

The Yukiwariso Declaration

From the International Conference on Rare Diseases and Orphan Drugs (ICORD)

The need for world-wide policy and action plans for rare diseases



This declaration, adopted by the Board of ICORD in November 2011, was launched at the Annual ICORD Meeting in February 2012 at the Komaba research campus, University of Tokyo.

The flower Yukiwariso (*Hepatica*) is the chosen symbol for this declaration, to recognise Japan as the place this declaration was launched, and the special role of this rare and precious flower as a symbol of new life, as it breaks through the late winter snow in cold northern climates.

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Introduction

There are more than 6000 and perhaps as many as 8000 different rare diseases that occur less often than 1 per 2000 people in the European population¹ or affect fewer than 200,000 people in the United States². Other countries have different legal definitions of a rare disease. In Japan a rare disease is one that affects fewer than 50,000 patients. Australia utilizes a definition of a rare disease as one with a prevalence of less than 2000 individuals. In Taiwan, the official definition of a rare disorder is a disease with prevalence less than 1:10,000 people.

Many rare diseases are diagnosed at the age of childhood, making diagnostic awareness and knowledge on treatment and care particularly important for paediatricians. The vast majority of the rare diseases are genetic in origin, determined by our genetic makeup, but many others arise from gene-environment interactions. The environmental causes include drugs, chemicals, pollutants, viruses, parasites and certain trauma.

Rare diseases share many of the problems and challenges of common diseases. These include: privacy of information, ethics and consent issues, professional/patient relationships, the need to translate research into better healthcare, access to quality treatment and care across the lifespan, reimbursement of treatment, and treatment costs. However the rarity of these diseases can create special problems for affected populations including the following:

- Difficulty in obtaining timely and accurate diagnosis, often leading to a delay of treatment with the occurrence of irreversible symptoms
- Lack of experienced health care providers involved in the care and treatment of patients with rare diseases
- Useful, reliable and timely information is harder to find, for professionals, patients and families, making the decision-making process more difficult
- Research activities are less likely to occur than for common diseases
- Developing new medicines may not be economically feasible for drug companies
- Treatments are sometimes very expensive
- In developing countries the problems are compounded by poverty, scarcity of medical expertise and other resource limitations.

Rapidly expanding scientific knowledge and technological advances are greatly improving our ability to intervene in a wide range of health conditions, including rare diseases. Notably, clinical trials using already existing drugs may result in new, affordable, treatment strategies. Moreover, rare diseases may teach us about common disorders. In order for this potential to be realized it is essential that rare diseases are the subject of a particular focus in health policy and in service delivery, if the needs of those affected or at risk are not to be overlooked.

In the US and EU, legislation in the form of the Orphan Drug Act, 1983³ and Orphan Regulation No 141/2000⁴ to promote the research and development of orphan drugs (in the US and EU) and medical devices (in the US) for rare diseases, has had clear and identifiable benefits in bringing a number of treatments into clinical practice. Rare disease issues feature regularly in US and EU policy papers,⁵ and rare diseases are increasingly discussed in published literature⁶ and EU policy papers, such as the EU Council Recommendation on

rare diseases (2009), new action plans (www.euoplanproject.eu), the EU Committee of Experts on Rare Diseases reports on the state of art of rare disease policy and research (www.eucerd.eu), and the International Rare Disease Research Consortium.

However, numerous challenges lay ahead as many more rare diseases remain unresearched and untreatable, with very few active research studies underway. Many countries do not yet have rare diseases and orphan products research and development policies. Treatments for some rare diseases remain very expensive, even though the total cost to the health system may be limited, due to disease rarity. For some diseases the manufacturers and providers of orphan products have committed to make these products available through special distribution programs to all who are in need of treatment.

The International Conference on Rare Diseases and Orphan Drugs (ICORD) is a non-profit society, drawing together members from academia, patient advocacy, medicine regulatory, healthcare industry, health care services, and public policy agencies and organisations around the globe. Our mission is to improve the health and welfare of patients with rare diseases and their families world-wide through better knowledge, information and awareness and by fostering research, care and treatment. ICORD organizes conferences about rare disease and orphan drug issues, and reflects on rare disease policies for the future.

