Draft Recommended Practices/Proposals for ERN stakeholders in activities pertaining to Clinical Practice Guidelines

Output of RD-ACTION and DG Sante workshop

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Document History

This document originated as an output of the Workshop co-organised by RD-ACTION and DG SANTE, hosted by the ISS, which took place in Rome on 6th -7th December 2017. A draft was generated by the Workshop Organising Committee in May 2018. This is the current document. Please note that this has not yet been finally published by the authors

Contents

Responsibilities of European Reference Networks: the legal and policy picture

European Reference Networks (ERNs) are networks connecting providers of highly specialised healthcare, united for the purposes of improving access to diagnosis, treatment and high-quality care for patients with conditions requiring a particular concentration of resources or expertise. Composed of healthcare providers (HCPs) able to demonstrate the highest levels of care and research excellence, there are currently 24 approved ERNs, each dedicated to a broad rare disease area/highly specialised intervention. Almost 1000 units across 370 hospitals in 26 European countries[1] are involved as direct (full) members, with access from 2018 onwards for 'affiliated' partners (to enable the participation of countries without a full member in any given network).

[1] For details of membership per ERN and per country, see https://ec.europa.eu/health/ern/policy_en

(Text to include the relevant text from the Del and Implementing Acts, and the fact that ERNs had to declare they have a formal process for developing and selecting and disseminating CPGs but this is something they could opt to 'develop' if not in place at time of the assessment. So room to develop this/change what one proposed in the application)

SECTION 1: Terminology and Methodology for Generating Guidance

Key Points from Discussion:

There has long been confusion around the terms used to describe 'Guidelines.' Terms such as Clinical Practice Guidelines, Standards of Care, Best Practice Guidelines, etc. are used interchangeably, which is not helpful.

One **Recommendation** will be that ERNs should adopt and utilise the shared Terminology document originating from the December 2017 workshop, as a baseline to ensure harmonisation of terminology pertaining to 'Guidelines' activities. This document provides consensus definitions for terms such as Clinical Practice Guideline.

However, the next step is to agree whether ERNs should focus on generating/endorsing a particular *type* of output -in terms of guidance on how best to diagnose, treat, and care for patients afflicted with rare diseases/complex conditions requiring a concentration of expertise- and if so, what this type/these types should actually be called.

There are two broad options here:

Firstly, Guidance emanating from robust evidence base and a strategic review. Where possible, the optimal methodology for generating such Guidance is the GRADE approach.

Secondly, there was very strong support for the validity and usefulness of guidance produced by consensus building i.e. not generated by a traditional, systematic review of a solid evidence base enabled via RCT. Where the evidence does not permit the traditional approach -as will be the case in the majority of rare diseases- the workshop participants proposed that sometimes, the *quality* of the evidence –or at least the convictions of the experts based upon the available evidence- is more important than the quantity of evidence. For rare conditions, one will always struggle to build a vast evidence base, but this should not be an excuse not to create the best consensus guidance one can. A carefully planned and well-executed consensus-building process (involving for instance a Delphi process) has yielded invaluable sets of Guidance in some disease communities, and there are ways to ensure the optimum quality of the Guidance issued (see **Recommendations** below).

What to call the outputs of an ERN (and what should these encompass)?

The terminology for the type of outputs the Networks should create/co-create could be agreed using a 'one-size-fits-all' approach OR by categorising two or three types of output. These two main options are explained below:

1. Option 1: Avoid use of the term 'Guidelines' entirely, in relation to outputs emanating from ERNs, but class all types of guidance together under one (more neutral) term, such Consensus Practice Recommendations. These could then encompass *any* type of Guidance, regardless of the levels of evidence upon which it is based. A single template would be completed, populated with as much evidence as possible.
    a. Pros: given the country-specific legislation associated with the term Guidelines, terming them something else even when evidence is sufficient for GRADE could help to avoid legal complexities and the need to adhere to a multitude of (perhaps contradictory) laws.
    b. Cons: a particular effort would be needed with the country authorities, to ensure that despite not bearing the name 'Guidelines', and not adhering to the methodologies necessary for a CPG in certain countries, the Guidance would nonetheless be usable at the national level. It may be the case that international standing of the Guidance is diluted somewhat, if not in fact referred to as a CPG despite having a fairly sound evidence basis and having been produced in a methodologically rigorous fashion.

