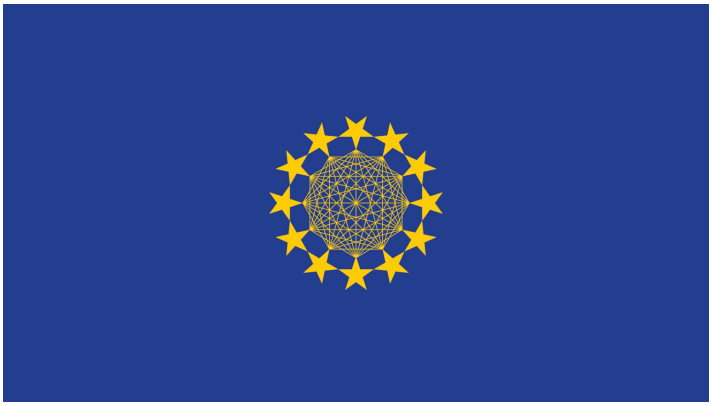
PIERRE ROBIN EUROPE



2021 Annual Report

Stichting Pierre Robin Europe
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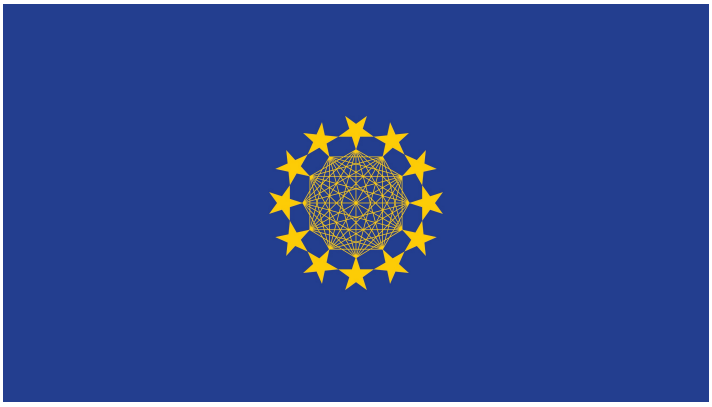
PIERRE ROBIN EUROPE



Articles of Association

In the Netherlands, those wishing to establish a Stichting with ANBI status, which is a non-profit tax-exempt charitable organization, must engage the services of a notaris. A notaris works with the founders of the organization to draft a deed of incorporation which contains the by-laws of the legal entity. What follows is a copy of the deed of incorporation, also called the Articles of Association, in Dutch.

Stichting Pierre Robin Europe
Gerard Terborgstraat 51 2, 1071TL Amsterdam, the Netherlands
www.PierreRobinEurope.com

Ref: DU/SGR (14 december 2018.1)
Dos: 2018.3329.01

STICHTING

Heden, achttien december tweeduizend achttien,
verschijnt voor mij, mr. Ingeborg Marguérithe Duyverman, notaris te Utrecht:
de heer **Jean-Phillippe Auguste Pakter**, geboren te New York, Verenigde Staten van Amerika op twaalf juni negentienhonderdtweeënzeventig, wonende te Genève 1201, Zwitserland, 29 Rue de Neuchâtel, paspoortnummer: BLFLR3F69, uitgegeven op vier juni tweeduizend vijftien te Haarlemmermeer, geldig tot vier juni tweeduizend vijfentwintig, ongehuwd (zonder geregistreerd partnerschap), hierna te noemen: **de oprichter**.
De comparant verklaart bij deze akte een stichting op te richten en daarvoor de volgende statuten vast te stellen:

STATUTEN

NAAM EN ZETEL

Artikel 1.

1. De stichting draagt de naam: **Stichting Pierre Robin Europe**. De Engelse benaming van de stichting luidt: Pierre Robin Europe Foundation.
2. Zij is gevestigd te Amsterdam.

DOEL

Artikel 2.

