International Niemann-Pick Disease Registry

Scoping exercise report

Background and Introduction

The International Niemann-Pick disease registry (INPDR) has been co-funded under the 2012 EU Health Programme by the Directorate General for Health and Consumers (DG-SANCO) via its Executive Agency for Health and Consumers. The INPDR is a collaborative disease registry owned by patient groups, clinicians, scientists and researchers involved in the care of patients with Niemann-Pick disease (NPD). The registry collects clinical, genetic, diagnostic and outcome data from patients as well as a patient reported dataset designed for patients and family members to complete. The registry will enable progress in the field of NPD by allowing authorised access to anonymised clinical data, helping to identify and recruit patients to clinical trials and coordinate research efforts globally. This will stimulate a step change in the volume and quality of research into NPD which will help to improve patient outcomes.

Niemann-Pick (NPD) type A, B and C diseases, <0.02, 0.10 and 0.75 cases/100,000, respectively are rare genetic diseases with distinct but overlapping clinical spectrum that ranges from a neonatal fatal disorder to an adult onset chronic debilitating neurodegenerative disease. The diseases usually progress to death in early adulthood. Patients are distributed throughout the EU, and there are as yet no disease specific orphan drug treatments available for NPD.

The vision of the INPDR is to make the EU health service a more supportive environment for NPD patients, to reduce morbidity and premature mortality, and to improve quality of life. Our strategic objective is to support efficient diagnosis, treatment, and research for NP diseases in Europe. We will achieve this by implementing an EU registry for NPD. We expect to achieve high usage of the registry by linking it to rapid diagnostic testing, accurate information, and teaching resources.

This will support equality of access to diagnosis and care in the EU; educate health professionals; and empower patients.

This project will fulfil our vision and the vision of the EU of a more supportive equitable environment in Europe by causing an improvement in the quality of life for patients with NPD. This will be achieved by earlier diagnosis, prompt identification and management of complications and sharing good clinical practice. Achievement of our objectives will result in a step change in the way information, diagnostic and clinical services are provided to Niemann-Pick patients and how research is undertaken. The implementation of the INPDR, supported by rapid access diagnostic testing and easier availability of education material, will facilitate the following outcomes:

• The registry will be directly transferable to scientists from different disciplines exploring the mechanisms underlying common neurodegenerative diseases; and will be an important resource for pharmaceutical companies developing orphan drugs and specialist health care providers.

• We will have documented the natural history of the three Niemann-Pick diseases, and established genotype phenotype correlations for each disease.

• An improvement and uniformity of the clinical effectiveness of services for Niemann-Pick patients.

• The social context shows that: a) affected persons with Niemann Pick diseases are distributed across all sectors of the EU population without regard to socio-economic status; b) they feel socially isolated as they develop physical and mental disability; c) they feel medically isolated as health professionals fail to recognize their diseases; this is not clearly improving as services for these 3 diseases are underdeveloped across the EU member states. This project provides an EU-wide opportunity to support the development of centres of expertise, transnational collaborations, and research and services assessment for patient benefit.

• The cultural context is that patients are overrepresented in groups that practice first cousin marriages; and these patients are often, but not always, from the Muslim faith. The project will be developed with regard to the cultural and religious requirements of these groups (sensitive genetic counselling, provision of female chaperones in centres of expertise; information provided incorporating faith issues (e.g. organ donation, blood transfusions, cultural- and faith- specific dietary advice).

We have used qualitative questionnaires and focus groups of health professionals, to scope the support requirements of centres for submitting data to the registry. We have developed a consensus on a core dataset for the registry, and developed a multifunctional web based registry with user friendly browser based access. One of the key requirements of the scoping is that potential impacts are identified, and are avoided or reduced if at all possible. This can either be performed through targeted educational materials or specific help being available via download.

In this scoping exercise we review the methods of identifying core and extended data points required in the registry, the patient reported datasets, perform a literature review of current known barriers to data entry within a registry, hold and review focus groups that identify the learning needs of health professionals and the potential or known barriers to data entry within the NPD community, and produce surveys which are administered to a vast array of health professionals who could potentially enter data from Doctors, nurses, scientists, data managers, study co-ordinators and researchers.

The scoping exercise of this project has been carried out during the first phase of the action to ensure that any findings or possibilities are taken in to full consideration. This will ensure that any dangers to the project and/or barriers to data entry are identified and mitigated. At this early stage changes can still be incorporated in to the project designs.

Scoping exercise Literature review

A systematic review of published barriers to data entry and barrier to physicians completing online surveys to better understand what techniques and education materials will help to facilitate the complete and accurate data entry to the INPDR. The methods and results of this literature review have been discussed at INPDR focus groups and conclusions drawn regarding what information will be provided to all that enrol on to the INPDR, including patients and clinicians.

