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1) The deliverable has been sent to all relevant partners for review (i. e. in the same task/WP):	Y
2) The deliverable has been endorsed by the WP lead and co-lead:	Y
3) Input from other WPs has been sought, if applicable: ***Please specify:***	N

[1] **Type**: Use one of the following codes (in consistence with the Description of the Action):
R: Document, report (excluding the periodic and final reports)
DATA: data sets, microdata, etc.
DEC: Websites, patent filings, videos, etc.
DEM: Demonstrator, pilot, prototype
OTHER

[2] **Dissemination level**: Use one of the following codes (in consistence with the Description of the Action)
PU: Public, fully open, e. g. web
SEN: Sensitive, limited under conditions of the Grant Agreement

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Executive Summary

This deliverable publishes the set of domain-specific common data elements (DCDEs) tailored to neurodevelopmental RASopathies - SYNGAP1-related Developmental and Epileptic Encephalopathy (SYNGAP1), Cardiofaciocutaneous syndrome (CFC), Costello syndrome (CS) and Noonan syndrome (NS) - and outlines the methodology for creating it.

Weekly interdisciplinary meetings over the course of one year, involving neuropaediatricians, geneticists and patient representatives from Paracelsus Medical University Salzburg (PMU), Otto-von-Guericke-University Magdeburg (OVGU), SYNGAP Elternhilfe e. V. (PA) and Noonan-Kinder e. V. Deutschland, shaped the collaborative exchange. Approximately 40 key Human Phenotype Ontology (HPO) items were compiled, based on clinical and patient-centred insights.

At the same time, a collection of genes relevant to the identified RASopathies provided a comprehensive molecular base. Bioinformatic analysis, enhanced by advanced computational tools, revealed intricate relationships and patterns within the dataset.

The methodology included a multi-stage Delphi process involving experts and patient representatives. This structured approach ensured the consensus-driven selection of the most relevant data elements. The final vote, the culmination of this collaborative effort, validated the scientific rigour and underscored the inclusive nature of the decision-making process.

This result not only establishes comprehensive DCDEs for neurodevelopmental RASopathies, but also serves as a paradigmatic model for rare disease research. Our commitment to transparency and scientific dissemination is shown by the forthcoming publication currently under preparation, to be published in an open access journal, contributing to transformative change in the study of complex rare diseases.

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1 Introduction

Neurodevelopmental RASopathies, including conditions such as SYNGAP1, CFC, CS and NS represent a tapestry of genetically driven disorders with overlapping clinical features but diverse manifestations. Rooted in mutations within the RAS-MAPK pathway, these syndromes present unique challenges in understanding their heterogeneous nature and require an innovative approach to data collection. A compelling solution lies in the establishment of a domain-specific set of Common Data Elements (DCDEs) that not only navigate the complexity of each syndrome, but also serve as a dynamic tool for identifying and analysing cohorts of similar patients.

1. Clinical heterogeneity and phenotypic diversity:
Neurodevelopmental RASopathies exhibit significant clinical heterogeneity, even within a single syndrome. For example, SYNGAP1 mutations manifest as a spectrum of neurodevelopmental disorders including intellectual disability, epilepsy and autism spectrum disorders. CFC, CS and NS each bring their own unique clinical features, resulting in a mosaic of symptoms. DCDEs will be essential in capturing the multifaceted clinical nuances, allowing the identification of groups of patients with similar phenotypic profiles across these diverse syndromes.

2. Personalised therapeutic approaches:
The advantage of DCDEs lies not only in their ability to standardise data collection, but also in their role as a catalyst for personalised therapeutic interventions. As our understanding of the genetic and clinical landscape of neurodevelopmental RASopathies deepens, the need for tailored treatments becomes more apparent. DCDEs designed specifically for each syndrome provide a starting point for identifying patient cohorts with shared characteristics, thereby facilitating the development of interventions tailored to the needs of these cohorts.

3. Facilitate cross-syndrome comparisons:
The creation of DCDEs serves not only to explore the unique aspects of each syndrome, but also to enable meaningful cross-syndrome comparisons. By harmonising data elements across SYNGAP1, CFC, CS and NS, researchers will be able to identify similarities and differences. More importantly, DCDEs enable the discovery of groups of patients that transcend syndrome-specific boundaries, providing a holistic view of shared genetic pathways and phenotypic traits.

