# Introduction

The Orphanet nomenclature of rare diseases is a unique standardised system aimed at providing a medical terminology specific to rare diseases.

This clinical coding system (ORPHAcodes) provides a common language for the coding of rare diagnoses across healthcare and research systems, contributing to better monitoring and statistical reporting on rare diseases, and enabling cross-border interoperability (through alignment with international terminologies & availability of the nomenclature in several languages).

The Orphanet nomenclature is organised by medical specialty according to diagnostic and therapeutic relevance, in a multi-hierarchical and polyparental classification system that reflects the multidimensional nature of rare diseases and enables to carry out epidemiological and statistical studies for research purposes.

The common node that the ORPHAcodes represent also organises an extensive collection of manually-curated and expert-validated data, thus promoting RD-focused research and the generation of knowledge.

The present collaboration was initiated by request from the eUROGEN/ARM-Net members to implement the Krickenbeck classification into the Orphanet classification of ARMs, which is currently subdivided into 2 groups: "Isolated" ARMs and "Syndromic" ARMs.

The previously recognized international classification of anorectal malformations, referred to as the Wingspread classification, which is currently reflected in the Orphanet "Isolated ARM" group, was based on detailed embryological and anatomic findings distinguishing between high, intermediate and low anomalies in the male and female.

The Krickenbeck classification was developed as a more clinically-oriented classification system, determining the diagnosis, operative procedure category and functional outcomes of ARM patients after surgery.

Several issues regarding the transposition of the currently available expertise on ARMs into the Orphanet database were raised throughout the discussions, which took place in 5 teleconferences (the latest one on 15/04/2021).

# Participants

The discussions involved the following participants:

* **Orphanet:** Houda Ali, Annie Olry
* **eUROGEN/ARM-Net:** Eberhard Schmiedeke, Ivo de Blaauw, Célia Crétolle, Sabine Sarnacki, Michelle Battye, Dalia Aminoff, Nicole Schwarzer, Darren Shilhan, Jen Tidman. Wout Feitz included in email exchanges.

# Summary of issues discussed and conclusions

**The detailed list of ALL ORPHAcodes that were reviewed in the framework of this collaboration, with the decision validated for each code, is provided in the Excel « Master file » attached to this document. The file also includes the before/after versions of the ARM classification.**

1. **The "Isolated ARMs" group should be renamed "Non-syndromic ARMs"**, to more accurately reflect the possible association with other anomalies in some cases (but the diagnosis is still considered as non-syndromic).
2. **The implementation of the Krickenbeck classification into the Syndromic ARMs group is not possible due to the inconsistencies it would create in RD coding across different scopes of expertise**:
   * + 70% of rare disorders registered in Orphanet are multiclassified, meaning that they involve more than one medical specialty.
     + Affected patients should be coded uniformly throughout different information systems and networks of expertise (eg: national patient registries, ERN patient registries…).
     + Orphanet provides an ORPHAcode for each known rare syndrome (e.g. Cat-eye syndrome ORPHA:195).
     + **The ORPHAcodes are used to code diagnoses, not the patients phenotypical description.** The creation of more precise codes specific to a given specialty within a known rare syndrome would create coding discrepancies across different systems, as each one of these precise codes would only be pertinent to one medical domain, and more than one code would be used for the same diagnosis, thus compromising statistical and epidemiological studies.

Hypothetical example:

* + - Digestive tract/anorectal surgery specialists request the creation of "Cat-eye syndrome with anorectal malformation"
    - Ophthalmologists request the creation of "Cat-eye syndrome with iris coloboma"

Issue: a Cat-eye syndrome patient can very well have iris coloboma and an ARM. Therefore 2 different ORPHAcodes will exist for patients sharing the same diagnosis, which will lead to inaccurate monitoring and counting across different registries and health information systems.

