Conclusions and Next Steps from the workshop 'How ERNs can provide added value in the area of clinical research'

Organised by RD-ACTION, EMA, DG SANTE, and the ERN Research Working Group

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Summary of Key Discussions and Action Points:

RD-ACTION, EMA and DG SANTE Workshop: How ERNs can provide added-value in the area of clinical research

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Executive Summary

The workshop united 65 participants from many different stakeholder groups, to explore one fundamental question: How can ERNs provide added value in the area of clinical research? 22 of the 24 ERNs were represented directly, through a combination of Coordinators, Research Leads, and (ten) ePAG advocates. Several EMA staff members participated, along with DG SANTE, DG Research, and a representative of the Board of Member States of ERNs (BoMS). A range of experts from RD-ACTION and research-related initiatives also participated. The workshop had four main goals:

1. **To share the state of the art of tools and resources which exist in 2018 to streamline and optimise each 'point' in the clinical research pipeline**
2. **To better understand the priorities and needs of the ERN community specific to clinical research, and explore case studies (both of pre-ERN successes on the part of research networks, and early ERN-era achievements/goals) in particular detail**
3. **To elucidate the type of support and opportunities offered by the European Medicines Agency which are of relevance to clinical research in rare and highly specialised domains**

4. **To identify concretely *how* and *where* ERNs could make a positive difference to each 'timepoint' in the clinical trial pathway, including points of engagement specifically with the EMA, to lay down the basis of a 'roadmap' to a more strategic and streamlined interaction and possible collaboration in the future.**

The first day of the workshop sought to establish the status quo around ERNs and research, and to identify existing tools and resources available to support them in their mission to create added value in the field of clinical research. The second day was entirely dedicated to debate, structured around four key topics. **For each topic, the workshop participants highlighted challenges and opportunities, agreed conclusions, and proposed Action Points to help the ERNs move forwards. This document constitutes a summary of these multistakeholder expert discussions.**

The Action Points are amalgamated in the table below and are contextualised in the discussion summaries which form the remainder of this document.

List of Proposed Actions Points

Action Points from Topic 1/Transversal Points:
What sorts of activities under the heading of 'clinical research' will ERNs engage in, and what are the advantages of the ERN structure?

- The survey should be completed by the remaining ERNs and, if possible, a publication prepared, under the guidance of the Workshop Organising Committee
- It will be important to arrange further meetings -at least annually- to build upon this first workshop and continue to define how ERNs will conduct clinical research: plans for subsequent meetings should be elaborated
- Coordinators will revisit the question of ERNs' legal status, and, if demand is there, request the EC to explore possible routes to legal entity status or equivalent
- If the goal of the current document created by the Ethics & Legal WG does *not* extend to proposing ethically-sound, robust ways to interact with Companies, as well as how to avoid a CoI, the Research WG/Ethics WG or a collaboration of the two should explore possible forms of such engagement for ERNs
- The Research WG should continue to advocate for dedicated grant opportunities -especially via Horizon Europe-to enable the ERNs to perform certain types of research, logically in accordance with the outcomes of this workshop survey and additional mapping activities/Research Strategy conducted by an EC contractor
- Surveys conducted by individual ERNs could be shared with other Coordinators, to facilitate them in gathering similar information. Similarly, more information/a demonstration of the ERK-NET database could be provided, to ascertain the benefits of developing similar tools/a shared tool for all ERNs to use

- The WG on Research should begin to create a checklist for each of the various kinds of research ERNs might lead/contribute to, in consultation with stakeholders from the wider RD field, to ensure 'quality through consistency'

- The RD-ACTION 'Recommended Practice for Standardising Data in the Framework of the Operations of ERNs' proposed incorporating the HPO to the CPMS, to enrich the data captured therein and enhance its reusability – the implementation of this particular proposal could be supported to capitalise on this opportunity and added value of ERNs

- The WG on Research could organise a face-to-face meeting with key representatives from the biomedical ESFRI Infrastructures, to improve understanding of how each could benefit the ERNs and vice versa

- The mapping document (on Research Infrastructure services) produced by the EJP team could be revised a little and turned into a short report or summary after the aforementioned face-to-face meeting, and disseminated to the ERNs for further dissemination amongst their HCPs

- The WG on Research should follow-up with Stephane Lejeune and EORTC to discuss the invitation to host ERN Coordinators/Research leads at the Brussels EORTC HQ to demonstrate their resources and services

- Knowledge of the deliverables of IDEAl, ASTERISK, and InSPiRE projects and how to implement them would be beneficial, including the evolution of their regulatory acceptability – although methodological guidance is expected under the EJP, any existing summaries should be shared with Coordinators for dissemination through the Networks

- The precise plans under the IRDiRC TF on clinical research Networks should be elucidated, and steps proposed by the WG on Research as to how ERNs can engage here (e.g. it will be necessary to assess the current maturity of the plans, and agree whether immediate action is possible/desirable, or whether this should be a longer-term goal).

Action Points from Topic 2:
What opportunities exist under current EMA structures and resources presented on Day 1, and how might ERNs engage with these?

- The WG on Research (or other body) could explore and shortlist topics for cross-ERN scientific solutions in the pre-competitive space to be evaluated by EMA for qualification. These might be scientific solutions (novel methodologies) applicable to *all* Networks (such as trial methodologies) or else could be specific to Networks with logical areas of commonality (e.g. selection of disease end-points, methodology for use of brain MRI, registries, etc.)

- Interested ERNs should consider joining the EMA's Stakeholder Database in order to receive information relevant to their Thematic Grouping (e.g. information on upcoming events, awareness of consultation on regulatory guidance and guidelines) and further disseminate to the wider ERN members.

- The Research WG/each ERN representative should explore with the EMA how the process of expert consultation might work in practice, to identify ERNs as a 'go-to' referral group for rare diseases (including how to avoid conflicts of interest and how to reach experts working in HCPs outside of ERNs)

- ERNs should be invited to present at meetings of the Patients and Consumers Working Parties (PCWP) and Healthcare Professionals Working Party (HCPWP) and opportunities for strategic ERN representation in those bodies should be explored

- EMA offered a dedicated contact point to follow up on ERNs enquires – Networks should make use of this contact as and when relevant, but *all* ERN members should approach this single named contact for any Agency-related business, henceforth.

