members including clinical nurse specialists, dietitians, psychologists and play specialists. Education plays an integral role at each outpatient attendance and inpatient admission. The NCIMD has established links with patient and parent support groups both at a national and at an international level. Online access to patient/parent information and education is provided through our new NCIMD website (http://metabolic.ie).

31.2.4 Clinical Care Standards, Guidelines and Care Pathways

Guidelines for the emergency management of patients with IMDs have been developed since 1993 at the NCIMD, and are currently updated every six months using expert opinion and focused literature reviews. Details of a range of guidelines, information leaflets, policies and procedures are contained within Appendices 1-3.

31.3 REQUIREMENTS FOR SUCCESSFUL IMPLEMENTATION OF MODEL OF CARE

The fundamental requirements for future delivery of the service at the NCIMD are strongly related to:

i. consolidation of current standards of care for paediatric patients with IMDs
ii. expansion of the clinical spectrum of new diagnoses and new therapies.
iii. ability to provide emerging treatment options for the paediatric IMD cohort
iv. challenges for future management and future care standards, including expanded day care services and greater need for outreach clinics (hub-and-spoke model of care)
v. challenges for appropriate, effective and safe transition and transfer of (adult) metabolic patients to the Adult Metabolic Service.

The fundamental requirements at NCIMD Temple Street comprise increased multidisciplinary staffing levels at NCIMD Temple Street in order to provide safe, accessible, efficient services for our expanding cohort of children with complex IMDs.

Future demands and strategies at the NCIMD also include sustainable development of clinical studies, including new enzyme therapies and hepatocyte transplantation, and coordinating services to provide eligible paediatric patients with IMDs access to therapeutic trials as well as further development of audits and quality initiatives.

31.3.1 Staffing

The metabolic ward in Temple Street was reduced to a five-day service (Monday-Friday), however a Monday-Sunday service would be more appropriate for this patient cohort. Greater involvement of general paediatrics, in particular with inpatients, is recommended. A combined metabolic-general paediatric admission would be

best positioned to ensure safe delivery of holistic care and also serve to further educate paediatric trainees in the area of IMDs. A multidisciplinary team approach is also essential for the management of patients with IMDs. Multidisciplinary staffing requirements to deliver this model of care are summarised below:

Staff Category	Previously Agreed (WTE)	Current (WTE)	Proposed (WTE)
Consultant Metabolic Paediatrician	4	3.9	6
Specialist Registrar/ Registrar	4	3	4
SHO	1	1-2	1
Nursing (Total)	26	17.67	26 (including 1 research nurse and 1 ERT coordinator)
Dietitian (Temple Street funded)	8	4.4	8 (including 0.5 research dietitian)
Physiotherapist	0	0.5	1
Psychologist	3	2	3 (or 2 clinical psychologists +3 trainees)
Social Worker	2	1.5	2
Play Specialist	1	0.5	1
Genetic Counsellor	0	0	1
Speech and Language Therapist	0	0	1
Occupational Therapist	0	0	1
Administration	6	4.6	6

31.3.2 Education and Training

Medical students from University College Dublin (UCD), Trinity College Dublin (TCD) and the Royal College of Surgeons in Ireland (RCSI), and occasionally from international universities, are accepted on the metabolic team and are integrated into the teaching schedule for their attachments. Student electives are accommodated and encouraged, and a number of successful medical student projects have been completed. Formal teaching programmes are provided through affiliations with UCD, TCD and RCSI, and training of paediatric non-consultant hospital doctors (NCHD) with the Royal College of Physicians in Ireland (RCPI). Postgraduate medical education is an integral part of the metabolic unit, with formal teaching rounds each week for NCHDs as well as a weekly journal club and clinical-laboratory meeting.

The first week of each six-month NCHD term is dedicated to teaching to provide the knowledge base required for caring for children with IMDs. National metabolic study days are also held almost annually. Neuro-metabolic and multidisciplinary cross border meetings are conducted on a regular basis, i.e. monthly.