2. Option 2: Envisage a 2 or 3-tier approach for Guidance emanating from ERNs, ranging from a 'Clinical Practice Guideline' to a 'Consensus Recommendation', to a 'Consensus Statement'. Each of these three categories (or two, perhaps, if less granularity is necessary) would be termed according to what it is, **and each document would be constructed using a specific template.**

Further clarifications would be necessary, if this Option is pursued. For instance;

- Assuming the ERN community retains the term 'Clinical Practice Guidelines' where the evidence base IS sufficient to construct Guidance according to the GRADE approach: do we then sub-divide these into different types of CPG, i.e. those addressing very specific interventions/issues (such as use of a certain type of chemotherapy for a specific tumour type) and, on the other hand, those dealing with the whole course of disease and encompassing diagnostics, treatment and care? And if so, should these be called different things, or can this single term -CPG- be all-encompassing?
- Alongside the top-tier 'CPGs' there would be the 'everything else' i.e. the Guidance which is *not* based upon GRADE approach, due to lack of evidence, but is nonetheless very much in the scope of the ERN to produce. This Guidance could be classified as 'Consensus Recommendations' and possibly also Consensus Statements (if we go for 3 levels). It would be necessary to agree exactly what each of these entails, what *makes* Consensus Recommendations 'Consensus Recommendations' as opposed to a Consensus Statement (i.e. there would need to be a certain level of evidence to distinguish between the two, such as a set number of

diagnostic/therapeutic options for a consensus-building approach to choose between, perhaps, for something to be considered a Consensus Recommendation)

With both options, however, the question of Scope arises:

Scope of ERN Guidance: specific intervention or whole-disease-management?

For very rare conditions, there was a proposal -quite well-supported- that ERNs should really be aiming at very comprehensive guidelines, which cover diagnosis, management of all key symptoms, and also include where possible/appropriate paramedical advice (relating to diet and nutrition, speech therapy, psychosocial impact, etc.). **One fundamental question therefore is, for ERNs, is this broad approach preferable to generating very specific, technical advice (for instance on a controversial intervention or on the merits of one specific approach over another)?**

Structuring Guidance

Regardless of the decisions taken on the terminology, above, and the scope of ERN guidance, as above, there was strong support for a more organised construction and branding of Guidance relating to management of rare diseases/conditions requiring a concentration of expertise:

Recommendation: For many conditions, the idea of building almost a modular approach to Guidelines, by completing section after section as required, was proposed as a good way forward.

Appraising Clinical Practice Guidelines

Additional key points from the workshop:

The workshop pointed out that, although ERNs wll need to generate/co-create new Guidance (for diseases lacking guidance at present, or for diseases where it is wise to harmonise contradictory sets of guidance) It was agreed that a major issue with CPGs/other forms of Guidance or Recommendations is that, once generated, they will eventually become outdated and need to be reassessed/updated. Participants wondered if it was at all possible to set a 'recommended' period of time after which a CPG/other form of guidance should be reviewed (e.g. every 5 years), or whether this would be too artificial/too-disease-specific. (*(I think we need to pull together a few points and good practices here, to give some structure to this process e.g. how people do their literature reviews, how they Appraise the quality of the Guideline-generation progress (AGREE), how they score the Guidelines they review (good tangible proposal in ERKNET presentation)*

Participants proposed that an analysis -with report- of the potential to use registries to generate CPGs would be beneficial and highly encouraged (in collaboration with relevant stakeholders such as JRC)