- The Research WG will liaise with EMA to agree how best to incorporate information about the EMA on the on ERNs websites

Action Points from Topic 3:

Identifying concrete roles and recommended practices to involve patients in the various types of ERN-related Clinical Research

- A TaskForce/Working Group should be established (perhaps by ePAG representatives, for instance) to analyse the most effective strategies employed by the EMA (and other organisations) to remove barriers and facilitate full engagement of patients and families, with a goal to replicating some of these practices within ERNs

- It may be necessary to deliver training in some of the content of programmes like the EURORDIS Summer School to a bespoke ERN audience of high level researchers/clinicians (who would not be likely to attend a summer school but could benefit from a condensed course on regulatory issues etc.) – opportunities to organise this via the EJP should be explored by the Pillar 3 leadership team

- EJP Pillar 3 Colleagues will be asked to share the mapping of RD-specific training opportunities/resources with the Research WG and the corresponding ePAG transversal WG.

- The WG on Research/another body should develop a cross-ERN training event tailored to researchers on how to involve patients in research activities

- Dedicated projects/ pilots are necessary to explore more concretely how ERNs can develop and collect more appropriate health, clinical and QoL-related Outcomes (including PROs), and under which circumstances. Agreeing/creating scales and tools to capture these Outcomes (i.e. agreeing suitable Outcome Measures) should also be prioritised. ERNs also have an unprecedented opportunity to capture traditionally-overlooked holistic outcomes relating to a patient's quality of life *beyond* the purely medical sphere, e.g. concerning education, habitation, employment, relationships, etc. Opportunities to launch such work should be sought.

Action Points from Topic 4 ***(How can ERNs generate/link/exchange data to support the planning and execution of clinical trials and studies?)***

- A large workshop, involving representatives from each ERN and also all related initiatives, should be organised, to help Europe's RD registry stakeholders (perhaps ERNs specifically, with another workshop geared to national registries?) shape and progress with strategic, complementary plans concerning RD registration

Summary of Day 1:

The first day of the workshop was intended to establish the status quo i.e. to clarify the backdrop against which ERNs are operating. What relevant initiatives are taking place or emerging which could impact (foreseeably positively) on the ERN mission around clinical research? What are the current plans and priorities of the ERNs themselves in this area? And finally, what kind of support, tools and resources does the EMA offer in the field clinical research?

Victoria Hedley and Luca Sangiorgi summarised **the main messages from Day 1**:

- The ERNs are engaged in a very broad range of activities, across many topics. For example, the Networks are beginning to refer cases to the Clinical Patient Management System, CPMS; 5 ERNs secured a grant to establish/evolve registries; a set of common Indicators are being identified, for monitoring; coordination grants are available; the second call for ERN membership is under discussion; etc. In some areas then, the ERNs' deployment is well-underway: in others, including research, activities are just beginning.

- Workshop participants learned more about the political support for ERNs and the key activities being led by DG SANTE with relevance to the Networks. The EC's legacy of strong support to rare disease research was emphasized, and the opportunities offered by new projects like Solve-RD and ImmunAid were summarised. The European Joint Programme Co-Fund was also highlighted, which involves a number of ERNs in Pillar/WP leadership roles, and will build services open to all Networks under Pillar 4

- The main activities of the Research and Ethics WGs, respectively, were highlighted. A key topic for Day 2, in fact, was to what extent this workshop might influence and support the work of these Groups/propose future foci for them.

- The participants discussed key research priorities including the need for good epidemiological data and the importance of understanding the prevalence of the disease before launching clinical trials. the importance of defining lifestyle choices that are backed with sound evidence and the need to conduct natural history studies to understand the mechanisms and causes of the diseases.

- Patients shared their expectations for involvement in research, stressing the need to be partners across the clinical trial pathway. Training was deemed essential for patients but also for clinicians, researchers, regulators and payers, to allow stakeholders to participate in patient-centric ERN research-related activities.

- The results of a short pre-workshop survey, disseminated to ERNs, were shared. 21 responses were received by the date of the workshop itself, from 17 Networks. The results illustrate a number of important opportunities and advantages afforded by the Networks (see below, Discussion Session 1), and confirmed that the vast majority of ERNs have created dedicated WGs for Research. The survey also illustrated the sorts of research ERNs are envisaging to lead/participate to. For example:
    - When asked to select current plans and priorities pertaining to 'Research' over the first 5 years, the most popular responses were *Epidemiology*, *Therapeutic Options (Medicines*), and *Quality of Life* (all scoring 18) followed by *Translational Research* (14).
    - When asked to think further afield, and select research priorities *after* the first 5 years, the above options remained the most popular, but other types of research scored significantly higher than in the 'short-term' question, namely public health, socioeconomic research, basic/pre-clinical, and HTA-related research
    - The results also highlighted a number of barriers to ERNs fulfilling their clinical research 'mandate': the most highly-rated barriers were lack of funding (cited by 19 respondents); uncertainty over how ERNs can lead/participate to clinical trials and studies (12); lack of well-stratified patient cohorts for trials (10); lack of regulatory know-how (10)
    - More comprehensive details of the survey results can be found in the presentation slides.
    - **AP: The survey will be completed by the remaining ERNs and –if possible- a publication prepared, under the guidance of the Workshop Organising Committee**

- Finally, in Session 3, a number of key tools and resources provided by the EMA had been presented. At the present time, the regulators' role is increasingly evolving, from traditionally acting as a 'gateway' to actually facilitating and supporting the research which culminates (hopefully) in the approval of safe and effective new medicines. EMA together with the European Regulatory Network provides support and guidance to the development of new medicines, evaluates applications for marketing authorisation, and monitors the safety of medicines across their life cycle. The EMA has 7 main scientific committees, fed by thousands of experts, and many additional structures (such as Working Parties). EMA staff gave an overview of the most relevant regulatory activities underpinning the medicine lifecycle. Participants learned about how ERNs could make the best use of particular tools and resources, provide expertise and data-sources, and contribute actively to EMA-supported research networks: **there was a particular focus on how the EMA and ERNs could mutually benefit from an interaction based on robust reciprocal knowledge and commonality of goals.**

The second day of the workshop was designed to incorporate a series of semi-structured debate sessions, each addressing a different (though often inter-related) topic, building upon the sessions on Day 1. Discussion Facilitators were appointed for each Topic, and key questions were agreed following the presentations and discussions of Day 1, to ensure maximum applicability of the direction of debate and stimulate some concrete action points.

Discussion Topic 1 - What sorts of activities under the heading of 'clinical research' will ERNs engage in, and what are the advantages of the ERN structure?

Three key questions were presented, to orientate discussions

1. What are the concrete advantages of ERNs for clinical research?
2. How do we (collectively) define 'clinical research'? e.g. clinical trials 'of the network'?
3. Are ERNs planning to focus on particular types of clinical research only (e.g. natural history studies)? What would help you/them in achieving success in each of these?

