Virtual Networks For Exchanging Information And Biomaterials: Future Directions

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Abstract

Clinical and research networks for rare conditions are increasingly common nowadays. Given the rarity of many such conditions, there is a need to cover more conditions yet there is also a need to sustain and improve the quality and effectiveness of existing networks. This review will discuss the qualities that are required by a virtual network using some international clinical and research networks that are currently active in the field of rare endocrine conditions affecting sex and adrenal development as exemplars.

Introduction

There are approximately 5000 to 8000 rare diseases or conditions that affect 6-8% of the population (1). Patients with these conditions are often isolated and experience significant obstacles in accessing high quality healthcare and information. Research activity for these conditions is often poorly coordinated and lacks quality and effectiveness. The group of conditions, collectively labelled as Disorders of Sex Development (DSD), is a typical example where there is a substantial lack of knowledge about aetiology and long term outcome and initiatives in research are limited by the low prevalence of individual conditions and the scarcity of resources and expertise at a local level. Whilst centres of expertise can bring together multidisciplinary competencies around the needs of patients, the creation of virtual networks is becoming a necessity to coordinate the work of these nodes, speed up the pace of discovery by pooling scarce resources and ensure patient empowerment by creating a common strong voice on behalf of these patients.

The ideal qualities of a virtual network for rare conditions

An ideal virtual network for rare conditions places patient welfare at the heart of the project. It should be governed by a board composed of representatives of all stakeholders including advocacy groups, policymakers, researchers and clinicians, industry and Ethics and patients that play a central role in determination of priorities and evaluation of activities (2). This governing body ensures sustainability of the project, deals with administrative, ethical and legal issues and ensures coordination of all parties involved in the network. It also ensures communication and dissemination of activities to external members using various means including websites, newsletters, institutional bulletins, scientific meetings and peer-reviewed journals and creates and maintains secure infrastructures for communication between internal members that are organised on a regular basis so that the members can express their needs, share experiences and coordinate work. This communication is key to collaboration within a

high quality network so that fragmented initiatives in patient care and research can be consolidated into common projects that optimise the rational use of scarce financial and human resources and prevent duplication of effort. Good communication will also lead to a common vision which will be derived from similar challenges and creating consensus around disparate priorities in a democratic way. Within a network that focuses on clinical care, research priorities should be defined by all stakeholders and centered at patients' needs and preferences. A strategic plan should also be defined as well as standard operating procedures that govern research activities including sharing of data and bio-specimens. Registries and biobanks that are interoperable across geographical boundaries are the backbone of these research activities to allow pooling of data to reach sufficient statistically significant numbers for clinical research and public health purposes (3). There is also a need for linking existing biological samples to data in patient registries. To accelerate the pace of drug discovery, collaboration with industry is also needed and this can be best realised through the registries as well as the potential to deliver trials through a network of high quality clinical centres. By allowing efficient and secure communication between physicians to share experiences and discuss challenging cases, and by reducing the need for patients and professionals, networks for rare conditions can also have a direct impact on day to day health care. The traditional healthcare system which is often limited by financial and geographical constraints could be replaced by a patient centered system with equal access to multidisciplinary care and treatment across the lifespan and across geographic boundaries. Patients and their representatives should play a central role in all these network processes pertaining both clinical care and research activities as informed, engaged and interactive partners. The network should also implement capacity-building programmes to empower patient representatives with the knowledge and skills they need to ensure these roles (4) and increase general awareness by implementing educational programmes for both patients and the medical community. Due to the limited number of patients and experts in a local level, the network should have an international coverage to bring together national and regional

initiatives from around the world and advocate for rare disease as an international public health priority. To balance wide coverage of conditions and detailed focus on conditions, disparate networks of rare conditions should be integrated under a wider network that covers all these conditions to empower their position and coordinate their efforts. Having a network with common and standard operating protocols that are approved by regulatory agencies such as those that deal with ethics or information governance greatly helps existing as well as new members of the network. These ideal qualities of virtual networks for rare conditions are summarised in Table 1.

