RD-ACTION Workshop

'Exchanging Data for Virtual Care in ERNs'

28-29th September 2016

HIGHLIGHTS AND CONCLUSIONS

RD-ACTION WP6 Output

Contents

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Executive Summary of the Workshop

The topic for this workshop was selected because at the heart of the ERN concept is the opportunity to provide healthcare through virtual means, enabling expertise to travel as opposed to patients or physicians, where possible and appropriate. The workshop was very well attended, with over 55 participants across the two days: 21 Applicant Networks; 10 European Commission DG SANTE experts leading various aspects of the ERN work, including Mr Andrzej Rys and Enrique Terol; 10 European Patient Advocacy Groups (ePAGs); experts from RD-ACTION and several other projects with experience and expertise in the standardisation of data in the RD field; and a legal expert with many years of experience in addressing the legal challenges facing the field of eHealth, Petra Wilson.
The workshop focused on several aspects relating to the organisation and execution of 'virtual consultations' for complex patient presentations requiring access to the pooled expertise of the ERN:

- The form such encounters might take were explored (for example a real-time gathering of experts through virtual systems, the ability to review uploaded case information in the professional's own time through a secure platform, etc.)
- The legal issues around data protection -especially in view of the new General Data Protection Regulation- and the legal, ethical and social issues relating to consent for the sharing of data in the ERN framework
- Practical advice on the organisation and execution of efficient and effective virtual consultations, from colleagues engaged in this work at present
- Perspectives on how patients will enter/ be 'referred' to the expertise of the ERN for virtual care
- Experiences and recommendations on the standardisation of data in the RD field, in terms of disease coding and ontologies for phenotypic (clinical) information, to explore the good practices which should be embedded in the ERNs and identify additional standards of importance to the ERN community.

Below, one can find the conclusions/principles proposed under each session of this two-day workshop. For more detail, please refer to the full report.

Summary of main concerns highlighted at the invitation of Dr Andrzej Rys

- IT Platform: Several participants stressed that the lack of information on the IT platforms being reviewed and considered under the Tender is a concern. The IT platform will be central to the success -indeed to the operationalisation- of the Networks. The process of selecting the best contactor is not easy: there are many things that need to be incorporated in this platform and people are not operating in a vacuum – for instance, there are assets already in use by the EC that must be considered. Furthermore, the HCPs typically sit within broader institutions and these wider administrations will be keen to see what sort of IT platform they will be required to install/ link to. Many things need to align for this venture to be successful: **ERNs need a good platform, delivered through a competent contractor, with robust governance and a strong, engaged community to provide input for the effective functioning of the system.**

- **Funding** is, unsurprisingly, another major area of concern for the ERN stakeholders: several ANCs pointed out that there is tremendous spirit and enthusiasm driving these Networks forwards, despite a lack of funding. All ERNs will need coordination funding or 'glue money', not just the top rated Networks. The EC confirmed that it is seeking a means to provide funding for all approved Networks. It would be wise to view ERNs as start-ups: the first challenges will be to demonstrate the added value of these Networks to the world, and the EC is essentially providing seed money here. In 2018 the EC must prepare a report for the European Parliament on the implementation of the CBHC Directive: this means that in 2017 there will be a need to gather information and data. **This report will be a key moment, to demonstrate that the Networks are working and to highlight where greater support or attention is required, with the support of Member States.** This group may need to think creatively in order to identify future sources of additional funding. For instance, there may be scope to utilise the ERASMUS programme to promote the movement of academics and clinicians, especially young academics. The potential European Joint Co-Fund Programme for Rare Diseases offers opportunities to fund some of the research needs associated with ERNs

- **Industry Interactions** The fact that ERNs will seemingly *not* be legal entities was highlighted as a significant barrier to attracting funding, for instance from pharmaceutical companies. The ANCs discussed the possibility of establishing a foundation or similar, to act across all the Networks and make contracts. Dr Rys confirmed that the issue of interactions with industry was a major topic in the BoMS meeting earlier in the week, and that the Board is establishing principles to avoid conflicts of interest. It was emphasised that it is important to view 'interaction with industry' not only as a threat but as an opportunity; indeed, in the RD field, this engagement is essential, for therapy development obviously but also for registries, natural history studies, identifying patient relevant outcomes and study endpoints etc. A balanced approach is necessary, and there are examples of effective Terms of Reference/Industry engagement procedures which could serve as a model here (again, avoiding unnecessary duplication of efforts)

- **Integration of the Networks to health systems -** It will be important to engage the National Contact Points (NCPs) of the CBHC Directive more actively than hitherto, to ensure a seamless process for facilitating the movement of patients when necessary. Furthermore, for patient cases to 'enter' the Networks, the way in which the existing national pathways complement -and expand, where needed- to incorporate the ERNs must be clarified.