Many points were proposed, relating to Question 1 (some of these are reproduced here from the Survey):

What are the concrete advantages of ERNs for clinical research?

Permanence: ERNs are permanent structure – they are not time-bound projects but should, assuming the 5 year evaluations are positive, become sustained structures sitting alongside and complimenting existing national channels and entities.

Proximity of Research and Clinical Spheres: The Legal Acts upon which ERNs are based mandate the unity of clinical and research expertise. The added-value here is enormous, as it assures a proximity of the research to the patients, based upon the fact that the HCPs which make-up the ERNs are active clinical hubs, receiving patient referrals. This offers the opportunity for ERNs to make significant strides in translational research. Clinical research should be linked as much as possible with clinical care.

Comprehensive Disease Coverage: ERNs have a mandate to, in time, address all rare diseases under their 'Thematic Grouping'. The *EUCERD Recommendations on RD ERNs* proposed that such a development should logically be stepwise, as it would not be possible in any Network to fully address all conditions under a broad heading from Day 1 (some networks opted to begin by focusing on only a subset or a particular subdomain under their broad Thematic Grouping; others established the networks with comprehensive sub-domains -i.e. with all in place-, but with the understanding that identifying –and most importantly *building*- the expertise across all individual diseases would take time.) The mechanics of exactly *how* ERNs can mature and advance to indeed offer -and grow- expertise in all the conditions under their respective Thematic Grouping remain uncertain; nonetheless, the workshop participants affirmed the opportunities which the comprehensive scope offers. For the first time, conditions will all have 'a home' in theory, under at least one of the

Networks (sometimes more than one). This could foreseeably lead to research attention and activity in hitherto unexplored/untapped disease areas, which perhaps have not been the recipients of specific funding to date, and which do not have resources to stimulate clinical research.

Data Generation/Linkage Opportunities: ERNs provide unprecedented opportunities to collect good quality, relevant, and interoperable data which can be used effectively for a specific purpose at hand (e.g. a clinical consultation through the CPMS, or to elucidate genome-phenome associations through inclusion in an appropriate registry) but can also be *re*-used, for a number of essential purposes. In 2018, we have a much better understanding of the conditions/opportunities for data pooling/querying than ever before. Ontologies of particular benefit for the broad RD field are agreed, which, if employed, will support greater semantic interoperability. FAIR data concepts continue to grow in prominence.

ERNs are based upon centres which have demonstrable expertise in particular areas, but the Networking tools which connect these well-established centres are being created -or at least delivered- anew. This offers exciting opportunities for the almost 1000 individual HCPs across Europe to subscribe to best practices around collecting and pooling precious RD data which would support the provision of highly specialised care. Given the fine line between 'care' and 'research' in the field, the potential for the resources ERNs use/will use to build a critical mass of patient data for a myriad of purposes, is substantial. ERNs are very well positioned to build platforms and infrastructure - especially perhaps registries- for collaborative research with a standardized approach and broader focus (beyond a single disease). They can be perfect curators to collect real word evidence (RWE) and conduct natural history studies. There is a chance here to establish data collection infrastructure (e.g. CPMS, registries, etc.) 'optimally' from the start, and apply good practices to data collection, standardisation and sharing.

Cross-fertilisation of Expertise: Several survey respondents *and* workshop participants emphasised the added-value of the ERN structure. As above, broad disease groups are brought together under a single heading, and compartmentalised into subdomains. Groups attested the advantage of working and liaising with colleagues in different sub-domains, in terms of forging new collaborations, elucidating characteristics of the diseases they work on, sharing proposals for new research and therapy development etc., presumably none of which would have happened in the pre-ERN environment.

Patient Involvement: Patients sit at the heart of the ERN concept (indeed the concept *emerged* largely from the patient community in Europe). The Addendum to the EUCERD Recommendations stipulated that Patients should have a meaningful role in all levels of ERN activity, governance included, and good examples of how this has been realised exist across the Networks. The creation of the ePAGs and the approach of reaching out to patient organisations to support, strengthen and guide the work of certain networks, is positive and offers new opportunities to engage patients in the day-to–day work of the ERNs, but also to engage patient organisations across Europe and build a sense of common identity around a single ERN Thematic grouping. There are opportunities here to reach out to patients through the ePAGs/organisations who are formally affiliated with the Networks,

and to seek involvement to support clinical research in many ways, e.g. to establish/further populate registries, to support feasibility studies for trials, to spread information, to recruit patients for trials and studies, etc.

Also, by simplifying and streamlining recruitment of patients for trials, ERNs could contribute to bring the trials to the patients, rather than the other way around as is currently the case. The field 'mapping' which is ongoing at many levels within the ERN community is very applicable for patient organisations: the ERN has enabled organisations to find groups dedicated to the same/similar conditions, and to uncover organisations which they did not know existed. This builds solidarity and empowers citizens but also functions as a broader base for ERN clinical research

Reputational Excellence: ERNs have strong potential to represent a certain 'seal of approval'. On the one hand, it is important that ERNs are not viewed as an exclusive club: not all centres with expertise in rare and complex diseases will be part of these Networks formally, and indeed this was never the concept of an ERN (the idea was that, via a relatively small number of select centres, the combined expertise of the centres of expertise in a given country would be incorporated, through existing national channels/creation of national networks). On the other hand, the ERNs should absolutely be viewed as something unique, as a concentration of the expertise which exists in Europe. The HCPs which are formally members of an ERN have all met (or should have met) stringent criteria which confirms their expertise in care and research for people with rare/complex conditions. Therefore, when all due care is taken to include non-ERN actors with perhaps comparable expertise through broader collaborative (often national) channels, the combined expertise of an ERN and its composite centres/tools/resources should enjoy a certain reputation in the field, with the ERN logo signifying a 'trusted' badge of quality conveying reputational status for research activities.

Questions 2 and 3 were discussed together, as the issues are somewhat interconnected. A number of overarching points were made, to set the scene and initiate the discussions:

- **AP: It will be important to explore the possibility of having further meetings, involving EMA, to build upon this first workshop and continue to define how ERNs will conduct clinical research**; however, there was concern as to how this could be achieved, given that the RD-ACTION project ends this summer and no similar initiatives are planned in future.
- **AP: One proposal was to expand membership of the HCPWG (Health Care Professionals Working Group) by introducing direct ERN representatives to complement existing membership**; however, as the members of the HCPWG typically represent professional organisations (such as European Associations), it would be necessary to agree the best strategy for this.
- An important goal of this discussion topic was to propose activities and possible foci for the Research WG under the ERN Coordinators' Group (ECG) This is the first time this very broad topic (clinical research activities of ERNs) has been discussed in a major meeting/workshop, and all were in favour of using this session in particular to identify means of focusing the WG activities in a particular direction. The BoMS will also develop perspectives on these issues: in terms of the very broad range of activities ERNs could perform/participate to, under the

'clinical research' banner, it may be that the Member States will decide that their main interests for ERNs in this sphere lie with X and Y activities and less with Z.