- **Braithwaite D, Emery J, de Lusignan S and Sutton S. Using the Internet to conduct surveys of health professionals: a valid alternative? *Family Practice* 2003; 20: 545–551.**

The purpose of this study was to examine whether Internet-based surveys of health professionals can provide a valid alternative to traditional survey methods, such as telephone or postal surveys.
The paper identified 17 Internet-based surveys of health professionals. Whilst most studies sampled from professional e-directories, some studies drew on unknown denominator populations by placing survey questionnaires on open web sites or electronic discussion groups. Twelve studies reported response rates, which ranged from 9 to 94%.
Sending follow-up reminders resulted in a substantial increase in response rates. In the survey carried out in the paper, a total of 268 General Practitioners (GP) participated (adjusted response rate = 52.4%) after five e-mail reminders. A further 72 GPs responded to a brief telephone survey of non-respondents.
Respondents to the Internet survey were more likely to be male and had significantly greater intentions to use Internet-based decision support than non-respondents.

Conclusions of this paper include:
Internet-based surveys provide an attractive alternative to postal and telephone surveys of health professionals. The major obstacle was found to be external validity, and specifically how to obtain a representative sample and adequate response rate.

- **Surveying Clinicians by Web: Current Issues in Design and Administration Eval Health Prof (2013) 36 (3): 352-381**

This paper confirmed and built upon the idea of the versatility, speed, and reduced costs with which web surveys can be conducted with clinicians are often offset by low response rates. It was found that when administered online, design-based features affect rates of survey participation and data quality. These include sample frames, incentives, contacts (type, timing, and content), mixed-mode approaches, and questionnaire length.

- **Surveying Ourselves: Examining the Use of a Web-Based Approach for a Physician Survey Eval Health Prof (2011) 34 (4): 448-463**

Although physician surveys are an important tool in health services and policy research, this paper acknowledges that they are often characterized by low response rates. The authors conducted a systematic review of 66 published reports of efforts to improve response rates to physician surveys. Two general strategies were explored in this literature: incentive and design-based approaches. Even small financial incentives were found to be effective in improving physician response. Token nonmonetary incentives were much less effective. In terms of design strategies, postal and telephone strategies have generally been more successful than have fax or Web-based approaches, with evidence also supporting use of mixed-mode surveys in this population. In addition, use of first-class stamps on return envelopes and questionnaires designed to be brief, personalized, and endorsed by legitimizing professional associations were also more likely to be successful. Researchers should continue to implement design strategies that have been documented to improve the survey response of physicians.

- **A guide for the design and conduct of self-administered surveys of clinicians CMAJ (2008) 179 (3): 245-252**

This paper discusses how questionnaires can be descriptive (reporting factual data) or explanatory (drawing inferences between constructs or concepts) and can explore several constructs at a time. Questionnaires can be informal, conducted as preparatory work for future studies, or formal, with specific objectives and outcomes.

Rigorous questionnaires can be challenging and labour-intensive to develop, test and administer without the help of a systematic approach. In this article, outline steps were defined to design, develop, test and administer valid questionnaires with minimal bias and optimal response rates. Differences between postal and electronic administration of surveys were highlighted.

- **Registries for Evaluating Patient Outcomes: A User's Guide. 2nd edition. Gliklich RE, Dreyer NA. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Sep.**

This user guide is intended to support the design, implementation, analysis, interpretation, and quality evaluation of registries created to increase understanding of patient outcomes. Although registries can serve many purposes, this guide focuses on registries created for one or more of the following purposes: to describe the natural history of disease, which is applicable in the case of the INPDR, to determine clinical effectiveness or cost effectiveness of health care products and services, to measure or monitor safety and harm, and/or to measure quality of care.

- **Paul D. Clayton, Scott P. Narus, Watson A. Bowes, III, Tammy S. Madsen, Adam B. Wilcox, Garth Orsmond, Beatriz Rocha, Sidney N. Thornton, Spencer Jones, Craig A. Jacobsen, Marc R. Udall, Michael L. Rhodes, Brent E. Wallace, Wayne**

Cannon, Jerry Gardner, Stan M. Huff, Linda Leckman AMIA Annu Symp Proc. 2005; 2005: 141–145.

This paper evaluated whether physicians in an ambulatory setting will voluntarily choose to enter data directly into an electronic health record (EHR). This is important for the INPDR as it has been discussed that many physicians would prefer to enter data in this way. It was reviewed that currently, of 472 employed physicians, 321 (68%) routinely enter some data directly into the EHR without coercion. Twenty-five percent (80/321) of the physicians use voice recognition for some data entry. Twelve of our 95 ambulatory clinics have voluntarily adopted measures to eliminate paper charts. Of the 212 physicians who entered data in 2004, sixty-nine physicians (22%) increased their level of data entry, while 12 (6%) decreased. It was concluded that physicians will voluntarily adopt an EHR system, and will continue and even increase use after implementation barriers are addressed.