4. Cohort identification through comprehensive phenotyping:
One of the key roles of DCDEs is to help identify cohorts of patients with similar phenotypic profiles. The use of specialised data elements enables a comprehensive phenotyping approach, allowing the identification of distinct subgroups within each syndrome. The Cohort Analyzer, a tool that has been validated and published, serves as an exemplary model. By applying this tool to neurodevelopmental RASopathies, we can systematically identify and analyse cohorts of patients, revealing patterns and correlations that might otherwise remain obscured.

5. Integrating expert and patient perspectives:
The development of DCDEs for neurodevelopmental RASopathies requires the collaboration of medical professionals, researchers and individuals directly affected by these syndromes. The integration of expert and patient perspectives not only ensures the creation of data elements that reflect clinical reality,

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but also helps identify cohorts based on real-world experiences and priorities. This holistic approach enhances the relevance and applicability of the DCDEs in identifying patient cohorts that go beyond clinical presentations to include the lived experiences of individuals and their families.

In summary, the establishment of DCDEs for neurodevelopmental RASopathies not only addresses the challenges posed by clinical heterogeneity but is also proving to be a powerful tool for identifying cohorts of similar patients. By harnessing the potential of DCDEs, we are not only navigating the complexities of individual syndromes, but also illuminating the broader landscape of shared genetic pathways and phenotypic traits, paving the way for personalised and effective interventions tailored to specific patient cohorts. The integration of Cohort Analyzer[1] exemplifies how this approach can systematically advance our understanding of neurodevelopmental RASopathies and contribute to the advancement of precision medicine in this complex field.

Short description of the corresponding WP

The PATRAS registry (PATient-based registry for RASopathies), a collaboration between PMU, OVGU, Universidad de Malaga (UMA) and PA, aims to establish a comprehensive data registry for neurodevelopmental RASopathies, including SYNGAP1, CFC, CS and NS. The project plans to recruit at least 400 participants, emphasising a patient-centred, online-based approach to minimise travel and promote accessibility. PATRAS will use an online survey system to collect core patient data using a set of common data elements (DCDEs) for neurodevelopmental RASopathies. The data collection process will take place in five steps, covering different aspects of neurodevelopmental and neurological features. PATRAS integrates expert and patient perspectives to ensure a holistic approach to data collection. UMA's advanced bioinformatics will optimise the study by applying the Cohort Analyzer methodology for analysing phenotype depth and breadth, suggesting potential additional phenotypes, and using systems biology methods to investigate disease-related gene networks and mechanisms. The integration of PATRAS into a European Rare Disease Registry Infrastructure (ERDRI) platform enhances compatibility with existing databases and promotes interoperability with other registries and research projects. The project's phased data collection and early evaluation strategy will allow for continuous refinement and validation of results within the EURAS framework. PATRAS, which is expected to be run by the participating institutions, demonstrates a commitment to long-term data collection and research in the field of neurodevelopmental RAS disorders.

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2 Description of Activities

The systematic development of DCDEs for neurodevelopmental RASopathies, including SYNGAP1, CFC, CS and NS, is a collaborative and multi-dimensional process. This scientific methods text describes the comprehensive methodology used, which includes weekly meetings, gene collection, bioinformatic analysis and a structured multi-stage Delphi process. The goal is to provide a standardised framework for data collection that will facilitate meaningful research, improved clinical practice, and collaboration within the EURAS.

1. Weekly meetings and topic collection:
The initiative started with weekly meetings over a year involving neuro-paediatricians and geneticists specialised in SYNGAP1 (PMU) and CFC, CS and NS (OVGU). The EURAS-approved collaborative meetings were complemented by the active participation of patient representatives from PA and Noonan-Kinder e.V. Deutschland. These meetings served as a dynamic forum for knowledge exchange, fostering a collective understanding of the neurodevelopmental aspects of RAS disorders. Outcomes included the identification of topics of interest and key issues related to the disorders. Approximately 40 key Human Phenotype Ontology (HPO) items were carefully compiled based on the insights gained during these meetings.

2. Gene collection:
At the same time, a parallel effort focused on the collection of relevant genes associated with SYNGAP1, CFC, CS and NS. This critical step aimed to define the molecular landscape of these disorders and to lay the basis for the subsequent bioinformatic analyses.