- **AP: It was agreed that the discussion points of the day could be used to stimulate the next steps of the WGs.**

Identified Needs and Priorities of ERNs, and corresponding comments/action points

Needs and Priorities Identified by ERNs in the Pre-Workshop Survey	Relevant Discussion Points and Actions identified on Day 2
Clarity is needed on how ERNs can establish contracts to conduct clinical trials/clinical research activities - will ERNs become legal entities at some stage? Could one imagine foundations of some sort to channel funds (for numerous activities, in theory)?	• Significant discussions took place, relating to the potential for ERNs to become legal entities. Some ERNs emphasised that the system requires any funding to come only to the Coordinating centre, and consequently networks do not see how they could receive money to set-up or contribute to, for instance, natural history studies. It was suggested that the Consortium Agreement of the Networks should be used more, as a tool to support the movement of resources and the sharing of responsibilities. • DG SANTE confirmed that the issue of ERN legal status had been raised with Coordinators but it did not seem to be a topic the latter particularly prioritised. There *are* options which do not entail making ERNs legal entities, e.g. the ERIC (European Research Infrastructure Consortium) is one possibility; however, the ERIC route takes years and does not appear terribly popular. DG SANTE confirmed that if the Coordinators DO see this as a priority, they can revisit the question. And indeed, there was strong support from several participants for the EU institutions to draw upon their legal experts and find a way forward here. • Many participants seem to see the 'legal entity' issue as a pre-requisite for obtaining sufficient levels of external funding for the Networks. The concept of setting up a number of foundations (or one large single foundation perhaps) was raised, as a means of channelling funds into the Networks. • One important aspect to consider here would be ensuring sound corporate and financial governance of ERNs and transparency of accounts and auditing. The current system, where different HCPs from an ERN can bring in financial resources linked to different research projects, is bound to lead to challenges in terms of ERNs financial management and control • **AP: Coordinators will revisit the question of ERNs' legal status, and, if desired by the Networks request the EC to explore possible route to legal entity status or equivalent**
Clear regulations on how ERNs can engage with industry	• It is very important that all ERN stakeholders are aware of the activities of the WG on Ethics, Legal and Data Protection, specifically what this WG will and will not produce. It was explained that the individual Conflict of Interest statements which (most) ERNs created for the proposal submission in 2016 will be

	replaced by a single shared CoI statement, which exists in draft form and will soon be finalised as a 'Policy on Conflict of Interest and Disclosure Form', which will include the BoMS statement. • It was proposed that either the aforementioned document OR a complementary document should include guidance on how to engage with Companies, and not just how to avoid it. Responsible, ethically-sound, and mutually beneficial examples of engagement exist between Industry and various groups of rare diseases and rare cancers (some are highlighted in the workshop report, and are proposed as examples which could be reproduced in other communities) These examples and existing Codes of Conduct (as opposed to CoI statements) should inform either the Ethics WG document OR a second document generated by inter-WG debate. • **AP: If the goal of the current document created by this WG does *not* extend to proposing ethically-sound, robust ways to interact with Companies, the Research WG/Ethics WG or a collaboration of the two WGs could explore possible forms of such engagement for ERNs;** for instance, it could re-open the request posed by one question within this survey, asking Networks for examples of successful interactions with Industry (either in the pre-ERN era or in parallel organisations). Several examples were highlighted here at this workshop, including EORTC, TREAT-NMD, European Skeletal Dysplasias Network. Further details on how these interactions take place could be elicited and the examples discussed, to explore -with the BoMS WG- options which could be supported for ERNs.
'Funding streams specifically for ERNs are required, but these should be open for all HCPs in all countries i.e. UK as well.' Some participants specified here the need for funding for *investigator-initiated* trials and observational studies.	• All ERN HCPs have a strong research record, and it is necessary to somehow motivate these centres to engage in research related to the ERN. To do any kind of meaningful research, dedicated funding is necessary. It was proposed that Calls in Horizon Europe (FP9) should be created exclusively for ERNs (or their member HCPs if the legal entity does not materialise). The Chair of the WG for Research affirmed that indeed, his WG is building a picture of ERN research capabilities, and is attempting to influence future grant opportunities for the Networks. • **AP: The WG should continue to advocate for dedicated grant opportunities -especially via Horizon Europe-to enable the ERNs to perform certain types of research, logically in accordance with the outcomes of this workshop survey and additional mapping activities/needs assessment conducted by an EC contractor**

'It would be helpful to identify common tools designed to capture the research status quo and share this information between ERNs'	Many ERNs are conducting surveys/planning to conduct surveys of their HCPs, to ascertain the current extent and scope of research ongoing under the broad Thematic Grouping of the Network and mapping what HCPs are involved in which activities. • Surveys created and deployed successfully may be useful for other Networks. • Furthermore, actual assets – such as the research database set-up by the ERK-NET for instance- could be useful to all ERNs (and indeed a shared database would give a good impression of the extent of research ERN HCPs are involved in, and could also identify opportunities for cross-ERN research collaborations. • **AP: These two proposals could be suggested to the Coordinators (more information/a demonstration of the ERK-NET database would probably be required)**
'Reasonably robust infrastructures exist already (e.g. BBMRI, ECRIN) and others are just emerging (e.g. c4C Network for paediatric research, EJP) which ERNs should make use of' Clinical Research is a very broad area – how can ERNs ensure some level of commonality or consistency?	• **AP: The WG on Research could play a role in supporting ERNs to bring quality to research through consistency of process. The ERNs offer a real opportunity here to build quality through consistency, by essentially creating a checklist for each of the various kinds of research ERNs might lead/contribute to.** Each would have an associated checklist which encourages stakeholders to follow agreed procedures to enrich each stage of the research. ○ For instance, if the study/trial is multinational, there should be specific points on that checklist on engaging with ECRIN for X, Y and Z. ○ Then another section of the checklist would concern data: what you need to be aware of if your research involves collecting data; what costs to factor in for data stewardship; where to obtain guidance on GDPR compliance; what sorts of ontologies and standards should you use, and how to practically do this. ○ Similarly, if your research involves working with a paediatric population or young people, to seek advice from the new conect4children (c4c) network on ethics and paediatric researcher training, and engage with the Network of Young People's Advisory Groups, etc. ○ In this way, one breaks down each type of broad research into stages, and use knowledge of what constitutes the 'state of the art 'in each area to construct checklists of these sorts, professionalising ERN-led/ ERN-involved research and ensuring consistency of quality of the research.