<u>Barriers to Electronic Health Record Use during Patient Visits</u>

- **Jeffrey A. Linder, Jeffrey L. Schnipper, Ruslana Tsurikova, Andrea J. Melnikas, Lynn A. Volk, Blackford Middleton. AMIA Annu Symp Proc. 2006; 2006: 499–503.**

In this paper it was concluded that the effectiveness of electronic health record (EHR)-based clinical decision support is limited when clinicians do not interact with the EHR during patient visits. To assess EHR use during ambulatory visits and determine barriers to such use, there was a cross-sectional survey of 501 primary care clinicians. Of 225 respondents, 53 (24%) never or only sometimes used any EHR functionality during patient visits. Non-physician clinicians (e.g., nurse practitioners) were marginally more likely to be EHR non-users than physicians (39% versus 21%, respectively; p = .05). The most commonly reported barriers to using the EHR during patient visits were loss of eye contact with patients (62%), falling behind schedule (52%), computers being too slow (49%), inability to type quickly enough (32%), feeling that using the computer in front of the patient is rude (31%), and preferring to write long prose notes (28%).

- **National Research Council (US) Board on Biology; Pool R, Esnayra J, editors. Washington (DC): National Academies Press (US); 2000.**

Barriers to the Use of Databases were discussed in detail in this paper.

The form in which data have been entered into a database is critical, as is the structure of the database itself, yet there are few standards for how databases

should be constructed. Most databases have sprung up in response to the special needs of particular groups of scientists.

The most basic barrier found in this paper to putting databases to use is that many of them are unavailable to most researchers. Some are proprietary databases assembled by private companies; others are collections that belong to academic researchers or university departments and have never been put online. The audience of a registry or database is key, and with the INPDR the consortium will ensure that information is appropriately disseminated to ensure the project reaches targets.

Integration was discussed in this paper. Integration holds the promise of fundamentally transforming how biologic research is done, allowing researchers to synthesize information and make connections among many types of experiments in ways that have never before been possible; but it also poses the most difficult challenge to those who develop and use the databases. The problem is that interaction with a collection of databases should be as seamless as interaction with any single member of the collection. We would like users to be able to browse a whole collection of databases or to submit complex queries and analytic computations to a whole collection of databases as easily as they can now for a single database. Integrating databases in this way has proved exceptionally difficult because the databases are so different.

The simplest yet most unyielding difficulty is that biologists in different specialties tend to speak somewhat different languages. They use jargon and terminology peculiar to their own subfields, and they have their own particular theories and models underlying the collection of data. In the INPDR we will have to deal with the difference in terminology and recognize that there are differences and be careful with precision regarding data from different specialties. Some NPD patients are seen by pediatrics, some by neurologists, and some by endocrine consultants and so forth. This means that there is a multidisciplinary team to consider when deciding datasets.

Besides the differing terminologies, someone who wishes to work across many databases must also deal with differences in how the various collections structure their data. Another very important issue is the heterogeneity in user expertise. Addressing complex queries to large collections of databases requires significant sophistication in the user who is going to create a query of that form. The vast majority of users simply do not have that expertise today.

- **Gen Hosp Psychiatry. 2007 May-Jun;29(3):192-8. Implementing a clinical and research registry in obstetrics: overcoming the barriers. Bentley SM[1], Melville JL, Berry BD, Katon WJ.**

This study aimed to describe the obstacles and solutions in developing and implementing a prospective obstetric database registry that collects bio-psychosocial data on women during pregnancy and postpartum. Although the goals of this study were different to those of the INPDR, the methods were similar. The clinical goals of the registry were to improve both diagnosis of mental health and substance use problems and access to mental health care during pregnancy. The

research goals were to examine the impact of psychiatric illness and substance use on birth outcomes. A questionnaire that contained validated instruments for mental health, substance use and psychosocial stressors was developed and administered to all pregnant women in an academic medical centre obstetric clinic. Results were incorporated with reminder and decision support systems to ensure active follow-up of patients with mental health needs. Automated medical record information was collected for future analysis of outcomes.

Barriers to program implementation were overcome by a multifaceted intervention that included educational outreach to patients, providers and staff; integration of the registry into pre existing clinical protocols; reminder systems at workstations; provision of mental health decision support through peri-natal social work and psychiatric consultation; and utilization of a "stepped-care" model to delivering mental health services.

The conclusion of the paper was a mental health registry that merges clinical and research needs can be successfully integrated into the obstetric clinic setting. Although the setting of this registry is different the basic principles are similar and it is anticipated that similar barriers will present. In this paper educational materials and prompts are discussed which are pertinent for the INPDR.