3. Bioinformatic analysis:
The compiled HPO elements and relevant genetic data underwent rigorous bioinformatic analysis to extract meaningful insights. Using advanced computational tools, this multi-step process aimed to identify relationships, redundancies and novel patterns within the data. The iterative nature of the bioinformatic analysis allowed for the dynamic exploration of the dataset, uncovering hidden relationships and refining our understanding of the neurodevelopmental characteristics of RASopathies. (Figure 1)

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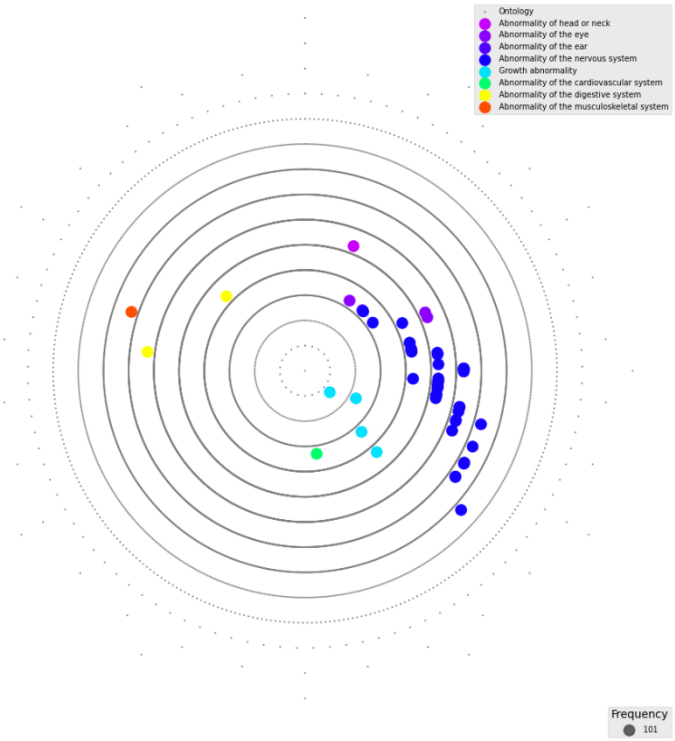

Figure 1: HPOs frequency distribution. Colour based on the HPO frequency.

4. Multi-stage Delphi process:

The enriched dataset resulting from the bioinformatic analysis served as the basis for a multi-stage Delphi process. This structured method involved iterative rounds of feedback and consensus building among a panel of experts. This panel was diverse, including neuro-paediatricians, geneticists and patient representatives. This ensured a holistic perspective, encompassing clinical expertise and the lived experience of people affected by neurodevelopmental RAS disorders. The aim of the Delphi process was to systematically select the most relevant items that capture the essential aspects of these disorders. The iterative nature of the Delphi method allowed for nuanced discussions, accommodating diverse viewpoints and converging towards the consensus-driven selection of items.

5. Final voting:

Following the multi-stage Delphi process, a conclusive final vote was held to ratify the selected items. This critical step served as the culmination of the collaborative effort and ensured that the selected DCDEs reflected a consensus among the various stakeholders involved in the process. The final vote not only validated the scientific rigour of the process, but also underlined the democratic and inclusive nature of the decision-making process.

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Publication of the methodology:
A commitment to transparency and scientific dissemination is integral to the scientific ethos of this endeavour. The precise methodology used throughout this complex process will be thoroughly documented and published in an open access journal. This commitment to dissemination will ensure that the scientific community, clinicians, researchers and patient advocates will be able to access, scrutinise and build upon the methods used to create the DCDEs for neurodevelopmental RASopathies.

In summary, the development of DCDEs for neurodevelopmental RASopathies embodies a meticulous, collaborative and multidimensional approach. It integrates physician expertise, research of genetic underpinnings of disease, bioinformatics analysis and an inclusive Delphi process. The resulting set of common data elements serves as a robust and standardised resource to advance research, clinical practice and collaboration within the EURAS. This methodology not only contributes to the scientific understanding of these complex disorders, but also exemplifies a model for interdisciplinary collaboration and patient engagement in rare disease research.