* + Adding to this complex issue, is the fact that a given syndrome known to possibly involve an ARM, will not be systematically associated with one specific ARM type. Creating as many specific syndromic ARM codes as there are ARM types (e.g. Cat-eye syndrome with perineal fistula, Cat-eye syndrome with rectourethral fistula… and so on) is not a viable option.

**Conclusions:**

* + the Krickenbeck classification will only be implemented in the Non-syndromic ARM group.
  + regarding the new ARM entities names: in many contexts, people involved in coding do not always search and visualise ORPHAcodes within the classification structure (i.e. they only see the main name and synonyms of the entity). Therefore, it is necessary to clarify the « non-syndromic » nature of the new ARM entities in their names, to discourage their use for syndromic ARM presentations, in which case the syndrome ORPHAcode (e.g. Cat-eye syndrome ORPHA:195) is the one that must be used.

1. However, the need expressed by ARM specialists for clear identification of the ARM type as a necessary condition for appropriate surgical management, follow-up and statistical analysis of affected patients, regardless of whether the ARM manifests on its own or as part of a syndrome, remained.

A suggestion was made by Orphanet that could be considered as a potential solution: for syndromic cases, in addition to the ORPHAcode used to code the patient’s main diagnosis, a secondary terminology could be used for phenotypical description, i.e. to indicate that the patient has an ARM, and if pertinent, which ARM type.

The [Human Phenotype Ontology (HPO)](https://hpo.jax.org/app/) could be particularly interesting for this. It is a well established terminology, well known to many rare diseases stakeholders including ERNs. If some ARM terms are missing or incorrect in the HPO terminology, a request can be made directly to HPO for their creation/correction.

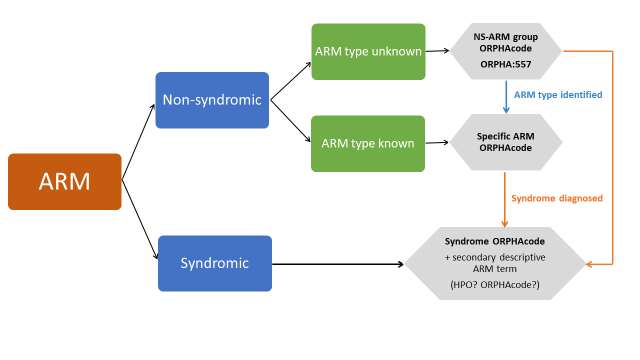
Alternatively, the ARM ORPHAcodes can also serve as descriptive terms (in addition to their main purpose i.e. to code the main diagnoses): in this case, it is important to clarify that the second ORPHAcode only has a purely descriptive purpose, and should not be mistaken for the main diagnosis.

However, and as emphasised by several experts, the use of terms containing « Non-syndromic » for the description of ARMs in patients diagnosed with known syndromes might be confusing for many users. In this regard, the HPO terminology might be a better option, but this should be decided by the concerned parties.

If the use of a secondary terminology to indicate the presence of an ARM in patients affected by multisystemic syndromes is formally decided, it is important to **establish and communicate clear recommendations** to ensure homogeneity of patient coding across different networks/information systems.

**This issue was extensively discussed and debated, and pertains to the inherent complexity and multidimensionality of rare diseases, since a majority are multisystemic and require a multidisciplinary management. It relates to a larger question that extends far beyond the scope of Orphanet and ORPHAcodes: how to structure, and ensure homogenous and consistent representation of RD patient data across different registries, research, and health information systems, in a fashion that enables optimal data sharing and exploitation.**

1. In addition to the major ARM clinical entities based on fistula location, some rare/regional variants were added to complete the perimeter of all known ARM presentations, which are also mentioned in the Krickenbeck classification: congenital pouch colon, rectal atresia, rectal stenosis, rectovaginal fistula, and H-type fistula. The experts confirmed that these rare variants and the major entities do not overlap, and cover all well-defined ARM types.
2. ARMs are usually observed at birth, but the definitive diagnosis of the patient may take some time to be established, due to variability of onset of other features defining known syndromes involving ARM. The coding should follow the evolution of the clinical knowledge on the patient (see figure below).
3. Rectal duplication is not officially defined as an anorectal malformation and should be reclassified in intestinal malformations.
4. Following a previous review done by Dr Peter Reifferscheid in 2017, some syndromes were removed from the ARM group (see Masterfile).