ICORD is a society that is very well placed to contribute leadership on topics that include:

- Active participation in the classification of rare diseases and identifying the scope of an already known disease and hence, when another disease category should be recognized.
- Advice on definitions of rare diseases that aim for consistency in national and international health policies.
- Advice on strategies that may be adopted to ensure safety and efficacy in the development of therapies for rare diseases, when very small patient numbers are involved in research studies.
- Available for advice on potential use of existing approved or experimental therapies for other rare diseases.
- Advice on matters that should be considered within cost effectiveness criteria when therapies for rare diseases are evaluated.
- Advice and perspectives from patients and family members regarding:
 - Relative safety and risks in participating in clinical trials and regulatory decision-making of products for rare diseases.
 - Ethical criteria for screening and predictive genetic testing for rare diseases.
 - The design and delivery of health care and support services, and assurance of patient safety within those services.

We present this position statement as a basis for discussion with national governments and with international health bodies about rare disease policies to assist with their role of providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

Health needs, health priorities, and legal, ethical and social issues

The United Nations Universal Declaration of Human Rights (Article 25.1) states: “Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including ... medical care and necessary social services, and the right to security in the event [of] ... sickness, disability, or other lack of livelihood in circumstances beyond his control”.⁷

The International Covenant on Economic, Social and Cultural Rights (Article 12.1) includes “the right of everyone to the highest attainable standard of physical and mental health” (Article 12.1). Article 12.2 of this covenant further provides: “to realise these rights, steps must be taken by the state to reduce infant mortality, to improve hygiene, to prevent, treat and control diseases and assure all medical service and medical attention in the event of sickness”.⁸

The United Nations Convention on the Rights of the Child includes the right to the highest attainable standard of health care.⁹

While the implementation of these instruments is subject to the laws, policies and budgets of each state, approaches to health planning and services often place priority on common diseases, leading to the neglect of those affected by rare diseases. This has meant disadvantage for those populations affected by rare diseases and limited compliance in many states with the UN Convention and the International Covenant.

Moral philosophy offers additional guidance on the importance of equitable attention to rare diseases. The ethical principle of Justice¹⁰ requires that the needs of rare disease populations are specifically addressed, as they should be for any minority or underserved community. This is an important part of the goal of reducing health disparities between populations.

A global approach to rare diseases is needed to utilize the rare diseases research, and orphan products development experiences and knowledge gained by many government agencies, academic research investigators, patient advocacy groups, foundations and the pharmaceutical industry dating from 1983.¹¹

Key principles for adoption in health policy include:

1. Rare diseases are a significant public health issue¹². Together they may affect up to 8% of the population¹³ and when the immediate family and friends are factored in, rare diseases may impact nearly 25% of the population of any country.
 - In many countries 8% is equivalent to the size of significant minority populations. Just as leaving the health needs of such a population unmet would be unacceptable and discriminatory, so is the neglect of equivalent populations affected by rare diseases.
2. Health care and treatment for rare diseases is a human rights issue. Non-discrimination, justice and equity of access to health care,¹⁴ all require that specific policies are put in place to address the needs of people affected by rare diseases.

- Responses such as prioritization and the need to ration resources, as reasons for lesser attention to rare diseases in health research, planning and service delivery, are not ethically sustainable arguments. A balanced and equitable approach is needed.
3. Every country is encouraged to have a rare diseases research and orphan products development program, with emphasis adjusted to its existing capabilities.
 - Significant advances gained from nearly 30 years of experience with rare diseases are readily available to all, from those countries whose legacy efforts and regulations and national plans have been in place since 1983.¹⁵
 - Moreover, support for clinical trials using already registered existing drugs and other treatments but for new indications should also be considered since this may be effective and cost-effective, as shown in many childhood cancer where remarkably improved outcomes have been achieved by repeated clinical trials using established drugs in new combinations.
 4. A comprehensive approach to rare diseases is needed, including education, research, prevention, diagnosis, care and treatment, social support and inclusion.
 - Services and support for patients and families need to be holistic and integrated to provide for the health, disability and social issues often associated with them.
 - Specific funding from governments for research projects on rare diseases is needed, since research on rare diseases or small patient groups tends to receive lower ranking in the competition for grants.
 - Multi-stakeholder platforms are important tools to define and act upon issues in the field of rare diseases. Such collaborations are essential to overcome the complexity of these issues.
 - International patient registries and biospecimen repositories for rare diseases should be encouraged and available for appropriate use by the rare diseases community.
 5. Quality information, informed consent and autonomous decision-making are critical for upholding the rights and protection of patients and their families in all aspects of prevention, research and treatment.
 - Combining genetic knowledge with screening in the pre-natal and newborn periods, plus later screening and other detection methods to identify risk, should be actively pursued to afford choices about prevention, but this must be balanced with careful attention to informed consent and autonomous decision-making.
 6. Patient groups play an important role in the development of knowledge about rare diseases, and must be included at all levels in the development of their policies and services, including recognition of the important role of these groups in providing information and support to patients and their families, health care providers and the public.
 - Patient groups need to have adequate resources allocated to them to ensure their contributions to patient and family interests, and their involvement in policy and service development are encouraged and supported.