ERNs are well-placed to gather data for observational and natural history studies, for instance – it is necessary to make data more interoperable, to bolster these efforts.	Coming largely from University Hospital environments, many of the HCP colleagues are familiar with capturing deep phenotypic data: this is something quite unique to this sector, which is not traditionally done by Companies, for instance. • The ERNs could play an important role in continuing and expanding this deep phenotyping, which is very relevant for this workshop. Good phenotypic data -e.g. collected using the Human Phenotype Ontology, HPO- when combined with genetic or other -omics data is often needed for diagnostics but it also enables a better understanding of the natural history of a disease, and facilitates the identification of clinically-relevant endpoints, etc. • **AP: The RD-ACTION 'Recommended Practices for Standardising Data in the Framework of the Operations of ERNs' proposed incorporating the HPO to the CPMS, to enrich the data captured therein and enhance its reusability – the implementation of this particular proposal could be supported to capitalise on this opportunity and added-value of ERNs**
'It would be very beneficial to have a Clinical Trial Office for the ERN, perhaps for all ERNs to share.' 'A dedicated structure for the ERNs, to support with all issues related to clinical research would be very welcome.'	Several survey respondents and a number of workshop participants expressed strong desire for some sort of accessible clinical research support for ERNs. This could be a clinical trials office for the ERNs to use, as one specified. It might be supplied through the EJP, Pillar 4 of which will establish a Clinical Research HelpDesk to support ERNs in particular. Or, perhaps each Network would obtain support individually, from existing Research Infrastructures (see next point)
A better understanding is needed of what Research Infrastructures can offer and how they can support the sorts of research ERNs will engage in (especially around the complexities of conducting multinational trials and studies)	Several survey respondents reported a desire for a 'dedicated structure that would help with regulatory affairs' or 'Toolkits to help navigate regulatory differences across Member States, particularly in the context of GDPR'. These requests led to substantial debate on the services already available to *any* researcher, in theory, via existing pan-European clinical research infrastructures. ECRIN, for instance, should be perfectly positioned to offer expert advice on how to conduct trials across multiple jurisdictions, on ensuring consent is valid in all countries, on advising on how to exchange biosamples between countries, etc. • Participants noted that there is a general lack of knowledge on the part of researchers of what some of these large pan-European Research Infrastructures (e.g. the ESFRI Infrastructures) are actually there to do i.e. what they can tangibly provide.

	• This is partially because that 'service offering' and the way in which researchers can call upon the expertise of the RIs is still not clear, in many cases, and partially because researchers themselves are sometimes simply not aware of these enterprises and thus do not engage. • The EJP should, to a large extent, clarify this service officering with RIs, to promote better understanding of how and where RD researchers – ERNs included- can benefit from what the RIs provide, both in terms of RD-specific and non-RD-specific services. • **AP: To this end, it was proposed that the WG on Research organise a face-to-face meeting with key representatives from the biomedical ESFRI Infrastructures** most closely connected with the research mission of ERNs (ECRIN, ELIXIR, BBMRI, EATRIS as a start) , to elucidate the opportunities for support and collaboration as they stand today, as well as where we expect the EJP to improve procedures and ways of working. Background to this meeting could be the result of a mapping exercise conducted in the EJP proposal preparation, which stipulates the RD-specific and non-RD-Specific services RIs offer (this is important, as there are generic services and tools developed by the RIs which are nonetheless applicable to the RD filed) • **AP: This mapping document produced by the EJP team could be revised a little and turned into a short report or summary after the face-to-face meeting**, to describe for a relatively lay audience a) what these different infrastructures offer, b) who to approach for what service at present, c) what *will* be delivered by the RIs in the near future (i.e. what is in development) and, d) in particular, what will come through the EJP of particular relevance to ERNs. It could also incorporate the best way to engage with the new c4c network, which should be on the radars of ERNs when conducting/participating to paediatric research. • Such a 'guide' would be important for not only ERN Coordinators, but equally for the researchers working in each of the 1000 HCP units formally participating to the Networks.
It would be logical to explore the potential application of EORTC resources to the ERN community	In the same vein of 'seeking support from existing Clinical Research infrastructures' several survey respondents *and* workshop participants highlighted the achievements of the EORTC (European Organisation for Research and Therapies for Cancer). Stephane Lejeune, representing EORTC as well as ERN EURACAN at this workshop, confirmed that EORTC would be open to collaboration here, and the following actions were proposed: • EORTC should also join the aforementioned meeting with RIs, to elucidate the tools and resources it has to offer.

	• EORTC would be willing organise a visit of its HeadQuarters in Brussels for ERN representatives, providing presentations to explain their approaches, procedures, tools, etc., to facilitate discussions on which aspects would be transposable to other disease fields. • **AP: The WG on Research should follow-up with Stephane and EORTC to discuss this invitation** (e.g it could proceed to co-organise a visit to EORTC GQ, as above, and/or include EORTC representatives in a larger meeting with RIs as above)
Development of Registries is a major priority – this requires: *funding* to establish/expand/connect/harmonise registries… *guidance* as to the type of registry ERNs should be developing/expanding… and finally *clarity* on which tools/approaches to use.	• It was proposed that developing natural history studies, complete with deep phenotyping conducted according to existing good practices, should be a priority for the ERNs. • It would be useful for the other 19 ERNs -and indeed the wider RD community- to hear more about the technical plans of the 5 funded ERNs, concerning registry development/connectivity: what type of registries are they building/developing? What purposes will they serve? What other structures will the data interoperate with? • Registries should always serve a specific purpose – however, how far is it possible for the same registry to serve several such purposes (e.g. can a single registry elucidate the epidemiology and natural history of conditions, whilst also supporting feasibility studies for trials and facilitating recruitment?). • There were suggestions, in view of the EMA Patient Registries Initiative presentation, that the EMA can support the ERNs with their registry activities (for example through provision of scientific advice and qualification). However, others pointed out that the EMA Initiative is focused particularly on registries' suitability for PMS activities. The Joint Research centres (JRC) plans to develop a EU Platform for RD Registration have evolved to propose a ERDRI – a European Rare Diseases Registry Infrastructure platform. This has been briefly presented at various meetings by the JRC team, but the plans have become much more concrete and ambitious in the last year, and it would be very useful to have a proper workshop -perhaps organised by the JRC team- to really explain what this ERDRI will offer and answer many key strategic questions; therefore… • **AP: A large workshop, involving representatives from each ERN and also all related initiatives, should be organised, to help Europe's RD registry stakeholders (perhaps ERNs specifically, with another workshop geared to national registries?) shape and progress with strategic, complementary plans concerning RD registration.** The workshop could: a) Elucidate the types of registries which exist, and what value they add/what purposes they serve – this could help to advise ERNs on the sorts of registries they should be seeking to build/expand,