31.3.3 Governance

Current governance structures comprise the Temple Street Chief Executive Officer, Temple Street Board of Directors and (paediatric) Clinical Director at Temple Street, and the NCIMD Clinical Director Dr. A.A. Monavari. There are close links to the HSE National Clinical Programmes. There are established collaborations with a variety of international societies and working groups with a view to improving patient outcomes, and developing international guidelines and consensus procedures. Multidisciplinary team members have been involved with high level presentations at scientific meetings on the latest clinical innovations, networking and collaborating with colleagues from a range of disciplines all working to improve the care of individuals with IMDs. An external review of the metabolic department at Temple Street by Walter and Levy (2005) recommended that all primary managerial responsibilities were centralised under the authority of the Clinical Director with named individuals in particular disciplines having some managerial responsibility for their area of work. Subsequently a dietitian manager and clinical nurse manager III were appointed.

Strong clinical governance is also evidenced by:

- NCIMD Temple Street is a CoE designation for paediatric metabolic care since 2006 and a National Centre since 1986.
- Nurse- and dietetic-led clinics were recognised as an excellent development by the external review in 2005
- Large multidisciplinary team have developed clinical practice guidelines for a range of conditions
- Established newborn screening programme, with proposals under consideration to expand the national newborn bloodspot screening programme to include two additional inborn metabolic disorders (medium chain acyl-CoA dehydrogenase deficiency and glutaric aciduria type 1)
- Established collaboration with international working groups, i.e., European Galactosaemia Network (EGN); Homocystinuria (E-HOD); Niemann Pick Diseases (INPDR); Mucopolysaccharidoses- International Consensus Procedures; Tyrosinaemia Type 1 Surveillance Programme; Liver cell therapy: Urea cycle defects – SELICA-clinical trial program.
- Established collaboration with national and international societies and metabolic working groups and high-level presentations at international scientific meetings (e.g. IPA, SSIEM, SIMD, BIMDG and others) to ensure the highest possible level of patient care and medical knowledge. Members of our team are serving at the committee of the Irish Society of Inherited Metabolic Disorders (ISIMD), including the president, treasurer, and board.

The issue of 'ring fencing' the budget for the NCIMD is complex, and has been further exacerbated by financial cuts which adversely affect services, e.g. delayed admissions for diagnostic investigations, waiting times are now 6 months to first appointments for new patients (excluding newborns and emergencies). The budget for the NCIMD should be ring fenced, as well as that for new treatments such as enzyme replacement therapy.

31.4 PROGRAMME METRICS AND EVALUATION

The introduction of national initiatives will include:

- A national patient register for children with IMDs at NCIMD Temple Street
- A national database of paediatric research trials and clinical outcome studies
- Annual audit and governance report

A database of patients with IMDs is currently held in NCIMD Temple Street. With support from Temple Street ICT team, this database is kept at the highest possible standard and is eligible for anonymized patient-oriented clinical research. Key performance indicators have been identified to measure and evaluate performance of the service, and clinical audits are conducted regularly.

31.5 KEY RECOMMENDATIONS

- Increase multidisciplinary staffing levels at NCIMD Temple Street in order to provide safe, accessible, efficient services for children with IMDs.
- Develop and implement protocols for appropriate transition of metabolic patients in Temple Street to enable appropriate and safe transfer of adult IMD patients to the adult metabolic service under formal arrangements between both hospitals (proposed: + 1 WTE Consultant Metabolic Paediatrician at NCIMD). This has to incorporate the complex needs of this high-risk cohort, including their risk of acute metabolic decompensations. Transfer and transition from paediatric to adult metabolic services are at an early stage of development for these patients in Ireland as opposed to the UK and many continental European countries.
- Develop and implement protocols for future care standards, including expanded day care services, outreach clinics ('hub-and-spoke model of care') to improve paediatric care providers' ability to arrange for care within a reasonable driving distance for patients/families and to provide specialty care in patients' own communities where possible (proposed: + 1 WTE Consultant Metabolic Paediatrician at NCIMD). In addition, more effective treatments for IMDs in children along with improved survival rates is leading to a higher requirements for specialised clinical service to provide satisfactory acute and long-term management. The overall aim is to improve quality of care and outcome and to reduce avoidable risk for this vulnerable cohort.
- Increase the metabolic service in Temple Street from five to seven days. Move to combined metabolic / general paediatrics admissions for metabolic patients where possible.
- An Irish MPS1H transplant service is required.