Literature review findings

All of the literature reviewed mentioned low response rates for online surveys.

Online surveys have some disadvantages over traditional methods such as phone or post. However when conducting surveys that are pan-European, postal and telephone methods are impractical and costly. To keep project costs to a minimum online surveys are a better option for this project, however savings in cost often translate to lack of engagement and completion by physicians.

Although online surveys have downfalls in the amount of recipients that complete them, there are methods to mitigate this. Methods such as repeatedly sending emails to those who are yet to complete the survey, changing the appearance of the survey and only including a small number of questions.

One of the most widely used and easy to use survey services is SurveyMonkey (https://www.surveymonkey.com/home/). SurveyMonkey was used in the INPDR questionnaire of barriers to data entry as it is very easy to use, can be personalised and is widely known by most partners. The maximum amount of free questions that could be used in this system is 10, with any more than 10 questions requiring subscription to a bigger package at a cost. For the purposes of the INPDR scoping exercise 10 questions would be sufficient and would also serve to keep the total amount of time that physicians spend completing the survey down. It has been previously discussed that multiple pages of questions in a survey can be off-putting to those who are completing it and can either lead to no attempt at completing the survey, or the survey being closed part way through completion.

One downside to accepting the 'free' service from the company was that we were unable to include our project logo in the survey. This would have been available at the premium rate however not on the free version. The URL of the survey was **https://www.surveymonkey.com/s/GWNXLBN** which was sent out to all consortium members of the INPDR to complete, as well as other physicians from University Hospital's Birmingham.

Other literature looked at physician's directly entering data straight to the online system. There are many physicians who will be directly entering data to the INPDR as part of this project, so barriers to direct data entry were reviewed. It was found that physicians increased their data output on the whole if they did enter data directly to the system however there are reasons that were found to be barriers to this such as loss of eye contact with patients, falling behind schedule, computers being too slow, inability to type quickly enough, feeling that using the computer in front of the patient is rude and preferring to write long prose notes.

Barriers to data entry that have been previously identified in literature include how the data is entered, and the structure of the database. There are currently little or no standards for the construct of a registry, meaning that many different registries will have many different structures. This could be confusing and time consuming to those who enter data and need to lean different systems. By keeping the structure of the INPDR simple and the dataset easy to understand this should help to overcome this barrier. One option that has been discussed in the above literature is integration of registries and databases, however at this stage the INPDR is a standalone registry that serves the purposes set out in the introduction. As such integration is inappropriate at this stage.

Another barrier to data entry that was discussed is the multidisciplinary team and how this can impact upon a registry. This is particularly pertinent to the INPDR as within a department or hospital a patient with NPD could be seen by any number of specialties, from pediatrics to endocrinology, neurology, hepatology etc. Each of these specialties will have different terminology and different exams/tests which need to be carried out. This is also a registry that will be used all over the world, so language differences and terminology are also a major consideration.

Potential solutions to these problems include educational materials which will be provided as part of the INPDR and include guides on how to enter data and also leaflets promoting the registry and its aims. Integration into clinical protocols would be a greatly advantageous step but will vary from country to country as far as acceptability. Reminder systems at workstations will also be important as well as general NPD support and educational materials.

INPDR Focus groups

05/November/2013 rare disease clinicians focus group

This meeting was held at University Hospital's Birmingham, UK and involved clinicians in the hospital that specialise and treat in rare diseases.

Points discussed include financial incentives for investigators completing data sets. This was dismissed as the project does not have resources to be able to provide any finance incentives. The beneficiary/work package leaders in each partner country would take responsibility to gain ethical approval and encourage other institutions (if necessary) to participate and enrol patients. In some circumstances this may not be necessary as the project beneficiary will travel between sites gathering and entering the information to the registry. An example of this format will be the French site, where the lead investigator is Marie Vanier, collaborating partner. The French partner will employ a research nurse who will travel with Marie Vanier and aid in the entry of data. In the UK it is anticipated that data entry will be completed by a nurse employed by NPD UK who will travel between sites and collect the data on participants. The group were happy with this format for the UK.

Other discussions led to the individual skills and capacities of the investigator being an issue for upcoming data entry.

It was agreed that some of the investigators that will enter data as part of the INPDR have previously not had much experience. This could make the process of entering the data longer and could lead to data discrepancies.

It was decided that this may not always be the clinician/investigator that enters data. In some sites the data entry will be delegated to a research nurse, study co-ordinator, or a data manager. It was suggested that for the questionnaire there be a questions regarding who from each site enters the data.