1. De stichting heeft ten doel: informatie te verstrekken over het Pierre Robin Syndroom en andere zeldzame ziekten, om zodoende het belang van het tijdig opsporen van deze en andere ziekten, alsmede adequate behandeling ervan, onder de aandacht van patiënten en belanghebbenden te brengen en deze hierbij te ondersteunen, waar ook ter wereld, en voorts al hetgeen met één en ander rechtstreeks of zijdelings verband houdt of daartoe bevorderlijk kan zijn, alles in de ruimste zin des woords.
   De stichting beoogt niet het maken van winst.
2. Zij tracht dit doel te bereiken door onder meer:
   a. het belang van: “Patient gerichte zorg” en “Recht op toegang tot die zorg” onder de aandacht te brengen bij mensen die betrokkenen zijn bij deze ziekten; zoals onder andere patiënten en hun families, werkers in de gezondheidszorg, politici, juristen werkzaam in de wetgeving, onderzoekers, patiënten belangengroepen. Daarnaast ook in een bredere laag van de maatschappij;
   b. informatie te verschaffen over de EU wetgeving omtrent de mogelijkheid tot grensoverschrijdende gezondheidszorg in Europa. Over dit onderwerp zelf en richtlijnen over dit onderwerp te publiceren, om zodoende patiënten te wijzen op de mogelijkheid toegang te krijgen tot medische behandeling die hen niet geboden wordt door hun locale artsen en/of in hun eigen land;
   c. te wijzen op het belang van de verdere ontwikkeling en toepassing van een prenataal ultrasound systeem om de eerste verschijnselen van het Pierre Robin Syndroom alsmede andere zeldzame ziekten vroegtijdig op te sporen en waar nodig, zo snel mogelijk te kunnen behandelen;
   d. informatie te verstrekken in verschillende talen over het Pierre Robin Syndroom en andere zeldzame ziekten en de behandelingen daarvan;
   e. communicatie te bevorderen, contact tussen lotgenoten en belanghebbenden te faciliteren en het verspreiden van kennis over de zeldzame ziekte, het Pierre

Robin Syndroom alsmede andere zeldzame ziekten, zowel in Europa als daarbuiten.

VERMOGEN

Artikel 3.

1. Het vermogen van de stichting wordt gevormd door alle ontvangen bijdragen, subsidies, giften, legaten, erfstellingen, alsmede andere baten.
2. Erfstellingen mogen slechts worden aanvaard onder het voorrecht van boedelbeschrijving.

BESTUUR

Artikel 4.

1. Het bestuur van de stichting bestaat uit een door het bestuur vast te stellen aantal van ten minste drie personen. De meerderheid van de bestuurders mag geen familie van een andere bestuurder zijn. Onder familie moet in dit verband worden verstaan: bloed- en aanverwanten tot en met de vierde graad, waarbij samenwoning wordt gezien als een huwelijk.
2. Bestuurders worden benoemd door het bestuur. Indien een bestuurder op grond van een bepaalde hoedanigheid wordt benoemd, wordt daarvan in het benoemingsbesluit expliciet melding gemaakt.
3. Het bestuur wijst uit zijn midden een voorzitter, een secretaris en een penningmeester aan. Een bestuurder kan binnen het bestuur twee functies bekleden.
4. De benoeming van een bestuurder geschiedt voor onbepaalde tijd, tenzij in het betreffende benoemingsbesluit een bepaalde tijd is vastgesteld.
5. Bij belet van een bestuurder zijn/is de overige bestuurder(s) met het bestuur belast. Indien sprake is van een vacature in het bestuur, vormen de overgebleven bestuurders of vormt de overgebleven bestuurder een bevoegd bestuur. Het bestuur is echter verplicht zo spoedig mogelijk in de vacature(s) te voorzien.
   In alle gevallen waarin niet binnen drie maanden na het ontstaan van een vacature in de benoeming van een bestuurder is voorzien, zal de meest gerede bestuurder of overige belanghebbende de rechtbank van het Arrondissement waarbinnen de stichting statutair is gevestigd kunnen verzoeken een bestuurder te benoemen.
6. Een bestuurder defungeert:
   a. door zijn overlijden;
   b. door zijn aftreden;
   c. door het verlies van het vrije beheer over zijn vermogen;
   d. door zijn ontslag door de rechtbank;
   e. door zijn ontslag door het bestuur; het besluit hiertoe kan slechts worden genomen met algemene stemmen van de overige bestuurders.
   f. door verlies van de hoedanigheid op grond waarvan hij blijkens het benoemingsbesluit is benoemd.
   g. door het verstrijken van de tijd waarvoor hij is benoemd.
7. Het bestuur kan besluiten een bestuurder te schorsen. Een schorsing die niet binnen drie maanden gevolgd wordt door een besluit tot ontslag, eindigt door het verloop van die termijn.

TAAK, BEVOEGDHEDEN, BELONING

Artikel 5.

1. Het bestuur is belast met het besturen van de stichting. Het bestuur kan als zodanig één of meer van zijn bevoegdheden, mits duidelijk omschreven, aan anderen verlenen. Degene die aldus bevoegdheden uitoefent, handelt in naam en onder verantwoordelijkheid van het bestuur. Het bestuur dient jaarlijks een beleidsplan op te stellen.