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3 Results

The set of Domain-Specific Common Data Elements (DCDEs) for neurodevelopmental RASopathies:

Seizures
Seizure (HP:0001250)
Generalized-onset seizure (HP:0002197)
Generalized atonic seizure (HP:0032887)
Generalized myoclonic seizure (HP:0002123)
Generalized myoclonic-atonic seizure (HP:0011170)
Generalized non-motor (absence) seizure (HP:0002121)
Generalized-onset motor seizure (HP:0032677)
Bilateral tonic-clonic seizure with generalized onset (HP:0025190)
Myoclonic absence seizure (HP:0011150)
Absence seizure with eyelid myoclonia (HP:0011149)
Atypical absence seizure (HP:0007270)
Typical absence seizure (HP:0011147)
Development
Neurodevelopmental delay (HP:0012758)
Motor delay (HP:0001270)
Delayed ability to sit (HP:0025336)
Delayed ability to walk (HP:0031936)
Inability to walk (HP:0002540)
Delayed speech and language development (HP:0000750)
Poor speech (HP:0002465)
Absent speech (HP:0001344)
Global developmental delay (HP:0001263)
Severe global developmental delay (HP:0011344)
Developmental regression (HP:0002376)
Neurodevelopmental abnormality (HP:0012759)
Dyscalculia (HP:0002442)
Dyslexia (HP:0010522)
Mental function
Intellectual disability (HP:0001249)
Intellectual disability, borderline (HP:0006889)
Intellectual disability, mild (HP:0001256)
Intellectual disability, moderate (HP:0002342)
Intellectual disability, severe (HP:0010864)
Behavior
Atypical behavior (HP:0000708)

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Self-injurious behavior (HP:0100716)
Aggressive behavior (HP:0000718)
Reduced impulse control (HP:5200045)
Abnormal temper tantrums (HP:0025160)
Sensory behavioral abnormality (HP:5200046)
Short attention span (HP:0000736)
Attention deficit hyperactivity disorder (HP:0007018)
Hyperactivity (HP:0000752)
Reduced attention regulation (HP:5200044)
Sleep disturbance (HP:0002360)
Autistic behavior (HP:0000729)
Restricted or repetitive behaviors or interests (HP:0031432)
Abnormal communication (HP:0034434)
Abnormal peer relationships (HP:5200016)
Abnormal repetitive mannerisms (HP:0000733)
Recurrent hand flapping (HP:0100023)
Drooling (HP:0002307)
Pain insensitivity (HP:0007021)
Nutrition and growth
Failure to thrive (HP:0001508)
Growth abnormality (HP:0001507)
Feeding difficulties (HP:0011968)
Nasogastric tube feeding (HP:0040288)
Growth delay (HP:0001510)
Short stature (HP:0004322)
Malformations and physical abnormalities
Abnormality of brain morphology (HP:0012443)
Hearing abnormality (HP:0000364)
Abnormal heart morphology (HP:3000001)
Abnormality of vision (HP:0000504)
Nystagmus (HP:0000639)
Strabismus (HP:0000486)
Scoliosis (HP:0002650)
Abnormality of pain sensation (HP:0010832)
Gait disturbance (HP:0001288)

The elements are complemented by the Set of common data elements for Rare Diseases Registration released by the EU RD Platform[2].

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The set of DCDEs for neurodevelopmental RASopathies obtained through the outlined methodology contributes significantly to the overall goals of the PATRAS work package. As explained earlier, PATRAS aims to establish a comprehensive data registry for neurodevelopmental RASopathies, including SYNGAP1, CFC, CS and NS. Here we show how the results of the DCDEs fit in with the overall objectives.

Standardisation of data collection:
Link to DCDEs: The DCDEs provide a standardised set of data elements specifically tailored to capture the nuances of neurodevelopmental RASopathies. This ensures consistency and uniformity of data collection across different patient cohorts.

Inclusion of patient perspectives:
Patient-centred insights: The DCDEs, developed through collaborative meetings with patient representatives, capture not only clinical perspectives, but also the lived experiences of individuals and families living with neurodevelopmental RASopathies. This inclusion of patient perspectives is in line with PATRAS' goal of incorporating real-world experience into the registry.