RECOMMENDATIONS FOR ERNs AND THEIR CONSTITUENT CENTRES, RELATING TO METHODOLOGY AND TERMINOLOGY

1. The AGREE instrument is recommended as the most appropriate means of appraising the methodological quality of Clinical Practice Guidelines
2. Where evidence is adequate, Clinical Practice Guidelines should be generated in accordance with the GRADE II approach
3. ERNs should consider supporting the training of key personnel in the use of relevant methodologies for CPG creation and appraisal, including GRADE and AGREE
4. Where the evidence base is *inadequate* to use GRADE criteria as a guide for Clinical Practice Guidelines, a Consensus-building approach to generate some sort of guidance – termed in the ERN sphere 'Consensus Recommendations' should be employed.
5. Consensus Recommendations should be generated based upon the following:
    a. Use of a Delphi or similar methodology to assess the statements on which there is greatest consensus
    b. Participants involved in generating/ assessing/ ranking a range of possible practices or approaches must disclosure any Conflict of Interest
    c. The process of generating/assessing/ranking a range of possible practices or approaches should clearly illustrate the most popular options but also highlight the most contentious (that is to say, those which despite emerging as popular recommendations for some contributors, also received significant negative comments/ratings from other, thus identifying areas of particular controversy or dissent in the final document.
6. Further work is necessary to explore and define the specific steps to be taken, in generating these Consensus Recommendations or other forms of Guidance which do not meet the criteria for full CPGs
    - For example, will 'Consensus Recommendations' be a sufficient catch-all term for this 'level 2' Guidance (i.e. Guidance falling short of full CPG level) or will we need to think of something less 'robust' still, perhaps a 3rd level such as 'consensus statement'
        - If so, the differences between these categories, practically and methodologically, need to be made crystal clear for the ERN community.
        - It is necessary to agree the best method of gathering the consensus for these latter two 'types' of Guidance; e.g., do we advocate Delphi alone for 'Consensus Recommendations', or others too, such as AAN (which is really for published data?) For the lowest category, the Consensus Statement as we may call it, a less stringent 'expert review' is often performed, which is fine, but we also need to agree some definition as to how one performs such an expert review, what the basic 'rules' are etc.
7. ERNs should develop /update/appraise CPGs in conjunction with other Networks, to avoid duplication of effort but also to contribute cross-ERN expertise in complex multisystem disorders

8. ERNs should create a shareable and updatable roadmap of diseases/disease areas for which they plan to develop CPGs, to support this sort of collaboration.

- It was proposed that ERNs should seek to generate/endorse CPGs which address the transition phase from childhood care to adulthood – this should be facilitate by the age-inclusive approach adopted by almost all ERNs (i.e. by the decision not to create separate Networks for adults and children)
- Several participants requested a 'template', which ERNs could use to complete CPGs in future.
- It may even be possible/preferable to provide all ERNs with a single online platform to generate these Guidance documents (the example being developed by the MetabERN was briefly presented) – further exploration of the benefits/complexities of having a single template (and whether this should be provided in an e-format) is necessary. More centrally still – the feasibility of producing a Eu-Level platform for these Guidelines, such as the JRC uses now for the breast cancer screening, should be explored in more detail
- To avoid overly-long documents, whilst still covering the detail required to best serve the needs of patients, chapter-end summaries/checklists could be ensured.
- The ERNs will need to agree a means of prioritising which diseases/disease areas they should target, in which order – it is important to develop a few criteria or at least a transparent voting process for selecting these disease/disease areas (and of course, this process must have no input from Industry actors)

SECTION 2: Exploitation of Existing disease-agnostic Resources geared towards the rare disease field

(*Summarise status quo of existing tools and resources and repositories for CPGs, as presented in Rome*)

RECOMMENDATIONS FOR ERNs AND THEIR CONSTITUENT CENTRES

1. ERNs should review the 'Tool-kit' of transversal (i.e. disease agnostic) tools created through the fruits of European Commission funding, such as outputs of RARE-BestPractices and Orphanet.

2. When seeking *existing* Guidelines to appraise/endorse, ERNs should consider using the Search Strategy proposed under the RareBestPractices initiative (link)

SECTION 3: Engaging Patients in Guidelines-related activities

Points of relevance from workshop discussions:

- The group seemed to accept unanimously that patients/patient organisations should be engaged as fully and meaningfully as possible in all aspects of Guideline Generation, Appraisal, Dissemination, and Use.