2. Het bestuur is niet bevoegd te besluiten tot het aangaan van overeenkomsten tot verkrijging, vervreemding of bezwaring van registergoederen noch tot het aangaan van overeenkomsten waarbij de stichting zich als borg of hoofdelijk medeschuldenaar verbindt, zich voor een derde sterk maakt of zich tot zekerheidstelling voor een schuld van een ander verbindt.
3. Bestuurders hebben recht op vergoeding van de door hen in de uitoefening van hun functie (in redelijkheid) gemaakte kosten en voorts op een niet bovenmatig vacatiegeld.

BESLUITVORMING

Artikel 6.

1. Bestuursvergaderingen worden gehouden zo dikwijls de voorzitter of ten minste twee van de overige bestuurders zulks wensen, doch ten minste éénmaal per zes maanden.
2. De bijeenroeping van een bestuursvergadering geschiedt door de voorzitter of ten minste twee van de overige bestuurders, dan wel namens deze(n) door de secretaris, en wel schriftelijk, waaronder begrepen per elektronische gegevensdrager, onder opgaaf van de te behandelen onderwerpen, op een termijn van ten minste zeven dagen, de dag van de oproeping en die van de vergadering niet meegerekend.
   Indien de bijeenroeping niet schriftelijk is geschied, of onderwerpen aan de orde komen die niet bij de oproeping werden vermeld, dan wel de bijeenroeping is geschied op een termijn korter dan zeven dagen, is besluitvorming niettemin mogelijk, mits ter vergadering alle in functie zijnde bestuurders aanwezig of vertegenwoordigd zijn.
   In spoedeisende gevallen kan de voorzitter van het bestuur besluiten van de wijze van oproeping en/of de termijn van oproeping af te wijken.
3. Bestuursvergaderingen worden gehouden ter plaatse te bepalen door degene die de vergadering bijeenroept.
4. Toegang tot de vergaderingen hebben de bestuurders, alsmede zij die door de ter vergadering aanwezige bestuurders worden toegelaten. Een bestuurder kan zich door een schriftelijk door hem daartoe gevolmachtigd mede-bestuurder ter vergadering doen vertegenwoordigen.
5. Iedere bestuurder heeft één stem.
   Voor zover deze statuten geen grotere meerderheid voorschrijven worden alle bestuursbesluiten genomen met volstrekte meerderheid van de geldig uitgebrachte stemmen.
   Blanco stemmen worden beschouwd als niet te zijn uitgebracht.
   Staken de stemmen bij benoeming van personen dan beslist het lot; staken de stemmen bij een andere stemming, dan is het voorstel verworpen.
6. Alle stemmingen geschieden mondeling, tenzij een bestuurder schriftelijke stemming verlangt.
7. De vergaderingen worden geleid door de voorzitter. Bij zijn afwezigheid voorziet de vergadering zelf in haar leiding.
8. Van het verhandelde in de vergadering worden door de secretaris of door een door deze onder zijn verantwoordelijkheid en met instemming van het bestuur aangewezen persoon notulen opgemaakt. De notulen worden vastgesteld door het bestuur en ten blijke daarvan door de voorzitter en secretaris van de desbetreffende vergadering ondertekend. De vastgestelde notulen zijn ter inzage voor alle bestuurders. Afschriften worden aan hen kosteloos verstrekt.
9. Het bestuur kan ook buiten vergadering (schriftelijk) besluiten, mits alle bestuurders zich schriftelijk omtrent het desbetreffende voorstel hebben uitgesproken, waaronder

begrepen per elektronische gegevensdrager. Van een besluit buiten vergadering wordt onder bijvoeging van de ingekomen antwoorden door de secretaris een relaas opgemaakt, dat na mede-ondertekening door de voorzitter bij de notulen wordt gevoegd.

10. In alle geschillen omtrent stemmingen niet bij de statuten voorzien, beslist de voorzitter.

VERTEGENWOORDIGING

Artikel 7.

1. De stichting wordt vertegenwoordigd door het bestuur. Voorts kan de stichting worden vertegenwoordigd door twee tezamen handelende bestuurders.
2. Het bestuur kan besluiten tot het verlenen van volmacht aan één of meer bestuurders alsook aan derden, om de stichting binnen de grenzen van die volmacht te vertegenwoordigen. Het bestuur kan voorts besluiten aan gevolmachtigden een titel te verlenen.
3. Het bestuur zal van het toekennen van doorlopende vertegenwoordigingsbevoegdheid opgave doen bij het handelsregister.