It was further discussed that data entry could be delegated to a research nurse or study coordinator/data manager. Concerns were brought up about the accuracy of the data entry in this case. It was discussed that in some cases medical knowledge is essential for reviewing and interpreting data in notes. It would not be appropriate for a junior member of the team to make these calls without speaking to clinicians who understands more about the disease. This is particularly the case when reviewing diagnostic data. It was confirmed that for complete data that did not need interpretation a data manager or study coordinator could enter the data. It was also pointed out that not all centres have access to these staff members and for many sites it would be the clinician who enters the data and enrols patients.

The group thought that personal goals and priorities, respectively, or lack of motivators could have an effect on the data entry to the registry.

An investigator who sees the registry as a high priority with clear benefit would enrol more patients and work at completing the full data set whereas an investigator who does not comprehend the project may not approach/enrol as many patients and may not look for hard to obtain data as they do not see the importance. The group discussed that education is the best way to prevent this from happening and clear information is required. Please see INPDR dissemination plan for explanation of external methods to disseminate information about the project. One of the main tools for informing health professionals is the public access project website (www.inpdr.org).

The website has health professional specific information in an informative and user friendly format.

28/29 January/ 2014 Birmingham UK focus group

This was a meeting to discuss the dataset and potential barriers to data entry now and in the future. During this focus group the ownership of the registry was discussed and partners in France, and Italy spoke about patients being unwilling to join a registry that was held by industry. It was confirmed that after the funding for the registry has finished the French institution would need the registry to stay with University Hospitals Birmingham in the UK rather than be held by industry. The group agreed that the registry would not be handed over to industry at any point. Industry are key to future planning of the registry as they will eventually become its customers, however at no point will the registry be industry held.

The French team also brought up the fact that it is illegal for them to enquire about a patient's ethnicity or background to enter to a registry. This issue highlighted the fact that each EU member state will have different laws around data protection and what can and cannot be recorded in the registry and this needs consideration when designing the dataset.

07/November/2013 Department of Health focus group

This focus group was held to discuss patient's feelings towards data entry in to a registry. DoH experts were invited with informatics and health service backgrounds:

Sophie Wheeley, Head of informatics, Simon Ball, consultant Nephrologists

DoH representatives

It was also important that this scoping exercise took into consideration the expertise of those involved in registries but not as part of the NPD community. A meet was organised with key informatics staff members from UHB and the Department of Health (DH). The DH have a strong focus on rare diseases and have been involved in implementing many registries so key informatics were invited to discuss potential barriers to data entry.

At this focus group security was mentioned and the group used an example of a recent initiative at University Hospitals Birmingham NHS Foundation Trust where a patient portal called 'MyHealth@QEHB' was developed. On launch day there were several hundred attempts to 'hack' the system and get the data. This is something the IT team based with Richard Sinnott have been working on and have much experience with. The teams experience includes other EU funded registry projects. The group felt that security around the registry is very important. The group also discussed geographical distance and the impact that may have upon the number of patients enrolled to the INPDR. Both geographical distance from the patient to the clinician, and distance from the patient to the coordinating centre in the UK. It

was suggested that if a patient lives a greater distance from the centre providing their care they may be less likely to enrol to the registry.

One point that was mentioned in several meetings was the need to keep the dataset user friendly. Time to complete data was discussed and this group felt that time would be the major constraint on data entry to the registry. One way of combating this would be to keep the dataset as user friendly as possible, and by keeping the dataset to a minimum. The group felt that the dataset created for the INPDR was long but it was essential to keep all data points in. If the investigator did not enter all the data it should allow. This would mean that some data could be completed at another visit or at another time. The group also felt that it would be important to include a 'manual' for those who enter data to read with simple process maps and a how to guide. In this document would also be the phone number and email address of the help desk.

01/August/2013 Baltimore focus group

This was a biannual Niemann-pick meeting for both health professionals and patients/family members. This presented the opportunity to hold two focus groups; one for professionals and one for patients/families.

In the patients/families the main topic was patient reported outcome measures (PROMS), later termed patient reported dataset by the team.

The collection of patient entered data, or PROMs was agreed to hold great value and importance at the present time and in the future could assist in providing evidence to support the approval of new treatments and therapies. The aim is to understand the impact of the disease on a patient's daily life and to ascertain the difference made by treatments/therapies.
The information collected will be anonymised and made available to view by patients themselves and by professionals.
The design and questions should be simple. There should be categories/sections of information to complete, keeping the time needed to complete each section to a minimum. Suggested categories include:

- Activities of daily living
- Social interaction
- Physical health (could include pain, fatigue)
- Emotional health and Well-being (could include depression, bullying, self-image)
- Communication
- Mobility

It was noted that some of the categories will be different for ASMD and NP-C.

It was agreed that enabling patients to view the data and download anonymised

reports would be a powerful incentive for patients to continue participating in the registry and would increase patients' willingness to join and their levels of empowerment. From this meeting a PRD sub committee was formed to review current PROMs and assess their usability for this unique group of patients.