- **Compensation** - There are concerns from some ERNs that the time taken to provide virtual consultations and reviews will never be reimbursed, and will continue to fall outside of the CBHD and the social security regulation. Without a route to reimbursement, ERNs may struggle to dedicate ever-increasing amounts to time to providing expert opinion on patients from other jurisdictions

Conclusions: Good practices for organising virtual consultations

The workshop participants agreed that, if the number of cases reviewed via an ERN becomes at all significant (which it surely will - for the groups doing this already, numbers are bound to exceed

current levels) then **it will be essential for these virtual consultations to be conducted as efficiently as possible. The Group brainstormed several ways to ensure this:**

- **The IT platform must enable the efficient exchange/viewing of data, including large files and video streams**. Interruption to ECG feed or video footage, for instance, will severely hamper the effectiveness of the meetings. X-Rays, MRI scans, CT scans etc. must be high quality images, and should ideally be storable within the platform (something which is not possible in the case studies at present)

- It is important that virtual consultations -especially when real-time- provide the expert teams with **all appropriate data in appropriate forms** for each patient under review, to support discussions on diagnosis, treatment and care. **Organisation upfront pays dividends here, as seen in the case studies. Each ERN will need to agree on the clinical dataset they require for each patient being referred.** The case studies affirmed that when data on a particular patient case is incomplete, the teams go back to the referring doctor to request more information/better quality images etc.

- **Each ERN will need to agree the homogeneity -or lack thereof- across different specialities within its own network scope.** For instance, there may be a logic to agreeing datasets at the level of the subdomain, as opposed to attempting to mandate a single clinical dataset for every patient reviewed in, for instance, a rare endocrinology ERN. Paediatric patients, for a start, will logically require data elements not relevant for adults (e.g. around birth and real-age, in the case of infants, and concerning pubescence for older children, etc.).

- The ERNs will surely consider -especially the larger networks- the level at which there is clinical value in a MDT: for instance, as above it probably makes sense to generally arrange virtual consultations for each sub-domain of a disease-oriented network (e.g. rare inherited neuromuscular or rare peripheral neuropathies). There may be occasions where experts from different subdomains need to be involved, and perhaps different 'transversal groups/working groups' (for instance it may be deemed beneficial to have an expert from a NGS diagnostics group, along with a physiotherapist). **To ensure that people participating in these virtual consultations, especially when real-time, are all in fact needed and their time is being spent wisely, the judgement of the 'screener' or gatekeeper and the person organising the virtual consultation must be second-to-none.** Otherwise, one risks involving many experts for limited input.

- Finally, patients must only 'enter' these virtual care services of the ERN when there is a genuine need to do so (i.e. when the more 'ordinary' causes of the patient's symptoms have been considered and ruled out). A good example is the case of rare anaemias: to ensure that only the more complex, challenging cases are brought to the attention of the ERN in a virtual consultation, a gatekeeper role is absolutely critical. How ERNs choose to organise this depends upon their disease focus: for some, an online 'tool' to conduct a first screen (e.g. a 'haematocrit measure' or a questionnaire such as the eCare open point) may be appropriate. For others, ERNs may request information to be conveyed to a gatekeeper for 'human' review and a decision made as to whether additional experts should be consulted/whether the patient should be reviewed comprehensively by a dedicated MDT.

In summary, there was significant emphasis not only on carefully selecting the data for clinical reviews but also structuring and standardising it in some way, to enable smoother, more efficient consultations.

Key principles on patient pathways and 'referral' to an ERN

- National referrals and pathways are national prerogatives and responsibilities
- Ideally, all European MS will, by now have followed the guidance espoused by the **2009 Council Recommendation on an action in the field of rare Diseases**[1], in particular the call for countries to identify and designate centres with expertise in RD, making this expertise visible in each country. Where this *has* been achieved, an assessment of how the ERNs will complement the existing structures and national networks should be far simpler, because one can assume a certain level of awareness at the national level of the RD expertise already available in-country, making it easier to refer patients from primary and secondary care into specialised tertiary care systems, which will likely be the nearest gateways to the ERNs. If there is a lack of awareness, nationally, of existing RD expertise and gaps, it will be more difficult. If one relies on tertiary service specialists, it is necessary to have a strong baseline knowledge, and not all of the countries seem to have this yet.
- Access to a virtual consultation within any given ERN will clearly be easier in cases where a country has at least one member HCP. In these cases, it is imperative that ERNs strengthen (and in no way supersede or undermine) the national networks and help to streamline the pathways, where there is scope for this. For the countries which do not have members in particular ERNs, a particular effort will be necessary to avoid *de facto* exclusion of patients to the services of the ERNs when needed - this is why the 'affiliation' concept is so important.
- If a broad awareness of the ERN concept is lacking in any given health system, the impact of the Networks can only ever be minimal. A major communication effort will be needed, in each country, and ERNs will need to be carefully 'marketed', to truly become the next frontier in specialised care.