- Various possible 'levels' of engagement were discussed: these ranged from:
    i. no involvement in the CPG generation but being asked to create a patient-friendly version after publication;
    ii. to asking patients to review and make minor comments/changes at the end of the generation process i.e. when the Guidance is nearing finalisation;
    iii. to surveying or interviewing patients on some aspects of the content of the Guidelines, before taking this insight back to assist in developing the scope and content;
    iv. to the most meaningful levels of engagement, where patients actively propose symptoms/stages of disease to be addressed in the Guidance and are included as 'voting' members of the CPG-generation team

- There were several examples of patient groups being asked to review CPGs only at the late stage, i.e. to ask people to identify any gaps just before publication, by which point little could be changed (or there was little willingness to add overlooked sections/topics).

- Therefore the group agreed that a clear *good* practice, very much valued by patients but also acknowledged by clinicians, was to engage patients from the beginning, and seek their input in activities such as the following:
    i. *defining* the various components of the Guideline i.e. defining the scope, in terms of the sorts of management and prevention 'topics' or headings to be addressed (e.g. diagnostics; management of particular sets of symptoms, such as cardiac symptoms, renal symptoms; speech and swallowing; ventilation, etc)
    ii. then proposing the different activities that might be described under each heading (e.g. *options* for diagnostics; *options* for management of cardiac symptoms, etc.)
    iii. and providing patient and family perspectives on which of the proposed components/approaches would be most effective (in the case of a Delphi-type approach, for instance, providing some prioritisation on the options available)

- The rare and highly specialised community has numerous examples of well-established, meaningful and systematic engagement of patients at many levels. Examples of such 'mature' patient communities discussed in Rome were Duchenne Muscular Dystrophy, Haemophilia, Ichthyosis, certain rare lung conditions (through the European Lung Foundation).
    i. The group was strongly in favour of isolating particular examples and case studies, working through these to distil specific good practices which might be replicated in other fields
    ii. Opportunities should be found for patients from the more 'mature' areas mentioned above (and others) to impart their knowledge and experiences to others, perhaps through the ePAG network.

- Patient-involvement at each stage of CPG generation/appraisal should be mapped out in a 'good practice' document for clinicians perhaps, to elucidate the sorts of approaches patients would find helpful (in terms of how to engage people in the process, the sorts of timeline patients/carers might need to provide input, perhaps financial arrangements to reimburse people for travel and time etc.)

- The extent to which patients can practically be involved depends somewhat on the existence of appropriate patient organisations or advocacy groups. This has hampered efforts to involve patients in the past:

i. It is hoped that here, too, as in many other areas, the 'mapping' activities of ERNs will make it easier to find individual patients/patient organisations in future.
ii. The fact remains that for some very rare conditions there will be no 'formal' organisations. In such cases, a greater understanding of which Centres see patients with which conditions (which will also hopefully be enabled in time, through the ERN structures) will make it easier for clinicians to approach patients and families who may wish to be involved in CPG activities. Furthermore, resources such as RareConnect and secure social media platforms could hold potential to actually find patients to participate in such activities.

- It is important to provide adequate training opportunities and resources to support patients in participating actively to the CPG generation/appraisal activities (examples in the workshop were the ESMO courses, and the European Patient Ambassador Programme operated by ELF) – the ERN framework should somehow facilitate this 'professionalization' of patient involvement in CPG activities. There was a general understanding that there is a need to go from sporadic examples of successful achievements in this area to a more professional and strategic involvement of patients and patient organisations ('from a cottage industry to a more industrialised scene!' was one quote)

- The workshop participants, when discussing how ERNs might partner in CPG generation and appraisal with Professional Societies, noted that these Societies perhaps do not involve patients as frequently and as fully as would be desirable; therefore, there may be a need to raise awareness of the value of this sort of involvement for rare and complex conditions amongst the Professional Societies too, in a 'parallel' effort. Examples were shared (for instance from the haematology community) of instances where patient organisations signed Memoranda of Understanding (MoU) with European Societies/Professional Societies, and co-published the resulting Guidance

SECTION 4: Engagement with Professional/Learned Societies

(Summary of key issues)

It is important not to overlap or compete in some way with the well-established CPG-related activities of the Professional Societies in Europe. New ways of collaboration should be found to build mutual trust and avoid duplication.