31.6 ABBREVIATIONS AND ACRONYMS

CoE	Centre of Expertise
EUCERD	European Union Committee of Experts on Rare Diseases HSE Health Service Executive
IMD	Inherited Metabolic Disorders
MPS1H	Mucopolysaccharidosis Type 1H
MSUD	Maple Syrup Urine Disease
NCIMD	National Centre for Inherited Metabolic Disorders
NCHD	Non consultant hospital doctor
NNSP	National Newborn Screening Programme
PKU	Phenylketonuria
RCPI	Royal College of Physicians in Ireland RCSI Royal College of Surgeons in Ireland
SHO	Senior House Officer
SpR	Specialist Registrar
UCD	University College Dublin
UK	United Kingdom
WTE	Whole Time Equivalent
ISIMD	Irish Society of Inherited Metabolic Disorders

31.7 REFERENCES

Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. Paediatrics. 2000 Jan;105(1):e10.

Blau N, Duran M, Gibson KM, Dionisi-Vici C. IEMBASE. Metabolic-Genetic Knowledgebase. In Blau N, Duran M, Gibson KM, Dionisi-Vici C (eds). Physician's Guide to the Diagnosis, Treatment, and Follow-up of Inherited Metabolic Diseases. Springer Heidelberg, 2014. *http://www.iembase.org/*

British Inherited Metabolic Disease Group Guidelines (*www.bimdg.org.uk*) 2012/2013.

Buraczewska M, O'Leary D, Walsh O, Monavari A, Crushell E. Parental experience of enzyme replacement therapy for Hunter syndrome. Ir Med J. 2013 Apr;106(4):120-2.

Casey JP, McGettigan P, Lynam-Lennon N, McDermott M, Regan R, Conroy J, Bourke B, O'Sullivan J, Crushell E, Lynch S, Ennis S. Identification of a mutation in LARS as a novel cause of infantile hepatopathy. Mol Genet Metab. 2012 Jul;106(3):351-8.

Coss KP, Doran PP, Owoeye C, Codd MB, Hamid N, Mayne PD, Crushell E, Knerr I, Monavari AA, Treacy EP. Classical Galactosaemia in Ireland: incidence, complications and outcomes of treatment. J Inherit Metab Dis. 2013 Jan;36(1):21-7.

EUCERD recommendations 2011-2013. *http://www.eucerd.eu/*

Hawkes CP, Walsh A, O'Sullivan S, Crushell E. Doctors' knowledge of the acute management of Inborn Errors of Metabolism. Acta Paediatr. 2011 Mar;100(3):461-3.

Hoffmann B, Schwarz M, Häussinger D, Mayatepek E, Wendel U. Situation of adult patients with inborn errors of metabolism. A survey in Germany. Med Klin (Munich). 2005 Oct 15;100(10):617-23. PMID:16220250.

Hughes J, Ryan S, Lambert D, Geoghegan O, Clark A, Rogers Y, Hendroff U, Monavari A, Twomey E, Treacy EP. Outcomes of siblings with classical galactosemia. J Pediatr. 2009 May;154(5):721-6.

Jones SA, Parini R, Harmatz P, Giugliani R, Fang J, Mendelsohn NJ; HOS Natural History Working Group on behalf of HOS Investigators. The effect of idursulfase on growth in patients with Hunter syndrome: data from the Hunter Outcome Survey (HOS). Mol Genet Metab. 2013 May;109(1):41-8.