REGLEMENTEN

Artikel 8.

1. Het bestuur is bevoegd één of meer reglementen vast te stellen, waarin die onderwerpen worden geregeld, waarvan nadere regeling wenselijk wordt geacht.
2. Een reglement mag niet met de wet of deze statuten in strijd zijn.
3. Het bestuur is te allen tijde bevoegd een reglement te wijzigen of op te heffen.
4. Ten aanzien van een besluit tot vaststelling, wijziging of opheffing van een reglement vindt het bepaalde in artikel 10, leden 1 en 2, overeenkomstige toepassing.

BOEKJAAR, JAARSTUKKEN

Artikel 9.

1. Het boekjaar van de stichting valt samen met het kalenderjaar.
2. Het bestuur is verplicht van de vermogenstoestand van de stichting en van alles betreffende de werkzaamheden van de stichting, naar de eisen die voortvloeien uit deze werkzaamheden, op zodanige wijze een administratie te voeren en de daartoe behorende boeken, bescheiden en andere gegevensdragers op zodanige wijze te bewaren, dat te allen tijde de rechten en verplichtingen van de stichting kunnen worden gekend.
3. Het bestuur is verplicht jaarlijks binnen zes maanden na afloop van het boekjaar de balans en de staat van baten en lasten met bijbehorende toelichting van de stichting te maken en op papier te stellen. Deze stukken dienen te worden ondertekend door alle bestuurders; ontbreekt de ondertekening van een of meer van hen, dan wordt daarvan onder opgave van redenen melding gemaakt.
4. Het bestuur kan, alvorens tot vaststelling van de in lid 3 bedoelde stukken over te gaan, deze doen onderzoeken door een door het bestuur aan te wijzen deskundige. Deze brengt alsdan omtrent zijn onderzoek verslag uit.
5. De balans en de staat van baten en lasten, met bijbehorende toelichting, worden door het bestuur vastgesteld.
6. Het bestuur is verplicht de in de leden 2 en 3 bedoelde boeken, bescheiden en andere gegevensdragers gedurende zeven jaren te bewaren.

STATUTENWIJZIGING, FUSIE, SPLITSING

Artikel 10.

1. Het bestuur is bevoegd deze statuten te wijzigen en tot fusie en splitsing te besluiten. Het besluit daartoe moet worden genomen met een meerderheid van ten minste tweederden van de uitgebrachte stemmen in een vergadering, waarin alle

bestuurders aanwezig of vertegenwoordigd zijn. Is een vergadering, waarin een dergelijk besluit aan de orde is, niet voltallig, dan wordt een tweede vergadering bijeengeroepen, te houden niet eerder dan twee en niet later dan vier weken na de eerste vergadering. In deze tweede vergadering kan ongeacht het aantal aanwezige of vertegenwoordigde bestuurders rechtsgeldig omtrent het voorstel, zoals dit in de eerste vergadering aan de orde was, worden besloten, mits met een meerderheid van ten minste twee derden van de uitgebrachte stemmen.

2. Bij de oproeping tot de vergadering, waarin een statutenwijziging zal worden voorgesteld, dient een afschrift van het voorstel, waarin de voorgedragen wijziging woordelijk is opgenomen, te worden gevoegd.
3. De statutenwijziging treedt eerst in werking nadat daarvan een notariële akte is opgemaakt. Iedere bestuurder is afzonderlijk bevoegd gemelde notariële akte te verlijden.

ONTBINDING

Artikel 11.

1. Het bestuur is bevoegd de stichting te ontbinden.
2. Op het besluit van het bestuur tot ontbinding is het bepaalde in het vorige artikel van overeenkomstige toepassing.
3. De stichting blijft na ontbinding voortbestaan voor zover dit tot vereffening van haar vermogen nodig is. In stukken en aankondigingen die van haar uitgaan, moet aan haar naam worden toegevoegd: in liquidatie.
   De vereffening eindigt op het tijdstip waarop aan de vereffenaars geen baten meer bekend zijn.
4. De bestuurders zijn de vereffenaars van het vermogen van de stichting. Op hen blijven de bepalingen omtrent de benoeming, de schorsing en het ontslag van bestuurders van toepassing. De overige statutaire bepalingen blijven eveneens voor zo veel mogelijk van kracht tijdens de vereffening.
5. Een eventueel batig saldo van de ontbonden stichting wordt voor een door het bestuur te bepalen algemeen nut beogende instelling met een soortgelijke doelstelling besteed of voor een buitenlandse instelling die uitsluitend of nagenoeg uitsluitend het algemeen nut beoogt en die een soortgelijke doelstelling heeft.
6. Na afloop van de vereffening blijven de boeken en bescheiden van de ontbonden stichting gedurende zeven jaar onder berusting van de door het bestuur aangewezen persoon.