Discussion: guiding principles and good practices for standardising RD data

There was broad discussion on how the ERNs might recognise which 'tools' are genuinely useful and have 'staying power'. Participants pointed out that sometimes there are several similar tools available, and questioned whether it was desirable/feasible for all the ERNs to harmonise the tools they use. It was agreed that one should exercise caution in embracing any particular tool or 'instance' of a standard; **however, if we want to optimise the interoperability of data in the ERN framework -and by extension, the wider RD field- it is necessary to agree the core standards, where these have reached a sufficient level of maturity and acceptance and will not 'disappear'.** Orphacode and HPO have been endorsed in this way, although their effective usage requires forethought and preparation, if one wishes to harness their full potential for enriching the data. In attempting to agree good practices between the ERNs, the goal is not to *enforce* one entity or

[1] http://ec.europa.eu/chafea/documents/health/prague-rd-council-recommendation_en.pdf

another. ERN communities must decide themselves what they do with their data and where they deposit it etc. (e.g. if they wish to use particular variant-calling platforms); rather, **this debate is about enhancing the discoverability and reusability of that data.**

In the course of these discussions, several ERN coordinators identified a need to agree a means of coding not just diseases, but also therapeutics and medical devices, for instance – this is very important, and all ERNs were encouraged to share key standards and ontologies of particular relevance to their field with the RD-ACTION organisers.

The group discussed various issues around sharing/exchanging data. Rachel Thompson explained that the RD-Connect ELSI research[2] highlights the fact that patients have the right to *expect* researchers to share data, under appropriate conditions, and this does not mean waiting until publications are released. **To do this requires changes in the way in which data is collected and stored.** Again, it was emphasised that gathering robust phenotypic data may require some tailoring of the HPO within specific disease communities: some of the things people will wish to capture are not really 'phenotypes' e.g. wheelchair use. Therefore, effort upfront is required, but the message is that this will pay dividends.

There was lively discussion as to the *types* of data that will be shared in the ERN framework, and this included a 'diversion' into the topic of registries. An important issue here of course is how one actually *defines* the ERN framework. Most people agree that the ERNs will offer an unprecedented opportunity to increase the proportion of RD patients enrolled -or offered the *chance* to enrol- in appropriate, quality-assured registries. Whether these are somehow embedded in the ERN IT Platform, or sit outside of it (e.g. existing robust registries, or new ones that may be established) ERNs will surely encourage increased patient registration. As few registries are able to fulfil multiple purposes effectively, teams will need to consider what *sort* of registries they wish to enrol patients to, and where these sit. Alongside this, there is the highly relevant issue of what data the SaaS for a clinical patient management system will retain, and what this will be useful *for*. The Tender is clear: data will be shareable for virtual care, and will be pseudonymised and retained for re-use: the specifications demand that the service:

> "(xiv) encrypts and stores the data;
>
> (xv) pseudonymises patient data for sharing, use in clinical decision making tools, protocols, guidelines, case library or research;
>
> (xvi) hosts the data storage within EU borders and ensures that the hosting is single-tenant with stable, fast and easy data storage and retrieval, back-up and recovery;"

A key question, then, is what data one wishes to collect during virtual care encounters, knowing it will be available later for secondary purposes. One must balance the utility of the data stored in that platform against the efforts required to collect the data.

[2] http://rd-connect.eu/platform/ethics/

How the ERN platform will interact -or not- with *other* types of data seemed much clearer; for instance, it will surely *not* be possible to store raw WES or WGS data in the SaaS! One must envisage 'safe havens' equipped to store such raw data, such as the European Genome Phenome Archive (which is used as the raw data repository in RD-Connect.)

Several coordinators emphasised the need to provide for undiagnosed patients, and participants discussed how to 'code' such patients using OrphaCode. The group appreciated the importance of agreeing a common means of pseudonymizing patients in the ERN framework: this is a crucial issue, particularly as we move towards ever-greater reliance on eHealth. **If a set of PII has been agreed as the basis for generating a common means of linking data whilst preserving privacy (e.g. via a GUID–like system) then the ERNs should, logically, include these elements in any common dataset agreed for virtual consultations in the ERNs (and indeed, for any patient registration connected with each ERN).** Beyond this, one will need to consider if there are any *clinical* items that would be essential for all ERNs to collect, or if this will be too different from one Network to another (participants proposed there is more relevance to agreeing common data elements for certain types of *registries*, as opposed to clinical case report forms).