Knerr I, Treacy EP. Hereditary metabolic disorders may be under-diagnosed. Irish Medical Times. February 26, 2014. *http://www.imt.ie/clinical/2014/02/hereditary- metabolic-disorders-may-be-under-diagnosed.html*

Knerr I, Vockley J, Gibson KM. Disorders of Leucine, Isoleucine and Valine Metabolism. In: Blau N, Duran M, Gibson KM, Dionisi-Vici C (eds). Physician's Guide to the Diagnosis, Treatment, and Follow-up of Inherited Metabolic Diseases. Springer Heidelberg, 2014.

Lam O, Crushell E, Knerr I, O'Reilly E, Hughes J, Monavari AA, Treacy EP. Prevalence of Hereditary Metabolic Diseases in the Irish Traveller Population (abstract). Irish Journal of Medical Science, August 2013. UCD Student Summer student project. Poster presentation UCD SSRA August 2013.

Martín-Hernández E, Lee PJ, Micciche A, Grunewald S, Lachmann RH. Long-term needs of adult patients with organic acidaemias: outcome and prognostic factors. J Inherit Metab Dis. 2009 Aug;32(4):523-33. doi: 10.1007/s10545-009-1191-12.

McCarron E, McCormack O, Cronin T, McGowan A, Healy ML, O'Rourke D, Crushell E, Ravi N, Reynolds JV. Management of maple syrup urine disease in the peri-operative period. Ir Med J. 2013 Oct;106(9):277-8.

NICE guidelines on Familial Hypercholesterolaemia (FH) recommended that paediatric patients are referred to specialised IMD centres (*www.nice.org.uk*).

Rare Disease Centres Proposal, Advisory Group for National Specialised Services (www.bimdg.org.uk) 2012/2013.

Ventzke A, Hoffmann J, Crushell E, Monavari AA, Mayne PD, Knerr I. Dihydropteridine reductase (DHPR) deficiency in Ireland: Long-term follow-up and outcome of three patients. J Inherit Metab Dis, 2014, Suppl 1, S64.

Walter JH. Genes, patients, families, doctors-mutation analysis in clinical practice. J Inherit Metab Dis. 2009 Jun;32(3):441-6.

31.8 APPENDICES

31.8.1 Appendix 1: Examples of Protocols, Policies, Procedures, Guidelines and Care Pathways in NCIMD

Protocols
• Fasting study
• Hypoglycaemia work-up
• 24 hours Glucose and lactate profile
• Oral glucose load
• Lactate / pyruvate ratio studies
• Oral protein load
• Protocol for post-heparin lipoprotein lipase test in children
• Protocol for enzyme replacement infusion reaction
• Allopurinol test
• Phenylalanine load