The Group went on to discuss ways in which to encourage patients to participate in the Registry. The consensus was by providing information regarding the value of patient data and how it could positively impact upon the development of new treatments and therapies was felt to be the optimum way forward.

It was decided that Information about the Registry should be included in the 'Global Awareness Campaign for Health Care Professionals' lead by the INPDA which could help to raise the profile of the Registry and encourage both professional and patient participation.

For the health professionals focus group tools and techniques were discussed. It was mentioned that a help desk would be of use so that if there was an issue with data entry it could be resolved following an email or phone call. It was decided that this help desk will reside with the coordinating centre who if they could not answer the query could escalate it to the technical IT team. The INPDR inbox would act as a central contact point for all queries related to the project and registry, including technical help. Although a phone number is provided for all enquires, this will only be staffed between 09:00-17:00 GMT Monday to Friday, excluding UK bank holidays. Any calls received outside of these will not be answered.

At the end of the focus group sessions, there was an opportunity to discuss with patients and professionals together, the best way to encourage both groups to participate in the registry. Although the registry will be utilized in many different countries, it was acknowledged that many of the issues faced would be the same or similar and that this scoping exercise would aim at mitigating risk to the project.

This was discussed on a 'by country' basis.

- *UK - this could be done through the designated centres of expertise, plus diagnostic laboratories and the work of the NPDG (UK) Clinical Nurse Specialist*
- *Switzerland - it was felt that one designated person could undertake the task of promoting and enrolling patients*
- *France - the most appropriate option would be to approach the diagnostic laboratories and then to determine clinician contacts to directly discuss and promote the registry.*
- *Germany – establishing contact with clinician networks would be most effective*
- *Argentina – at present there is no collective database of information,*

therefore this project presents an excellent opportunity to establish networks and encourage collaboration; this could be coordinated through Associazione Niemann-Pick de Argentina

- *Spain – members of FNP would be easy to reach, whilst professionals could be reached through the clinical and diagnostic centres*
- *Canada – the issue here is geographic, with patients and clinical centres widely dispersed and a vast area to cover.*

The Registry should also be aimed, where possible, at collecting retrospective data, which could prove to be challenging in some countries. Some countries confirmed that they would not be able to provide any retrospective data and only prospective data could be used.

- It was emphasized that all countries would be required to obtain consent for plus country-specific approvals.

20/September/2013 Liverpool Focus group

The structure of the database was discussed in relation to being able to complete it. The group felt that the structure should mirror a physical exam and specific items will need grouping to reflect organ systems. This would mean the data set flows and is easy to complete.

The group discussed barriers to data entry at the scientific advisory committee in September 2013. Access to easily available patient records was discussed and it became obvious that not all records would be easily available. This could impact upon the data received, in particular the retrospective data. Some centres could not agree to enter retrospective data because getting access to old patient notes is too difficult.

The group were concerned about how the data is analysed and the differences between different countries. From a data analysis view, the way data is collected/ coded will need to be held in the registry in a uniform manner. One of the consortium suggested the possibility of using Logical Observation Identifiers Names and Codes (LOINC®)
The language barrier was discussed, and the question was asked if the registry should be translated into different languages or if it should only be available in English. The group thought that it would be best if the registry stayed in English to keep matters simple. To help with various barriers it was suggested that the coordinating centre produce standard operating procedures, process maps and frequently asked question documents to help with the website

The PRD was discussed and it was reiterated that patients are the driving force of the registry. The discussion moved to patient entered data within the registry and how patients would log in and what access would they have to see their own data.

It was discussed how accounts would be verified after an initial account request has been made. It was decided that this would be centrally coordinated by the coordinating centre who would filter hack attempts and those that genuinely would like to enrol to the registry. It was reiterated that the security of the database is highly important and clinicians will not enrol patients if they are not certain of the security surrounding their data.
One comment on the dataset was that there are free text boxes that allow patients and clinicians to enter the answer as they like. Issues with this are around confidentiality-what would happen if somebody entered personal identifiable information, or something abusive. The analysis of the free text boxes would be difficult. When one person enters 'headache' another could enter 'migraine' etc there is another issue regarding language and whether the person who enters data would write anything in another language, how would this be verified and analysed?

The group discussed whether or not the patients that log in and see their patient reported datasets could also view their clinical datasets. The group felt that there could be potential consequences to the patients seeing data about themselves, especially if the dataset showed a decline.