- It is essential that patient groups adopt a global approach to memberships and activities to provide better access to information and interventions to improve quality of life for all patients with rare diseases.

An action plan for implementing rare diseases policies

These points are provided as guidance for the implementation of rare disease policies:

1. **Action plans.** Governments should recognize that rare diseases create disparities and vulnerabilities in health status for affected populations and should put in place specific policies to address them.
2. **Specific programs and policies.** Governments should recognize the human rights issues inherent in rare disease care and treatment across the lifespan.¹⁶ They should adopt the principle that rarity of a disease should not be grounds for denying access to services or therapies, and that specific programs and policies will be needed to protect those rights.
3. **Allocation of resources.** Governments should adopt policies that aim to achieve equitable allocation of resources towards all aspects of rare diseases, including research, clinical care, information resources and development of treatments. Targeted budgets for rare disease research, incentives to encourage treatment advances by industry, the development of specialist services, and information services for professionals and the public, are just some ways this can be achieved. Moreover, support for clinical trials using already registered existing drugs and other treatments but for new indications should also be considered since this may be effective and cost-effective, as shown in many childhood cancers where remarkably improved outcomes have been achieved by repeated clinical trials using established drugs in new combinations.
4. **Specific counterbalancing policies.** Governments and health systems should offer incentives to encourage development of rare disease treatments by industry and public/private partnerships, as has been done in the United States and the European Union. However, there is a need to recognize problems with the research and development costs of such treatments. Regulatory and clinical trials requirements are important protections for patient safety, but review of these requirements needs to be made on the basis that risk management can be approached differently for small numbers and very serious diseases, compared to treatments intended for general populations as a whole.
5. **Cost effectiveness assessment should consider wider factors.** Health economics criteria, if used and if applicable, should take account of the personal, social and economic benefits of treating diseases, even where the unit cost of treatment may be more expensive.
6. **Specific benefits of research into rare diseases.** Research policies should note the specific benefits of research into rare diseases, especially single gene disorders, as an extremely valuable means of gaining information about the cause of more

common multi-factorial diseases. Taking advantage of this for the benefit of the whole population implies weighting of basic research funds towards rare diseases, in particular where high quality animal models offer opportunities for understanding disease processes.

7. **Recognition of gaining knowledge to aid prevention.** Governments, researchers and industry should recognize that gaining knowledge of disease processes from patient registries, natural history studies or clinical trials is as highly relevant to possibilities for prevention, as it is to treatment of those with the disease. This means that opportunities to prevent serious rare diseases should be a priority in research, along with development of treatments, even in the face of significant scientific or technical challenges.
8. **Encouragement of industry to contribute to rare disease knowledge.** Industry should be encouraged to increase its “public good” contributions to rare disease knowledge. In particular, industry should examine its intellectual property holdings and consider public good donation of products or techniques that may have little commercial application, but which may offer great opportunities for understanding or treating rare diseases.
9. **Patient advocacy groups participation in advisory groups and expert panels.** Health systems should note a changing dynamic in the role of patient advocacy groups. They provide important information and support, and consequently should be resourced by governments and health officials to carry out this important role independently. They should also be directly involved in advisory groups and expert panels set up to consider specific policy options, ethical controls, risk management and service planning, and ICORD will support their international collaboration.
10. **Development of information networks and support group capacity.** Good information is an essential component of good health care. Information technology enables many, but not all people affected by rare diseases to rapidly gain access to timely, reliable and useful information on their disorder and to become an expert in managing their own health, in partnership with their health care providers. Development of information networks and support group capacity is an important aspect of widening access to this information to the whole community.
11. **Criteria for ante-natal and newborn screening and ethical controls.** Criteria for ante-natal and newborn screening and ethical controls for other predictive testing need reconsideration in the light of changes in knowledge of disease causes, patient and support group awareness, new possibilities to improve the patients’ quality of life, and prevention possibilities.
12. **Recognition of the specific problems of rare diseases in developing nations.** Governments should recognize the specific problems of rare diseases in developing nations, and investigate and put in place ways in which support with screening, diagnosis, treatment and clinical training can be provided in aid programs or other arrangements to increase access to information about rare diseases and their interventions.