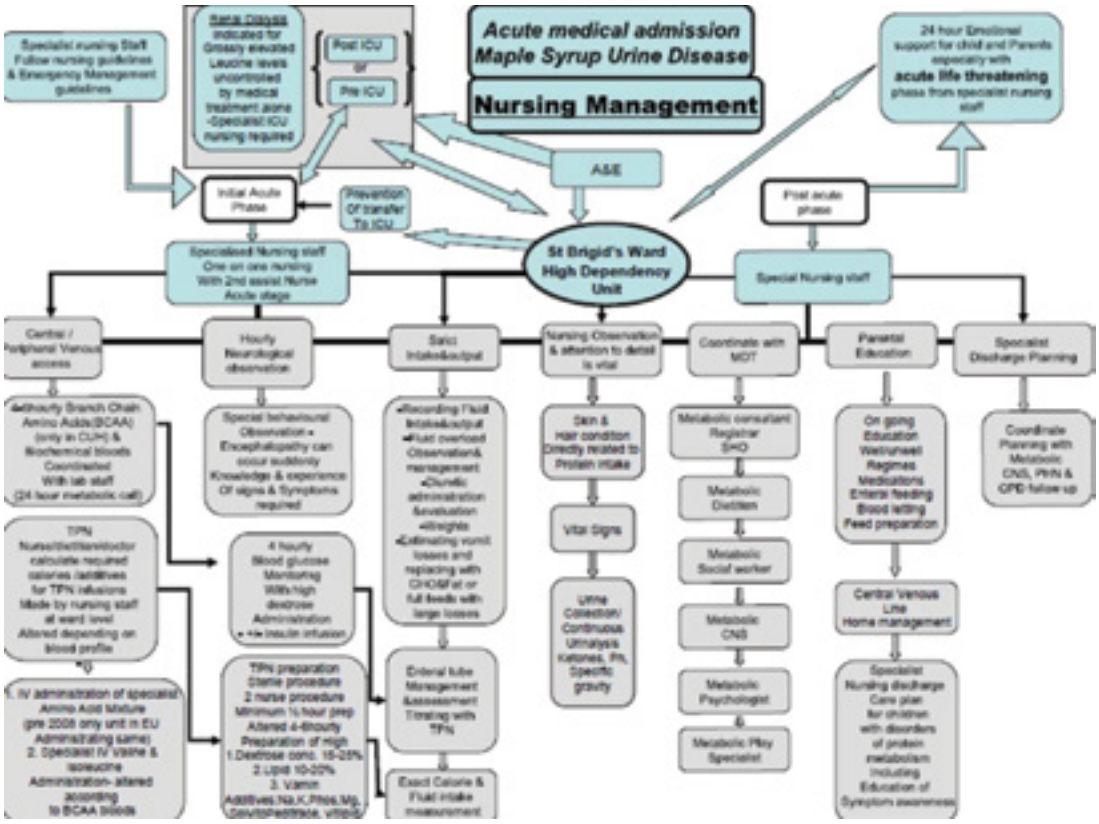
Policies and Guidelines for Dietary Management of IMDs
• Guidelines on the dietary treatment of a newly diagnosed infant with classical galactosaemia and on-going dietary management throughout the life cycle • Policy on treatment of newly diagnosed PKU baby • Hyperphenylaninaemia level reporting guidelines • Guidelines for the management of hyperphenylalaninaemia throughout the life cycle • Guidelines for protein exchange identification • Guidelines for dietary management of Smith Lemli Opitz Syndrome
Care Plans
• Metabolic investigation care plan • Protein load care plan • Altered nutritional requirements: Glutaric Aciduria Type 1 care plan • Urea Cycle Defects (new diagnosis) care plan • Potential / Actual Altered Neurological function secondary to Maple Syrup Urine Disease (MSUD) • Galactosaemia (new diagnosis) care plan • PKU (new diagnosis) care plan • HCU (new diagnosis) care plan • Potential / Actual Altered Neurological Function secondary to Hyperammonaemia Care plan • Enzyme replacement for Lysosomal Storage Disorders care plan • Glycogen storage disease care plan. • Hypoglycaemia care plan • Altered Nutritional Requirements: Methylmalonic aciduria (MMA) / Propionic aciduria (PA) Care Plan • Applying credit card sized emergency cards for patients (e.g. MSUD, GA1) that outline a simplified six-step acute management plan, based on international best practice (Hawkes & Crushell et al., 2011). Each of these cards is disease specific, and contact details of the patient's physician, nurse and on call metabolic service are listed on the alternate side. This was well received by physicians and patients. • Standard therapeutic pathways, emergency regimes and diagnostic flow-charts for the management of patients with disorders of branched-chain amino acids have recently been published in a medical textbook for reference by a member of our group (Knerr et al., 2014)