It was also discussed whether or not patients who have been granted access to their own data would understand it. Some members of the group felt it would be better for patients to request to see the data from their clinician, and their clinician to print out a copy of the data and go through it with the patient/their family.
It was conversed that patients need motivation to motivate their clinicians and this can be done by having limited categories and glossaries/help sections.
One other issue regarding patients seeing their own data is the fact that instant data has not been audited and this should be treated with a degree of caution.
The group did conclude that the datasets need to be separated into separate structures but that the structures should flow and mirror each other. This would keep the registry as uniform as possible and would be easy and user friendly for those entering data.

Findings

To effectively scope the barriers to data entry in EU member states the full dataset needs to be defined and understood. The dataset has been mentioned in nearly all of the focus groups and as such the dataset has been nominated as key in the process of identifying and mitigating barriers to data entry. A good structure and easy to navigate, user friendly registry has been most important to those questioned in our focus groups.

Dataset

There have been several dedicated dataset meetings since the start of the project. Dr Bruno Bembi, work package 4 lead created three dataset focus groups, one for the NPC dataset, one for the NPA/B dataset and one overarching dataset focus group.

These groups have a mixture of associated partners, collaborating partners as well as members of the project management committee and the scientific advisory committee. In some cases advice has been sought from interested parties with no direct links to the project, but whose expertise was considered advantageous. In this case the information shared has been carefully managed to ensure there is no breach of the terms of reference of the project.

As such communication has been key in implementing and maintaining these connections. Bruno Bembi has managed this internally by forums such as email, regular scheduled teleconferences, and face to face meetings. Final datasets can be found in appendix 1.

Bruno Bembi worked with the smaller working groups to initially draft versions of the dataset to share with the group. Some datasets had been previously drafted by members of the group for other internal initiatives. These drafts were utilised and built upon by the working groups. The group spoke via email and teleconference before circulating the first draft documents. The group then met in Barcelona, Spain to hold a focus group focussing on the datasets.

One of the major considerations when designing the dataset was digital continuity. Digital continuity is the ability to use the information held in the registry in the way that is needed for the length of time needed. It is very important that the registry produces good quality valuable data and the future planning of the registry was discussed at this early stage. The customers of the registry will eventually become industry (amongst others) who will pay to access certain data held within the registry. As such industry representatives have been involved in reviewing the draft datasets to ensure the data points are relevant. There have been many iterations of the dataset incorporating comments and changes from a multidisciplinary team. Input has been given from Adult and paediatric specialities and also from metabolic specialists, neurologists and those with experience in NPA/B and C. Industry representatives have been engaged since very early in the project, and have had several chances to review the dataset, under agreed confidentiality terms, to provide feedback where necessary. To ensure continuity the NPDR consortium has been liaising with a dedicated contact that has extensive experience in the field of NPD but also in registry development. The group feel that this expertise will ensure the future proofing of the registry.

Patient reported dataset

The INPDR provides an opportunity to pull together patient experience from across the world, so strengthening the evidence base on the impact of NPD. This patients' perspective plays an important role in the drug approval process. This patient reported data will be linked to the patients' clinical data which together will be a very powerful tool.

The Patient Reported section of the registry is a mechanism for patients (or carers) to report directly on the impact of the disease. Individuals will answer a questionnaire that seeks to gain insight into:

1. What it's like to live with the condition
2. What impact the condition has on daily activities
3. What impact the condition has on a person's psychological / emotional health
4. What impact the condition has on the lives of family members and carers

By aggregating answers to these questions, we strengthen the evidence base of the impact of the illness on the individual and their wider family and the burden of the disease and its severity. Over time it is expected that we can provide evidence of disease burden, severity, and progression which will mean that when trialling potential treatments, we are able to provide evidence of benefit.

All patients who enrol to the registry will be asked to complete the patient reported dataset. However it is up to the individual/family whether or not they do. These datasets can be completed as often as the patient attends a hospital and has their prospective visits entered to the registry. This will allow the clinical and patient reported datasets to be linked and analysed.

Although initially the plan was to use already validated questionnaires a review of currently available patient reported datasets (PRD) and questionnaires showed that there is no available questionnaire that suits the specific needs of NPD. As such, a PROM's management group were set up to plan, design, develop and test patient reported datasets that are specific for NPA/B and NPC.

One of the main issues that made developing PRD complicated is the fact that NPD can affect children and adults at all ages, however the outcomes are important to capture from both children and adults. As the PRD need to be age specific a separate dataset will be created for children and adults.

Around the feedback received in these focus groups questionnaires have been developed to send to each centre to complete. The questionnaires have been sent to representatives in many different countries to ensure we get a good picture of what barriers there may be around the EU and the world.