One good practice would be to build a formal relationship with the most relevant European Societies/Professional[2] Societies and to work very collaboratively with them in generating new Guidelines for rare and specialised diseases. There were proposals that the ERNs should clearly be defined as the go-go body for the rare subsets of the very broad fields, e.g. European Society of Cardiology takes care of Guideline generation for heart conditions generally, but GuardHeart would become 'the' place to advance rare heart Guidance.

[2] Enrique I need to check what term we agree for these Learned/professional/scientific societies !

Participants proposed establishing MoU with Eu Societies/Professional Societies along these lines.

It would also be good perhaps to think of arranging an 'understanding' whereby the Societies adopt all ERN-led Guidelines and vice versa

There is a challenge for some ERNs, in the sense that there is no obvious EU Association/Society…

The workshop participants, when discussing how ERNs might partner in CPG generation and appraisal with Professional Societies, noted that these Societies perhaps do not involve patients as frequently and as fully as would be desirable; therefore, there may be a need to raise awareness of the value of this sort of involvement for rare and complex conditions amongst the Professional Societies too, in a 'parallel' effort

UEMS Engagement – need to add a few points and recommendations about this engagement

E.g. UEMS is an excellent forum to disseminate the CPGs/other forms of Guidance produced or endorsed by the ERNs. They can circulate outputs in the form of white papers to all national UEMS members, they can review the Guidance and following approval (possible amendment) pass to Governments in each country.

It was proposed that by partnering more closely and formally with the Professional Societies, the Guidance emerging from /endorsed by ERNs will hold more 'weight' in terms of implementation at national level – The Societies can support the political 'clout' of these documents.

There were also several suggestions that Societies could form a bridge between Industry and ERNs – Companies could continue to allocated funding to Professional Societies, for them to use as they wish (i.e., without any stipulation as to the disease it is used to support). The Professional Societies could then make this funding available to ERNs, to organising their meeting and consensus building activities to generate new Guidelines in rare conditions. The feasibility of this would need to be explored, with the BoMS also, to ensure it would adequately circumvent the 'no Industry' involvement

SECTION 5: Translating and Disseminating Guidelines

The workshop participants agreed that it was important to generate CPGs in languages other than English, to really improve adherence to such Guidance; however, this can be expensive. The potential of more superior auto-translation tools should perhaps be explored here.

ERN websites should be logical locations to display CPGs/other Guidance a) generated by the ERN (either alone or in partnership with external actors and experts) or b) otherwise endorsed by the ERN (for instance, concerning pre-ERN-era Guidelines which are deemed to be still of relevance).

<u>If ERNs agree</u>:

i. CPGs/other Guidance generated by the Network or otherwise endorsed by the Network could- once appraised according to AGREE instrument- be added to the RAREGuideline Database (sustainability of the database would need to be ensured, of course).

ii. Similarly, CPGs/other Guidance generated by the Network or otherwise endorsed by the Network should be deposited in the Orphanet repository of Guidelines

These activities could afford optimum reach and dissemination to CPGs for rare and complex diseases.

Some of the roles which patients, in particular, can play in disseminating CPGs, were highlighted:

Several good practices emerged, regarding the practice of ensuring a lay-person-friendly version of any CPGs/other related Guidance. Some suggested that the only versions of CPGs created henceforth should be accessible to all; however, others countered that to actually deliver the appropriate standard of care, a high-level, detailed, specialist Guideline would usually be necessary, which could then be 're-created' in a more patient-friendly manner.

- patients have often resorted to taking physical copies of Guidance with them to appointments with GPs and less-specialist health and social professionals, as they sometimes have more insight to the resources available in rare and specialised fields than these 'generalist' physicians.