31.8.2 Appendix 2 Examples of Patient Information Leaflets in NCIMD

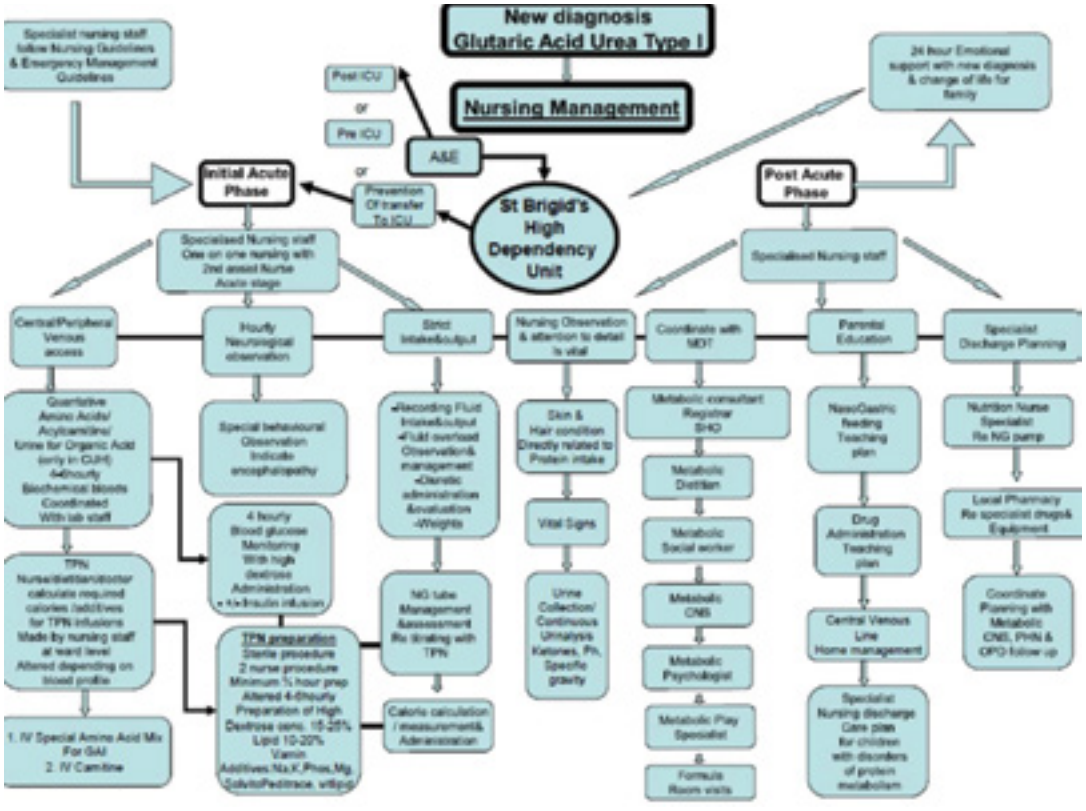
- Muscle biopsy
- Skin biopsy (parent)
- Skin biopsy (adult)
- Fasting study
- Glucose and lactate profile
- Oral glucose load
- Lactate / pyruvate ratio
- 'Welcome to St Brigid's Ward' – inpatient unit information
- Recessive Inheritance – an information leaflet for parents and families
- Mitochondrial illness
- New diagnosis handbooks for babies diagnosed with PKU, MSUD, MMA, PA, HCU, GA1
- Diet sheet for newly diagnosed Galactosaemia baby
- Weaning booklets for Galactosaemia and all protein disorders
- MCAD with information appropriate for babies through to adulthood.