International Networks in DSD

Several countries have DSD networks that organise patient care and research at a regional or national level (9, 10, 11). The importance of pooling the efforts of these national and regional networks into international projects has been emphasized by many European and international initiatives in rare diseases such as EURORDIS (European Organization for Rare Diseases), EUCERD (European Union Committee of Experts on Rare Diseases) and IRDiRC (International Rare Diseases Research Consortium). Some networks that have been created to work across international boundaries with an objective to improve clinical care, knowledge and research are discussed below.

I-DSD (www.i-dsd.org)

I-DSD is a registry based network and a model of collaborative international research that, at last review in March 2017, linked 61 centres from 31 countries from 5 continents, and allowed experts to enter standardised information aimed at improving clinical practice and research in DSD. The registry adheres to international standards that were set for high quality registries (12). It has a strong governance model which represents several stakeholders including patients. This governing body has a good oversight, ensures long term sustainability and

establishes standard operating procedures regulating all ethical and legal aspects. These registry protocols have been approved by ethics committees and sharing of data takes into account the rules for security, confidentiality and informed consent. Data quality assurance procedures have also been implemented to ensure high quality data that enabled several types of studies ranging from basic research aiming at characterizing the DSD population (13) to those exploring trends in practice (14,15) and contributing to better outcome of patients. The registry communicates the results of these studies and information about ongoing and future studies to a range of stakeholders through regular presentations at scientific meetings, via a website and through newsletters. A web-based module has also been created enabling patients to stay informed about registry activities to view their data and express their preferences in healthcare and research. By enabling such effective interactions, the I-DSD Registry is becoming a platform for international networking that allows the users to play leading roles in initiativessuch as EuroDSD, DSDlife, DSDnet, the recent global DSD update (16) the response to the EU Commissioner (17), a survey of DSD centres (10), a survey of clinical psychology support at DSD centres, and a biennial international meeting for DSD. Future directions are further development of the newly created patient web based module to provide more personalised information for patients, allow collection of patient reported outcomes and experiences in their own language and create a space where they can communicate with their clinicians. Each patient will have a unique global identifier that can allow linkage of their data through all databases and biobanks and the dataset will be revised to improve its interoperability with other registries. The registry is evolving towards covering additional modules involved in DSD care such as surgery, psychology, fertility, and is broadening its scope to cover more conditions.

I-CAH (www.i-cah.org)

An international network of researchers and clinicians looking after people with congenital adrenal hyperplasia (CAH) was created to speed up the pace of discovery of new management strategies and therapies and optimise the outcome of patients with CAH. This network is managed and administered by the I-DSD governing body and was supported by the TAIN project (Treatment of Adrenal Insufficiency in Neonates) which was an EU funded consortium dedicated to developing a new formulation of hydrocortisone. With the newly-created I-CAH Registry as its centrepiece, the network is supporting a number of longitudinal studies such as a study examining adverse events and a study of fludrocortisone and salt therapy. The longitudinal module also enables the registry to be used as a clinical tool in a clinic setting and enables the network to play a vital role in benchmarking clinical outcomes in order to improve the quality of care. This module is also the starting point for developing the infrastructure, compliance and quality framework to enable elements of the registry to be used as a post-marketing surveillance tool. I-CAH also supports patients and parents by providing educational material, support and links in different langages and organising educational days for patients and families. A new module will be developed to collect data on outcomes directly from patients including information on quality of life, adverse events and endocrine management and will be used as a personalised resource for patients and parents. These personal information could complement medical data provided by clinicians and help them to evaluate their practice from a patient view in order to optimize the holistic care for patients in DSD.