- Patient organisations have sometimes led on the development of translations of lay-person-friendly CPGs/related Guidance

- Patient organisations may have a role to play in advocating for use of particular Guidance when new services are established nationally for their disease/group of diseases

Patients/patient organisations might complete surveys, to assess the extent to which existing CPGs are used in their local/regional/national territory (as in the CARE-NMD initiative for instance)

However, further routes to dissemination of CPGs should be explored, to generate comprehensive guidance on where to 'upload' or advertise these resources, and how to disseminate to centres/hospitals/other actors who need them

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RECOMMENDATIONS FOR TRANSLATING AND DISSEMINATING GUIDELINES

- The workshop participants agreed that one good practice which often ought to be pursued is the generation of 'patient-friendly' or perhaps rather 'lay-person-friendly' guidance, to accompany the more technical and scientifically-oriented publications. Examples included the DMD Family Guide version of the Family Guide created to accompany the Guidelines, and XX.
    - Such Layperson-friendly versions should not necessarily be solely aimed at patients; indeed, they can be very useful for non-specialist professionals in the health (and sometimes even social) field, such as GPs and nurse practitioners.

- These Layperson versions of the Guidance should include a simple checklist of key actions/key points, for rapid understanding at more general practitioner appointments

- The tendency to generate CPGs and other relevant Guidance only in English is obviously a hindrance to the wider dissemination and consequently use of the documents. Options to produce reliable translations of all CPGs and other relevant Guidance emerging from/through ERNs should be explored.
- ERNs should include links on their respective websites to all CPGs generated by or otherwise endorsed by the Network, where there is an applicability to a disease/group of diseases under the scope of the ERN
- (If agreed, and if the sustainability of the resources is assured) – ERNs should deposit appraised Guidelines in to the RareGuideline database and upload any Guidance generated by or otherwise endorsed by the ERN to the Orphanet database, for maximum visibility and dissemination potential.

SECTION 6: Addressing Legal and National Barriers To Implementation Of European-Level Clinical Practice Guidelines

Key Points from discussion:

Traditionally, there has been a major issue with the implementation of CPGs generated by European networks/projects/initiatives at the national level (or indeed with the implementation of CPGs generated by country X in any other national territory.)

France and Italy, in particular have defined mandatory methodological approaches to the generation of CPGs , which need to have been followed for a Guideline to be used in the national territory. The feelings of participants were that these approaches are too rigorous and 'heavy-handed', and a simplified way of creating Guidelines should be found. More work is needed here, to asses for instance:

1. the actual contents of the relevant legislation in France and Italy (and Germany, which also attaches a specific meaning to 'Guideline', relating to liability for physicians etc). We need to map these against each other and see what baseline compatibility there is in the PNDS approach compared to what Italy and Germany mandate. BoMS could support this, perhaps.
2. It may be worth exploring whether, if we avoid the term Guideline altogether, and use Clinical Practice Recommendations for instance, for the top level of ERN-generated/ERN endorsed Guidance, we would avoid having to abide by these very strict laws and regulations (this would ideally be facilitated by emphasising to the relevant bodies/authorities in each country the added-value of the ERN approach, and proposing that ERNs should be seen as somehow special and exempt). We would need to explore whether we can 'get around' some of these issues simply by avoiding the term CPGs…

The workshop acknowledged that ERNs, as pan-European structures, will expose the tension between what is in the best interests of patients (as agreed by pan-European consensus, and embedded in a CPG

or Consensus Statement) and what actually is delivered at national level. For instance, if Guidance produced by the ERN recommends use of particular therapies or medicines and these are not available in a certain country, the inequalities of patience access will become increasingly clear.

There was some discussion on the potential of registries to illustrate the benefits of using particular clinical and therapeutic approaches, which will be important in terms of persuading countries to make available therapies/medicine they do not currently provide, perhaps.

RECOMMENDATIONS FOR ERNs AND THEIR CONSTITUENT CENTRES

1**.** The Board of MS (other?) should ascertain whether any other EU MS apply specific criteria/mandate a particular methodological approach to the generation/appraisal, use of CPGs.

2. The specificities of the Italian and French legal approaches to the generation/appraisal/use of CPGs in national territory should be analysed in detail, to ascertain the degree of commonality between the two (i.e. to clarify the baseline methodological approaches which would be acceptable to both)