	and to think of how other sources of data (e.g. EHRs, the CPMS, etc.) might also help to answer those questions/answer quite different questions and add a different value. b) Explain the registry plans of the 5 ERNs which secured grant funding c) To better understand what the EMA Patient Registries' Initiative has concluded from its work so far, what the next steps will be, and what guidance -if any- will be relevant for the ERN community considering building new registries/expanding or adapting existing systems. d) Help ERNs (and other key stakeholders) to understand the latest JRC plans, for instance: ▪ what do the different elements of the ERDRI platform actually do and at what stage of development are they? ▪ e.g. what is a metadata repository? How advanced is the Germany-based Metadata Repository the JRC is utilising here? What are the next steps to further develop this and how can stakeholders get involved? ▪ what data should be sent to the RD registry warehouse, and where is this? Who will be able to access the data contained therein? ▪ which sort of registries are the ERDRI tools aimed at? Just the 5 funded ERN registries? Any of the 600 standalone registries in Europe? National registries? ▪ what will be the benefits of the tools/resources provided for different stakeholder (e.g. for different sorts of registries) (see further Discussion Topic 4, below)
Lack of clarity on the most appropriate methodologies to conduct clinical trials in rare/complex diseases	The workshop participants emphasised that uncertainty of processes and appropriate methodologies can hamper trials. The IDEAl (Integrated DEsign and Analysis of small population group trial), ASTERISK (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence) and InSPiRE (Innovation in Small Populations Research) projects each created methodological guidance to perform trials in disease/fields with small cohorts. • **AP: Knowledge of the projects' deliverables and how to implement them would be beneficial, including the evolution of their regulatory acceptability.** To an extent, the validation of these methodologies will come under the EJP but for now, awareness that these outputs exist and their current status quo would be illuminating for the wider ERN research community. The WG on Research, or another body, could agree whether to await EJP advancement of this subject or else the parties involved in the aforementioned projects could address this issue directly.

How might IRDiRC plans concerning Clinical Research Networks have an impact on the ERNs?	Several participants mentioned the concept of Clinical Research Networks, based upon the CRNs in the US. These networks are supported by permanent funding which enables them, for instance, to operate registries which collect extensive natural history study data. If the EC was able to fund the clinical research activities of ERNs to a similar level, this would be very beneficial; however, this is not realistic at present. Nonetheless, the IRDiRC (International RD Research Consortium) is exploring the possibility of developing/identifying similar structures in Europe (as well as Australia and Japan) to collaborate with their 'counterparts' in the US: • **AP: The precise plans under the IRDiRC TF on clinical research Networks should be elucidated, and steps proposed by the WG on Research as to how ERNs can engage here (e.g. it will be necessary to assess the current maturity of the plans, and agree whether immediate action is possible/desirable, or whether this should be a longer-term goal).**

Discussion Topic 2 - What opportunities exist under current EMA structures and resources presented on Day 1, and how might ERNs engage with these?

The leading discussion questions here were as follows:

- **How could ERNs engage with the EMA for mutual benefit, in terms of:**
  - **Collaboration on solving mutual challenges?**
  - **Optimal use of EMA support tools?**
  - **Becoming a source of expertise?**
- **What needs to be put in place for this to happen? What sort of procedures could be envisaged?**

General comments included the following:

- More in-depth knowledge of the various activities/services provided by the EMA, as illustrated on Day 1 and as summarised in the full workshop report, is already a major step here.
- EMA strategies for meaningful patient engagement were praised, and it was proposed that ERNs replicate some of these practices where appropriate (extensive information can be found here - Patients and Consumers EMA web pages)
- The ERNs offer particular advantages for stimulating, facilitating and conducting clinical research. It would be beneficial to develop some strategic steps to optimise engagement with the EMA

Some concrete activities that could support engagement -of varying types- between the EMA and the ERNs were outlined, as follows:

- ERNs can interact with the EMA as active players in the development of therapies, and could take advantage of the ***scientific advice*** procedure available (it should be noted that the formal procedure is subject to fees; parallel EMA/HTA scientific advice is also available)

- ERNs can interact with the EMA as developers and enablers of new scientific ***solutions*** *(novel methodologies)*; for instance, the ERN community/ Coordinators could propose workshop ideas in the pre-competitive space, e.g. on points to consider for trial methodologies, end-points for particular disease areas, registries etc. Priority could be given to transversal topics so to maximise the scope of the outcomes.

- The ***qualification procedure*** grants **regulatory acceptability of the specific use of a method** in the context of research and development; for instance, this might be a novel methodology

for conducting a trial, or use of a new biomarker or innovative imaging approach. The method can apply to both clinical and non-clinical studies. Notably, registries can undergo the qualification procedure, which could be of particular interest for the ERNs. Such methodologies could be developed in a pre-competitive environment.

  - **AP: The WG on Research (or other body) could consider and shortlist topics for cross-ERN scientific solutions in the pre-competitive space to be evaluated by EMA for qualification. These might be scientific solutions applicable to *all* Networks (such as trial methodologies) or else could be specific to Networks with logical areas of commonality (e.g. selection of disease end-points, methodology for use of brain MRI, registries, etc.)**

- The EMA has a **Stakeholder Database** (meant for internal use only) of interested parties, such as healthcare professionals' organisations, centres of expertise, networks, academic institutions, pharmaceutical associations, etc. This database is not intended for enrolment of individuals. Registration in this database offers numerous advantages, including prompt awareness of new, relevant guidelines open for public consultation, EMA workshops, and safety communications.
  - **AP: The ERNs were invited to each consider how they might join this database, in order to bring their expertise and disseminate news to the other members of their ERN**. For instance, an ERN could sign-up through a relevant European Society/Professional Association, or could in fact register in this database *as* an ERN (the organisations do not need to be legal entities) provided that a reliable contact person and a backup are identified.