Conclusions

The diagnosis, prevention and treatment needs of patients with most rare diseases and conditions remain largely unmet despite the significant efforts of patients, families, research investigators, pharmaceutical, biotechnology, medical device and diagnostic industries, health care providers, foundations, advocacy groups and government research, regulatory prevention, and patient services agencies. For several selected rare diseases, remarkable basic research, clinical research and orphan products development activities have occurred, leading to suitable treatments. The dedicated individuals and organizations involved in these research and product development activities are to be commended for their commitment. However, more emphasis is required by the public and private sectors if we are to support appropriate research and development activities leading to the development of orphan products for the prevention, diagnosis and treatment of rare diseases.

Many of the current activities are based on needs identified by rare diseases communities in the period of 1978-1982. Periodic reviews of the needs of the rare diseases community and adjustment of specific activities is required. Unfortunately for most rare diseases, no interventions are available as approved products or as investigational products in ongoing clinical trials. ICORD offers specific activities to address the many and varied needs of this community of dedicated individuals, organizations, industry and government agencies. All discoveries and advances are to be shared with people from all nations. Rare diseases do not respect geographical boundaries. All countries are encouraged to implement specific research and development activities within their individual capabilities. Only when this has occurred, will all patients around the world have equal access to necessary information and interventions to maximize the potential of every individual.

¹ European Commission Communication on Rare Diseases. EC Regulation on Orphan Medicinal Products. Downloaded from:
http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

² Rare Diseases Act 2002. Public Law 107–280—NOV. 6, 2002. Downloaded from:
<http://bulk.resource.org/gpo.gov/laws/107/publ280.107.pdf>. Also available as a National Institutes of Health Fact Sheet: The genetic and rare diseases information center. Downloaded from:
<http://www.nih.gov/about/researchresultsforthepublic/GeneticandRareDiseasesInfo.pdf>

³ Orphan Drug Act 1983. Public Law, 97-141. Downloaded from:
<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/OrphanDrugAct/default.htm>

⁴ Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. 22 January 2000, Official Journal of the European Communities L 18/1. Downloaded from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>

⁵ Arrigo Schieppati, Jan-Inge Henter, Erica Daina and Anita Aperia (2008) 'Why Rare Diseases are an important medical and social issue'. *The Lancet* 371, 2039 – 2041;

National Institutes of Health (2007) *Biennial Report on the Office of Rare Diseases Research Activities at the National Institutes of Health*.

<http://rarediseases.info.nih.gov/files/BienniaReportRareDiseasesFY2006Final.pdf> FY 2006. Unpublished report by the Office of Rare Diseases. Bethesda, Maryland: National Institutes of Health; National Institutes of Health (1999)

Report on Steps to Coordinate Rare Diseases Programs and Report on the Rare Diseases and Conditions Research Activities of the National Institutes of Health, 1999.

<http://rarediseases.info.nih.gov/Wrapper.aspx?src=asp/html/reports/fy1999/SEP.html>

Unpublished report by the National Institutes of Health. Bethesda, Maryland: National Institutes of Health; Downloadable from: Commission of the European Communities (2008) *Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges*. Downloaded from:

http://ec.europa.eu/health/archive/ph_threats/non_com/docs/rare_com_en.pdf;

The Council of the European Union (2009) *Council Recommendation of 8 June 2009 on an action in the field of rare diseases* (2009/C 151/02). Official Journal of the European Union.

C151/7. Downloaded from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>.