31.8.3 Appendix 3 Patient Pathways / Algorithms

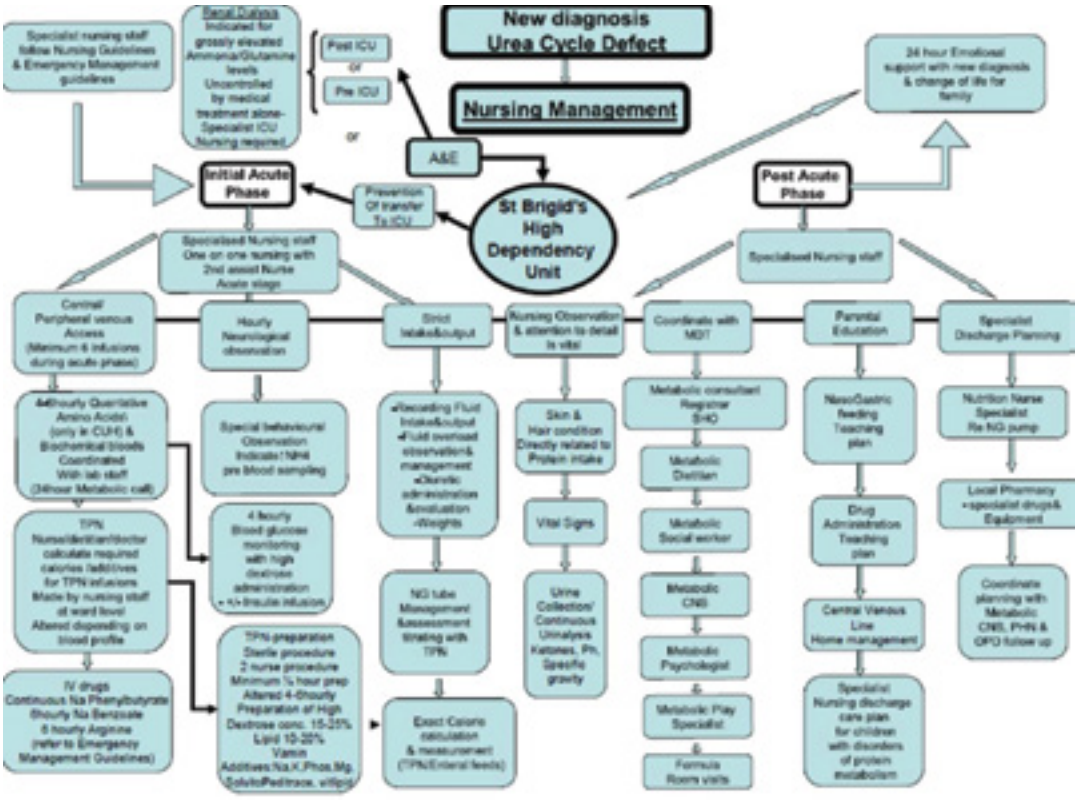
Pathway for Nursing Management of Maple Syrup Urine Disease (MSUD)



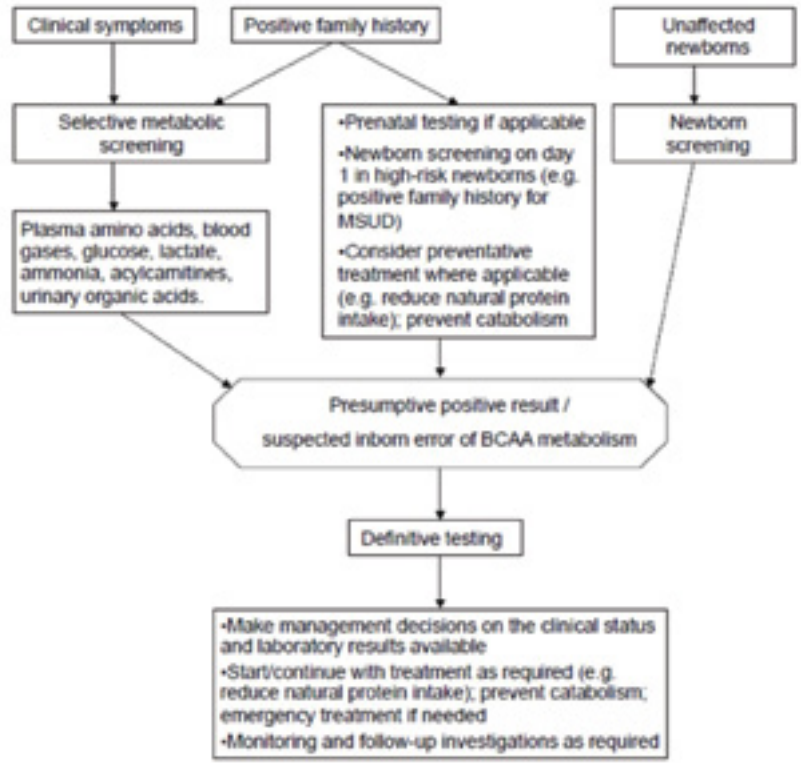
Pathway for Nursing Management of Glutaric Aciduria (GA1)



Pathway for Nursing Management of Urea Cycle Defect



Diagnostic Flowchart for Newborns with Suspected IMD



Standard Therapy and Emergency Flowchart for Children with IMDs