- The ERNs can offer unprecedented visibility and coverage for scientific expertise in the field of rare diseases. EMA could contact ERN experts to take part in its ***procedures activity***, which requires a prompt turnaround. For this to happen, ERNs would each need to nominate a small number of individual experts (e.g. perhaps one per Thematic subdomain) to act as specific contacts with the EMA. These contacts would foreseeably be enrolled in the Individual Expert database (they might also be endorsed by National Competent Authorities, sign Declarations of Interests, etc.) EMA can provide the framework of how this might be enacted, including the handling of conflicts of interest.
  - **AP: The WG/each ERN representative should explore with the EMA how this process of expert consultation might work in practice, to identify ERNs as the 'go-to' referral group for rare diseases (including how to avoid conflicts of interest and how to reach experts working in HCPs outside of ERNs)**

- ERNs could be invited to present during future meetings of the Patients and Consumers Working Parties (PCWP) and the Healthcare Professionals Working Party (HCPWP). This could open the way for more concrete engagement, knowledge sharing.
  - **AP: ERNs should be invited to present at meetings of the Patients and Consumers Working Parties (PCWP) and Healthcare Professionals Working Party (HCPWP) and opportunities for strategic ERN membership of those bodies should be explored**

- ERNs could closely follow and participate to EMA research networks such as EnprEMA and EnCePP.

- It is advisable to put in place a coordinated EMA/ERNs contacts points system (reactivity, accountability, transparency).
    - **AP: the Agency offered a dedicated contact point to follow up on ERNs enquires. It is essential that henceforth, all ERN members seeking to contact the Agency on matters which are of any relevance to the ERN, go through this named contact point.** This will allow the Agency to streamline its engagement with the ERNs, identify transferable approaches, and replicate activities efficiently when other ERNs get in touch.

- ERNs should, ideally, be seeking to map expertise in all conditions under their broad thematic grouping: in time, this should result in a comprehensive picture of what expertise exists in Europe, and where, for each disease. Crucially, this must (again, in due course, as this is a major undertaking) include also expertise *outside* of ERNs, i.e. experts based in centres of expertise which are *not* formal members of 'affiliated partners' of ERNs.

- **AP: The WG will liaise with EMA to agree how best to incorporate information on the EMA to the ERN websites (and in time perhaps, vice versa)**

Discussion Topic 3 - Identifying concrete roles and recommended practices to involve patients in the various types of ERN-related Clinical Research

The key discussion questions here were as follows:

- **How do we 'train' patients to participate in ERN-associated clinical research, and also train researchers/clinicians?**
  - **What exists externally to ERNs? (or will exist) Is it enough?**
  - **What can be done within the ERNs?**
  - **What is working well in some Networks that can be shared?**
- **Patient centred/derived/reported outcomes – how should ERNs support the identification of these outcomes for clinical trials and studies, to address research needs?**
- **How could ERNs make clinical research more-patient friendly**

Key comments included the following:

<u>Good Practices: how to identify these and deploy them in the ERN framework?</u>

- Patient inclusion in ALL aspects of research (including HTA) is important. This inclusivity means taking account of patient suggestions for the areas of research to be pursued, in the drafting of research questions, etc. Only then are patients actually shaping research and contributing fully.
- There should be an overarching and comprehensive involvement of patients when setting-up resources such as registries, verifying data, and in all the aspects related to governance (processes to access and use the data) (see EUCERD Recommendations on Rare Disease Registration and Data Collection).
- Traditionally, meaningful patient involvement in research has been lacking, although the EMA was singled out for laudable practices in this regard. It was therefore proposed that a TaskForce/ Working Group should be established (perhaps by ePAG representatives, for instance) to analyse the most effective strategies employed by the EMA (and other organisations) to remove barriers and facilitate full engagement of patients and families, with a goal to replicating some of these practices within ERNs. For instance, good practices highlighted in the workshop itself included:
  - communicating research opportunities *and* research results, via newsletters to ensure patients feel their participation time was well-spent (i.e. that something emerged from the research they were involved with)
  - organising meetings in the national language with patients and clinicians, to engage them in research/share research findings: it was proposed that ERNs, via local HCPs, could engage and inform patients/patient organisations in the national language (which is important as not everyone has a good command of English).

Training for patients and researchers:

- To improve patient involvement in clinical research, training is essential: both training of patients and families, on the one hand, but also training for researchers, to help *them* understand how best to involve the patients in their work.
- Webinars are useful but hands-on training (for instance involving tours of laboratories another research fora) facilitate understanding. Mentoring was also proposed as a way forwards for ePAGs, in particular.
- Fortunately, various robust training opportunities and programmes exist in this area, for instance the EURORDIS Summer and Winter Schools, EUPATI programmes, etc.
- The group debated whether the programmes which exist are essentially adequate, and it is merely a case of rolling these out to train *more* individuals, or whether the content of existing training opportunities is sub-optimal. If the former, the EJP will increase the capacity of identified organisations to expand their training to a greater number of stakeholders. If the latter, these gaps should be identified and solutions to address them should be proposed.
    - **AP: It may be necessary to deliver training in some of the content of these aforementioned programmes to a bespoke ERN audience of high level researchers/clinicians (who would not be likely to attend a summer school but could benefit from a condensed course on regulatory issues etc.) – opportunities to organise this via the EJP should be explored by the Pillar 3 leadership team**

- It might be useful to make all existing training opportunities relevant to RD research available via a single site/ compendium of links, to support patients and researchers in locating these resources. The EJP performed a comprehensive mapping, as part of the process of elaborating Pillar 3; perhaps these findings could be shared.
    - **AP: If possible, EJP Pillar 3 Colleagues could share the mapping of RD-specific training opportunities/resources with the Research WG and the corresponding ePAG transversal WG. If there are elements of, for instance, eTraining, which might be relevant for ERNs to promote to their members and associated patient organisations already, these could be made available (perhaps a teleconference could be arranged between these two groups, to further define and take forwards these action points?)**
    - **AP: The WG on Research/another body should develop a cross-ERN training event tailored to researchers on how to involve patients in research activities**

Patient centred/derived/reported outcomes

All agreed there is significant potential to better involve patients in the definition and collection of **outcome measures** and **patient-reported outcomes**, in various ways:

- Outcome Measures (OMs) traditionally used to evaluate medicines and devices in the rare disease and specialised healthcare field are often not fit for purpose. ERNs are perfectly

poised to evaluate outcome measures/propose more suitable and sensitive OMs in future. Patients must be full partners in such activities, to capitalise on their unique role of 'experts by experience'.