Integration with the European Rare Disease Registry Infrastructure (ERDRI):
ERDRI compatibility: The DCDEs are designed to be compatible with ERDRI, ensuring seamless integration with existing databases and platforms. This will enhance interoperability, facilitating data sharing and collaborative research efforts, in line with PATRAS' goal to be part of a broader European rare disease registry infrastructure.

Long-term data collection:
Structured data collection: The DCDEs facilitate long-term data collection by providing a structured and comprehensive set of data elements. This supports the PATRAS objective of continuous data collection at annual intervals, thus ensuring the sustainability of the registry beyond the initial project phase.

Bioinformatics support:
Bioinformatics integration: The DCDEs, enriched through bioinformatic analysis, are in line with PATRAS' goal of using advanced bioinformatics in data processing. This integration will allow for meaningful analyses, stratification of patient cohorts and identification of disease-related gene networks, contributing to a deeper understanding of neurodevelopmental RASopathies.

Patient stratification and cohort analysis:
Improved phenotypic stratification: The DCDEs, developed through a multi-stage Delphi process, will lead to improved patient stratification based on phenotypic profiles. This is in line with the objective of PATRAS to perform cohort analyses to unravel patterns and correlations within different patient groups and to gain insights into disease mechanisms and progression.

In summary, the set of DCDEs for neurodevelopmental RAS disorders serves as a fundamental tool within the PATRAS work package. It addresses the specific needs of the patient cohorts, ensures standardised and patient-centric data collection, integrates seamlessly with existing infrastructures, supports long-term data gathering and takes advantage of bioinformatic tools and research- all of which

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contribute to the overall goals of advancing research, diagnosis and personalised treatment strategies for neurodevelopmental RASopathies within the PATRAS initiative.

4 Conclusion

The culmination of this methodology to establish DCDEs for neurodevelopmental RASopathies represents a synthesis of interdisciplinary collaboration, scientific rigour and patient engagement. The multifaceted approach of this initiative underlines its importance not only as a data collection effort, but also as a paradigmatic model for rare disease research.

The careful integration of weekly meetings, drawing on the expertise of neuropediatricians and geneticists from PMU and OVGU, has fostered the dynamic exchange of knowledge. The active participation of patient representatives from PA and Noonan-Kinder e.V. Deutschland brought a human-centred perspective to the discussions, enriching the understanding of the neurodevelopmental complexity of RASopathies. The result was not just a compilation of data elements, but a nuanced representation of the lived experiences of individuals coping with these complex disorders.

At the same time, the systematic collection of relevant genes elucidated the molecular basis of SYNGAP1, CFC, CS and NS. This dual focus on clinical and molecular aspects provided a holistic understanding of the disorders, transcending traditional disciplinary boundaries.

The subsequent bioinformatic analysis, carried out with precision and depth, revealed complex relationships and patterns within the dataset. The iterative nature of this exploration allowed for the refinement of phenotypic nuances, contributing to the robustness of the DCDEs. The bioinformatics approach not only complemented the clinical perspective, but also added a layer of complexity that increased the depth of understanding.

The multi-stage Delphi process, involving diverse expert perspectives and patient representatives, exemplifies a democratic and inclusive decision-making model. The iterative nature of the Delphi method allowed for the inclusion of diverse viewpoints, fostering a consensus-driven selection of data elements that truly capture the essence of neurodevelopmental RASopathies.

The conclusive final vote served not only to validate the scientific rigour of the selected elements, but also as a testament to the collaborative spirit that drove this initiative. Beyond the creation of DCDEs, this methodology provides a blueprint for future rare disease research, emphasising the need for interdisciplinary collaboration, patient involvement and a dynamic approach to data collection. As the methodology will be published in an open access journal, it will not only contribute to the scientific knowledge of these rare diseases, but also catalyse a transformative shift in the approach to understanding and addressing complex rare diseases.

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5 Deviations, if applicable

Not applicable

6 References

1: Rojano E, Córdoba-Caballero J, Jabato FM, et al. Evaluating, Filtering and Clustering Genetic Disease Cohorts Based on Human Phenotype Ontology Data with Cohort Analyzer. J Pers Med. 2021;11(8):730. Published 2021 Jul 27. doi:10.3390/jpm11080730

2: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/CDS/EU_RD_Platform_CDS_Final.pdf

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