DSDnet (www.dsdnet.eu)

DSDnet is an international network of 19 European and 9 affiliated international partners that links scientists with professionals, patient support groups and policy makers in order to improve clinical care and promote research in DSD. This initiative is funded by a COST action (European Cooperation in Science and Technology) and five working groups were created composed by international experts with specfic duties working in close collaboration. DSDnet aims to promote

the development of partnerships that will allow improved elucidation of the cause of all forms of DSD. It also aimed at developing consensus on the assessment of clinical phenotype and and that can be incorporated into registries such as I-DSD and I-CAH. Other activties include the harmonisation of diagnostic investigations as well as a collaboration with patients and professionals. Patients and advocacy groups are actively involved and through holding a workshop the network is integrating their views into clinical and research guidelines. DSDnet has also played a central role in the European Reference Network (ERN) project by designation of centres of expertise in DSD. The network is also supporting training and research of early stage professionals by organising training schools and short term scientific missions that strengthens collaboration between centres. DSDnet is promoting research proposals and results are disseminated through scientific papers and meetings, via the website and the press in order to inform all stakeholders including political decision bodies.

ENSAT Registry (www.ensat.org)

ENSAT-CANCER is an EU-FP7 funded initiative dedicated to develop prediction and management of adrenal tumors. This is a virtual research network that connects specialized clinicians with research communities to conduct collaborative research in malignant adrenal tumours. This digitally interconnected infrastructure collects data in a secure platform and places a great emphasis in biobanking and other enabling services including sample barcoding, bio-sample exchange mechanisms, an integrated linkage scheme to other trials and studies, summary statistics, report generation and image hosting (18). Projects are focused on studying genetics and treatment of adrenal tumors, discovering new molecular mechanisms of their growth, and providing insight into associated areas, such as the role of peptides and steroids in hypertension. The project has demonstrated its ability to conduct international collaborative research by collecting data and biomaterial of a large number of cases despite the rarity of these tumours, importing new data-sets from other smaller country specific repositories, and

supporting large data export projects in order to perform several types of studies including clinical trials in collaboration with pharmaceutical companies.

Interaction of registry-based detailed disease networks with European Reference Networks

The Chicago consensus Conference (19) and the UK guidance on the initial evaluation of an infant or an adolescent with DSD (20) led to significant changes in the management of patients at an international as well as a local level. However, an international survey of 124 paediatric endocrinologists in 2014 reported that only 40% of DSD centres had a sufficiently adequate multidisciplinary team for quality care of patients and there were substantial variations in practices and access to specialist tests between these centres (10). Through the preparatory work for Endo-ERN, the European Reference Network for rare endocrine conditions, DSDnet has embarked on the development of criteria for centres of expertise for DSD. DSD and Congenital Adrenal Hyperplasia are two of the eight themes that will be covered by Endo-ERN (https://endo-ern.eu/), which was approved in December 2016, and is the largest ERN with 71 health care providers from 19 member states. The creation of this ERN for DSD will optimise possibilities for better patient management, by improving diagnostic trajectories between national healthcare providers and centres of expertise, ensuring access to multidisciplinary care across the lifespan, and equity of access to treatments, in order to improve the quality of life and socioeconomic potential of DSD patients. Communication between centres will allow better management of variations in practices, rational utilisation of clinical genetics and biochemistry and the development of clinical guidelines, new evidence based care models, e-health solutions and e-tools for tele-expertise and tele-consultation as well as e-learning and training opportunities for professional development. In terms of research, the creation of a common core endocrine registry will allow existing detailed disease registries to interact with each other and with other registries within Endo-ERN and beyond within a framework that will adhere to the

FAIR principles where data are findable, accessible, interoperable and re-usable (21). It is anticipated that participation in this registry will become a pre-requisite of centres of expertise that are members of Endo-ERN and will allow these centres to participate in benchmarking exercises that lead to quality improvement. In terms of patient involvement, a workshop was organised in Bologna in October 2016 by DSDnet in order to identify the needs of DSD patients in research, healthcare and education. Patients and families were also introduced to the project of ERN for DSD and to the concept of European Patient Advocacy Groups (ePAGs) that was developed by EURORDIS. These advocacy groups ensure that the DSD patient voice is heard throughout the Endo-ERN development process and allows the integration of the needs and preferences of patients with DSD into clinical care, education and research.

Conclusion

Coordinated networks for rare conditions are becoming a necessity to prevent duplication of work and to maximise the benefit of pooling resources and expertise. The use of new technologies has significantly promoted communication and collaboration between different stakeholders including patients and further attention needs to be paid to ensure long term sustainability.

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