- Patients/patient representatives should not be viewed merely as data *providers*, but instead should be involved from the beginning, supporting the selection and definition of OMs (not only health-related, but also wider quality of life-related OMs): this should increase the relevance of selected measures and minimise the level of discomfort/disruption patients' experience.
- ERNs could promote greater standardisation and harmonisation in the collection of OM data (whether the outcomes are reported by patients or by study personnel); for instance, Networks could agree to use specific assessment scores for recording and quantifying levels of pain, fatigue, cognitive functioning etc., yielding more comparable datasets. Patients/patient representatives should support the evaluation of scales and scores ('Measures') to be deployed for wider use.
- ERNs could enhance the opportunities for patients to report outcomes directly (PROs), through tools shared across the Networks (such as innovative apps or registries)
    - **AP: Dedicated projects/ pilots are necessary to explore more concretely how ERNs can develop and collect more appropriate health, clinical and QoL-related Outcome Measures (including PROMs), and under which circumstances. ERNs also have an unprecedented opportunity to capture traditionally-overlooked holistic outcomes relating to a patient's quality of life *beyond* the purely medical sphere, e.g. concerning education, habitation, employment, relationships, etc. Opportunities to launch such work should be sought.**

Additional comments included the following:

- Where clinical research relates to children and young people, the materials (e.g. on ethics, on training etc) developed by/promoted through the new conect4children initiative could be beneficial for researchers.
- ERNs should help to ensure a larger pool of educated patients who know their disease very well, but can 'represent' a much broader patient community through their role as an ePAG representative. The ePAG representatives have a unique potential to fulfil a vital role here, in the sense that they are not acting in their personal capacity as representatives of a particular patient organisation or community: instead they are there to support the engagement of, in theory all conditions under the thematic heading of that ERN. This should be a major asset to the clinicians and academics, although quite how the ePAG representatives can be supported to fulfil these roles remains to be seen.
- ERNs offer great potential to become 'testbeds' for mHealth applications, for instance apps to detect and monitor Adverse Events during the course of a trial.

Discussion Topic 4 - How can ERNs generate/link/exchange data to support the planning and execution of clinical trials and studies?

Key questions for the discussion were as follows:

- **What sorts of data can support clinical research? For each type:**
  - **What do we need and where can we obtain it?**
  - **How do we collect *good quality* data?**

Key discussion points included the following:

- Data is absolutely central to clinical research, in many different ways. There are *many* efforts underway (in the RD field and beyond) to optimise the utility and reusability of data from myriad different sources, to facilitate clinical research in the rare and specialised diseases field, including the following (this list is by no means exhaustive):
  - promotion of preferred ontologies for rare and specialised diseases, to capture diagnoses and phenotypic descriptions;
  - promotion of the concept of a PPRL (Privacy Preserving Record Linkage) and agreement on a preferred solution to 'roll-out' in the RD field, in order to link data from a single patient across myriad resources;
  - development of richer and better annotated metadata; the growing prominence of FAIR data principles and the emergence of a dedicated 'GO-FAIR Implementation Network for Rare Diseases'; (for a summary of these first 3 points, see here)
  - adoption of a European Minimum DataSet (MDS) for RD by the JRC;
  - functionality of the CPMS to search for pseudonymised data on complex cases;
  - exploration of options to extract data contained in EHRs for research;
  - agreement of document architecture standards for paediatric clinical trials in Europe via c4c, etc.
  - However – it is difficult to determine how ERNs (indeed any user) should make use of these resources/initiatives to enhance their research-related activities.
- Registries are an obvious and very important source of clinical research-supporting data: but registries can 'support research' in many ways; for examples, they can provide robust natural history data to stimulate *interest* in therapy development and facilitate the selection of clinically-relevant outcomes and endpoints; they can enable feasibility studies, to assess the chances of a trial being set-up in any given geographical area and enrolling the necessary numbers of patients with particular inclusion criteria; they can support the recruitment of patients further down the line, if a trial or study goes forwards (providing there is an ethical

way to cascade that information to patients without direct Industry contact); they can collect PMS data on therapies/therapeutic approaches; and more.

  - Consequently, ERNs are overwhelmingly still unclear as to the sort of registries they should be aiming to create/expand disease-wise.

  - Even where there *is* a clear goal (e.g. to create a basic registry of every patient in Europe with a condition falling under that ERN's Thematic Grouping/under a sub-domain of that heading, to support assessments of prevalence), Networks do not know *how* to proceed: they are approached by companies frequently, which offer to set-up registries for them. However, they are reticent to commit to expensive solutions if a more affordable -or even free- platform will be provided (alternatively, if a free platform is provided, but this would in fact be limited to a very simple registry which does not address, for instance, the sorts of purposes outlined above, Networks may still wish to purchase their own more multi-functional platforms)

  - Some participants shared their own plans for developing/evolving registries in their field; e.g., Neuromuscular field is developing a PMS platform, for all Neuromuscular diseases, given the emergence of promising therapy pipelines for a number of conditions; others (e.g. VASC-ERN) attested the value in registries which collect both clinician-entered and patient-entered data.

- The participants noted that, to optimise use of legacy data, working with FAIR data stewards seemed a logical approach; however, there is no funding to do this 'FAIRification' work.

- In emphasising the burden of data entry for busy clinicians populating registries, the workshop participants proposed a need for a Pilot(s) study to explore the latest options for extraction of data from EHRs (the Task Force on Interoperable Data-Sharing between the Rare Disease and eHealth communities, which emerged from RD-ACTION, would perhaps be a logical partner to these discussions)

- Renewed engagement is necessary, between the EMA Patient Registries Initiative and the JRC. RD-ACTION organised preliminary discussions between these two groups in 2017, but since that time the JRC plans have taken shape and moved forwards dramatically, and it will be important to identify points of mutual relevance/overlap and ascertain what 'messages' each is proposing, for which groups of stakeholders. (It was noted that, if the potential of registries to support regulatory decision-making e.g. PMS, is addressed, Industry's involvement should also be considered).

- Given the issues highlighted above, it is necessary to organise at least one standalone meeting on this topic of data and registries **(see also the Table of Needs/Opportunities above).**

- **AP: One of our groups (perhaps the Workshop Organising Committee for this workshop?) should, involving all relevant stakeholders, organise a TC on the 'Registries' topic, based upon the points captured in this document, to form a possible plan for a workshop/meeting. The organising party must also be identified (e.g. JRC should be asked to consider whether this would be within their capacity to fund and organise)**

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