⁶ Examples of recent research on rare disorders that focus on their relationship to the development of treatment protocols include: Robert C. Griggs, Mark Batshaw, Mary Dunkle, Rashmi Gopal-Srivastava, Edward Kaye, Jeffrey Krischer, Tan Nguyen, Kathleen Paulus and Peter A. Merkel (2009) 'Clinical research for rare disease: Opportunities, challenges, and solutions' *Molecular Genetics and Metabolism* 96:1, 20-26; Olivier Wellman-Labadie and Youwen Zhou (2010) 'The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity?'. *Health Policy*, 95:2-3, 216-228; Ségolène Ayme, Ana Rath, Virginie Thibaudeau, Bruno Urbero, Valerie Fonteny and Matthieu Levi-Strauss (2007) 'Maladies rares : quelles sources d'information pour les professionnels de santé et les malades?' *Réanimation* 16: 4, 276-280; Harald E. Heemstra, Sonja van Weely, Hans A. Büller, Hubert G.M. Leufkens and Remco L.A. de Vruueh (2009) 'Translation of rare diseases research into orphan drug development disease matters'. *Drug Discovery Today* 14: 23-24, 1166-1173; George J. Brewer (2009) 'Drug development for orphan diseases in the context of personalized medicine'. *Translational Research* 154: 6, 314-322.

⁷ United Nations Universal Declaration of Human Rights (Article 25.1). December 10, 1948, The General Assembly of the United Nations. Downloaded from:

<http://www.un.org/en/documents/udhr/index.shtml>

⁸ International Covenant on Economic, Social and Cultural Rights Article 12.1 and 12.2. Adopted and opened for signature, ratification and accession by General Assembly resolution 2200A (XXI) of 16 December 1966 entry into force 3 January 1976, in accordance with article 27. Downloaded from: <http://www2.ohchr.org/english/law/pdf/cescr.pdf>

⁹ United Nations Convention on the Rights of the Child 1989. Adopted and opened for signature, ratification and accession by General Assembly resolution 44/25 of 20 November 1989. Entry came into force 2 September 1990, in accordance with article 49. Downloaded from: <http://www2.ohchr.org/english/law/pdf/crc.pdf>

¹⁰ The Justice theory was first outlined by John Rawls and can be accessed in the following publications. John Rawls (1971) *A Theory of Justice*. (Cambridge: Harvard University Press).

624pp and John Rawls (2001) *Justice as Fairness: a Restatement*. Ed. Erin Kelly (Cambridge, M.A.: Harvard University Press) 214pp.

¹¹ Warren Kaplan and Richard Laing (2004) *Priority Medicines for Europe and the World* (Geneva: World Health Organisation). Downloaded from: http://whqlibdoc.who.int/hq/2004/WHO_EDM_PAR_2004.7.pdf

¹² 'News Alert: The European Commission and the US announce joint research efforts on rare diseases'. 28 October 2010. Downloaded from: <http://ec.europa.eu/research/index.cfm?pg=newsalert&lg=en&year=2010&na=na-281010>

¹³ Council of the European Union (2009) Council Recommendation of 8 June 2009 on an action in the field of rare diseases. Paragraph 5. Downloaded from: [http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32009H0703\(02\):EN:NOT](http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32009H0703(02):EN:NOT)

¹⁴ Anne F Bayefsky. The principle of equality or non-discrimination in international law. *Human Rights Law Journal*, 1990, 11:1–34; Council of Europe's "Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine". Oviedo, 4. IV. 1997. Refer to Chapter I – General provisions. Article 3 – Equitable access to health care. "Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality". Downloaded from: <http://conventions.coe.int/Treaty/EN/Treaties/Html/164.htm>

¹⁵ For example, "In the USA, this kind of legislation has been in place since 1983 when the US Orphan Drug Act was introduced. Since its inception, this legislation has been very successful in bringing more than 230 medicinal products for orphan diseases to the market, thereby facilitating treatment for an estimated 11 million patients in the USA, with even greater numbers being approved internationally." Warren Kaplan and Richard Laing (2004) *Priority Medicines for Europe and the World* (Geneva: World Health Organisation), p96. Downloaded from: http://whqlibdoc.who.int/hq/2004/WHO_EDM_PAR_2004.7.pdf

¹⁶ For a discussion of human rights issues and their relationship to equity within healthcare, see: Paul Hunt, Rébecca Steward, Judith Bueno de Mesquita, Lisa Oldring, World Health Organization (2007) *Neglected diseases: a human rights analysis* (Geneva: World Health Organisation), particularly p16.