E-mail archive: why the Krickenbeck classification cannot be implemented in the Syndromic ARM group

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| --- | --- |
| **Sujet :** | Re: Orphacodes - urgent consensus |
| **Date :** | Mon, 10 May 2021 09:39:05 +0200 |
| **De :** | Houda Ali <houda.ali@inserm.fr> |
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Dear all,

As the coordinator of collaborations with European and international networks of expertise for the update of the Orphanet nomenclature and classification of rare diseases, I would like to offer some comments on the issue discussed in this exchange.

The Orphanet nomenclature has been established to not only provide comprehensive, expert-validated, and structured information to health professionals involved in the pathway of rare diseases patients, but also as an answer to the previous lack of a specific and exhaustive terminology when it came to diseases defined as rare according the European definition (1999).

By providing clinical terms that precisely match each rare disorder known to the biomedical literature, the ORPHA coding system enables the identification of the diagnosis officially recognised for each affected patient, as well as their tracking across healthcare and research information systems and records.

A rare disorder may be unisystemic, or may be a syndrome associating several clinical manifestations and/or malformations affecting different biological systems.

Of the 6,000 rare disorders registered by Orphanet, 70% are multisystemic, and this clearly illustrates the multidimensionality of rare diseases: the pathway of one given patient across healthcare structures will necessarily involve specialised consults and management from different fields of expertise, and challenges specific to each medical specialty will arise.

For example, in a patient with a congenital syndrome associating cardiac defects, ocular anomalies, renal malformations, and respiratory anomalies, it will be important for each specialist to have a precise clinical description, especially when surgical intervention is involved - renal surgeons will want to identify the kind of renal malformation, and the same goes for the cardiac pediatric surgeon.

On the other hand, from a technical point of view, consistent data sharing and statistical reporting is not possible if the patient's "main diagnosis" is registered using a variable constellation of clinical terms, with these terms varying from one registry to another depending on the medical specialty of interest, and actually reflecting a detailed clinical description of the patient rather than the main diagnosis.

It is possible however to enrich the main diagnosis, represented by the ORPHAcode, with additional information as needed by the medical specialties.

But this calls for the design of information systems that cater and are adapted to these needs, and also and very importantly, for carefully crafted consensus recommendations to ensure that patient data are registered in a consistent fashion between different information systems and areas of expertise both at national and European levels.

This emphasizes that the issue at hand relates to the inherent complexity of rare diseases and the considerably broader problem of how to effectively share patient data while ensuring interoperability between different systems and registries. It cannot be reduced to a matter of arbitrary rigidity on Orphanet's part: Orphanet is as a rare disease knowledge base, that offers a standardised medical terminology for the identification of rare diagnoses, and cannot as such be expected to solve all these broader issues that extend far beyond its scope of action (although we do participate in numerous related discussions and European projects).

This has been extensively discussed throughout my numerous meetings with the eUROGEN/ARM-Net representatives, and I stressed out the importance of reporting these issues to the appropriate stakeholders, including ERN and cross-ERN representatives.

I explained in detail why the creation of codes for syndromic forms of clinical manifestations/malformations specific to one field of expertise (e.g. anorectal malformations) would be a problem rather than a solution, using several concrete examples.

However, we have responded favorably to the request to implement the Krickenbeck classification into the Orphanet classification of anorectal malformations, since when it comes to defining clinical diagnoses, we follow the definitions most widely recognised in the current knowledge and available expertise.

I hope this clarifies the context surrounding the current proposal.

Kind regards,

Houda

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Houda Ali

Rare disease nomenclature and classification

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