In response to a question about how to encourage MS to use the OrphaCode in their HIS, it was emphasised that the JA (RD-ACTION WP5) is attempting to provide as much hands-on support to countries as possible, to help them fulfil the Recommendations on coding for rare diseases. Once again, it was noted that ERNs have a unique potential to propel many of these initiatives into the mainstream, and optimise the way in which **data is collected and stored: ERNs, sitting at the crossroads between care and research and in a sense 'beginning from scratch', are a perfect ecosystem in which to 'get things right'.**

Summary of the 'Tool-Kit' resources to be finalised post-workshop and next steps

In summarising the workshop, Ana and Victoria made the following points:

- The ability to share and pool data is essential in the RD field, and in all fields requiring a specific concentration of expertise: only through data congregation can one attain a critical mass, which generates knowledge and drives forwards improvements in healthcare
- Additional legal support from the European Commission would be invaluable, relating to obligations of ERNs concerning data handling under the new GDPR[3]
- In legal terms, it is probably possible for patients to receive virtual care/ a virtual consultation in an ERN *without* providing explicit consent; however, the group was unanimous that informed consent should always be obtained, as a 'best practice'
- RD-ACTION will assemble papers which address relevant ELSI issues for rare disease data (research papers) and will also assemble as many sample IC forms as possible, for conveyance to the EC teams delivering the final Consent forms for the ERNs

[3] Several Tenders have subsequently been awarded, to address this important area:
- Tender SANTE/2016/B3/053: Analysis on the Impact of EU legislation on the operation of ERNs
- Tender SANTE/2016/B3/061: Informed consent for European Reference Networks implementation

- Use of agreed ontologies such as the ORDO and the HPO adds value to data, especially in terms of the **reusability** of that data – standards which exist already and have gained a certain level of 'acceptance' in the wider RD and specialised healthcare field should be promoted in the ERN framework, to enhance the value of the data which is collected, exchanged, and retained.
- In recommending standards for use with ERN-related data, it is important to note that the process is not unidirectional: what other standards should be embraced, which are used widely in the RD and/or specialised healthcare/ technology field and have been proven to enhance the utility of information/data (e.g. standards around coding medical devices)?
- There are practical questions from this audience on how one actually ***uses*** these different ontologies (e.g. how to use the OrphaCode and make it most useful for a particular disease area) and what they can do to enhance the work of ERNs. It would be useful to arrange a more hands-on demonstration for some of these tools, to explore what needs to be in place, how one can use Orphanet Nomenclature, HPO, Identifiers etc. to add value to the data and increase its interoperability through FAIR approaches, for instance.
- **It would be logical to produce a list of consensus recommendations on standardising data in ERNs, along the lines of:**
    - ERNs should prioritise use of OrphaCode because of x, y and z
    - ERNs should prioritise use of HPO as the best RD-sensitive standard for phenotyping, because of z, y and z
    - ERNs should collect the PII necessary to generate a GUID or similar, as a minimum, from all patients referred for virtual shared care in the ERN and indeed from all patients enrolled to registries.
    - As above, which other standards should be recommended (e.g. OMIM for genes? Lab standards?)
    - Is it also possible to agree on some core statements, such as 'Data should not be collected, used for 'direct' care and then destroyed, unless the patient wishes this'
- To have maximum impact, it is essential that the good practices recommended by this Group are actually *incorporated* to the SaaS for a clinical patient management platform – how do we achieve this?
- The ERN community can –hopefully- agree the ***way*** in which data is captured (i.e. agree the standards used, e.g. Orphacode). Would there be any benefit in attempting to agree a model Case Report Form (CRF)/template, with common data elements, **for the virtual consultations**, or would these differ too much across the ERNs? It is likely that it would <u>not</u> be feasible or meaningful to try to agree *clinical* data elements for collection in virtual consultations across all ERNs; however, this workshop has suggested **that there should be homogeneity in the demographic data (the PII).**
- It is necessary to think carefully about how CRFs –such as will be shared for virtual care- differ from **registries**, and perhaps begin discussions on what the best practices would be for enrolling patients of the ERN in registries (again, do ERNs routinely offer enrolment to patients seen in virtual MDTs, or expand this to all who come to the HCP?)