1. **Full name and Job title**
   Free text box

2. **Please name your primary hospital affiliation**
   Free text box

3. **How would you describe your experience of data entry on to registries?**
   - I have used many registries/databases (8+)

- I have good experience of using registries/databases (5-7 used previously)
- I have moderate experience of using registries/databases (3-5 used previously)
- I have little experience of using registries/databases(1-2 used previously)
- I have no experience of using registries/databases

4. **Do you have free access to a computer with internet access that you can use for data entry?** (please check all that apply)
   - No computer available
   - In office only
   - In clinic room/workstation only
   - In clinic room/workstation and office
   - Computer is available but without internet access
   - Other (please specify)

5. **Do you have access to patient records (electronic and/or hard copy)**
   - Records easily available
   - Records available upon request
   - Records not complete/not in one place
   - Records not available
   - Other (please specify)

6. **Which of the following tools would you consider useful in facilitating complete and accurate data entry?** (Please check all that apply)
   - Prose notes
   - Explanation windows with further details
   - Alerts for conflicting data (e.g. date of appointment is after the date of death)
   - Help page with Frequently Asked Questions
   - Auto save feature
   - Question proforma/worksheet to take to clinic and record all source data on
   - Other (please specify)

7. **The registry will be in English. Do you foresee this to be a barrier to data entry at your institution?** Please explain your answer
   Free text box

8. **Who would be the main person to enter data at your institution?**
   - Doctor
   - Nurse
   - Study Co-ordinator
   - Data Manager

- Scientist
- Other (please specify)

9. **What do you foresee as the main barriers to data entry at your institution?** (Please check all that apply)
    - Not having enough time
    - Internet access
    - Computer availability
    - Security concerns
    - Language
    - Other (please specify)

10. **What resources/training would help with data input to the registry?**
    - Registry explanation/manual (hard copy available at site)
    - Online 'help' section
    - Training on how to use the registry before being given access
    - Online demonstration of how the registry will work
    - Prior data entry on a 'beta' version of registry
    - Other (please specify)

These questions were chosen after reviewing feedback from the focus groups. Although no validated questionnaires exist to test such questions, these questions were felt to be strongest indicators of the potential barriers to data entry within the INPDR, and the promotional materials needed to facilitate complete and accurate data entry.

Responses and Conclusion

The questionnaire was completed by clinicians, research nurses and data managers in Spain, the Czech Republic, the UK, Germany, USA, Australia.

The experience of the staff member regarding registries was asked and the majority of clinicians reported that they had good or moderate experience of using registries. A small number of clinicians reported having little or no experience, which would mean there are parties who would be completing the data entry that may need more support.

Sub committees will be formed to develop, distribute and promote the educational materials produced as a result of this exercise. These will be part of work package 6 and 4 but will also be touched upon in the dissemination plan of the project with oversight from work package 1. After reviewing the responses to the questionnaires we can see that most clinicians do have access to a computer, if not in the clinic room in the office. This will mean that in the majority of cases the data can be

entered to the registry without query over the internet availability. One clinician commented that computer and internet access was available to them anywhere at any time.

When asked if patient records were easily available, 38.46% reported that they were easily available, 38.46% reported they were available upon request and 23.08% reported that they were not complete or not in one place. No clinicians reported notes were not available.

When asked what support would be of most use, 23.85% mentioned prose notes, 76.92% thought that pop up explanatory windows would be useful, 53.85% thought alerts for conflicting data and the same amount thought a frequently asked questions page would be useful.

69.23% chose an auto save feature and 46.15% chose a worksheet to take to clinic and 7.69% chose other, and answered 'not sure'

When asked if the registry being in English would be a problem, 15.38% chose yes, but 69.23% chose no and 15.38% chose unsure.

When asked who would be the main person to enter data, 53.85% chose the doctor, 23.08% chose nurse, 7.69% chose coordinator and 46.15% chose data manager.

When asked what the main barrier to data entry, 69.23% chose not having enough time, 23.08% chose computer availability, 23.08% chose security concerns and one person chose other, with a reason of 'Historical data not easily available'

When asked what support requirements they would like for the registry, 61.54% chose that they would like a hard copy of the dataset to take to clinic, 61.54% said they would like a help section on the registry, 61.54% said they would like training on how to use the registry, and 30.77% said they would need an online demonstration. 38.46% chose they would like to test a beta version of the registry, and one partner commented that they would like data on a fictional patient based on which success and comprehensiveness could be evaluated.

Due to these responses coupled with the focus groups held it can be concluded that the main barriers to data entry are not having enough time, and security concerns. To mitigate against this, an explanatory document of security has been created to reassure all entering data. There will also be a statement of security on the registry website explaining to patients and clinicians the security aspects.

Other help that can be provided to clinicians and those entering data are educational materials including a printed hard copy registry manual, an online help page, an online demonstration and software support such as prose notes, explanatory windows and alerts, FAQ pages and a printable worksheet that partners can take to clinics and record source data on. As such there will be specific working groups set up to design such materials as part of specific work packages.