SLOTBEPALING

Artikel 12.

In alle gevallen, waarin zowel de wet als deze statuten niet voorzien, beslist het bestuur.

OVERGANGSBEPALING EN EERSTE BOEKJAAR

Artikel 13.

1. In afwijking van het bepaalde in artikel 4 lid 2 worden de bestuurders voor de eerste maal bij deze akte benoemd.
2. Het eerste boekjaar van de stichting eindigt op eenendertig december tweeduizend negentien.

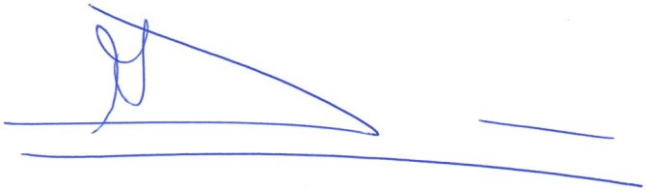
SLOTVERKLARING

Ten slotte verklaart de comparant, ter uitvoering van het bepaalde in artikel 13, dat voor de eerste maal tot bestuurders van de stichting worden benoemd:

a. de oprichter, en wel als voorzitter;
b. Neil Robert Russell, geboren op tien november negentienhonderdvierenveertig te Sydney (Australië), en wel als secretaris;
c. Lisa-Beth Harris, geboren op negen oktober negentienhonderdnegenenzestig te Californië (Verenigde Staten van Amerika), en wel als penningmeester.

SLOT ———————————————————————————————————————
De comparant is mij, notaris, bekend. ———————————————————————————————
Verder heb ik, notaris, de zakelijke inhoud van de akte meegedeeld aan de comparant en daarop een toelichting gegeven, inclusief de uit de inhoud van de akte voortvloeiende ——
gevolgen. ———————————————————————————————————————
De comparant verklaart van de inhoud van de akte te hebben kennis genomen en ————
daarmee in te stemmen. Tevens verklaart de comparant uitdrukkelijk in te stemmen met –
de beperkte voorlezing van de akte. Dadelijk na beperkte voorlezing is de akte door de —
comparant en door mij, notaris, ondertekend. De akte is verleden te Utrecht, op de datum aan het begin van deze akte vermeld.———————————————————————————
Volgt ondertekening.

UITGEGEVEN VOOR AFSCHRIFT



PIERRE ROBIN EUROPE

2021 Goals and Activities

We begin our 2021 End of Year Activity Report by first restating Stichting Pierre Robin Europe's goals:

- To promote communication and increase awareness among patients, families, healthcare providers, healthcare system administrators, lawmakers, policy advisors, patient advocacy groups, and the general public, about the rare disease, Pierre Robin Sequence, both in Europe and beyond.
- To provide in multiple languages, using various channels of communication, practical information about Pierre Robin Sequence, and Pierre Robin Sequence treatments, to parents whose babies suffer from this life-threatening illness, and to healthcare providers who are treating babies struck by this rare disease.
- To advocate for the development of a reliable Pierre Robin Sequence fetal ultrasonography screening protocol, validated with prospective clinical trials, to reduce the incidence of airway emergencies, oxygen deprivation and death in the delivery room; to furnish information to radiologists and delivery room teams on the techniques which have already been developed and are currently available to prenatally diagnose Pierre Robin Sequence.
- To provide information about various legal tools and resources which can be used by Pierre Robin Sequence patients and their families for the purpose of facilitating access to highly specialised Pierre Robin Sequence treatments which may not be available within their own state of residence. Examples of such legal tools include the EU's 2011 Cross-border Healthcare Directive, Regulation 883 on the Coordination of Social Security Systems, the fundamental principle of the freedom to provide and receive services in the EU under Article 56 of the Treaty on the Functioning of the European Union, and the established caselaw of the Court of Justice of the European Union; to engage with lawyers, academics and patients' rights organizations regarding the use of these laws, and foster their continued

development; to engage in public outreach, advocacy efforts, and possible legal action, when such laws are not respected.

- To advocate for patient centered care, and the right to access care, not only for the benefit of babies suffering from Pierre Robin Sequence, but for the benefit of all rare disease patients, wherever they may be.

What follows are the actions we have taken in 2021 in pursuit of these various goals.

On 22 February 2021, Reuters organized a special rare disease webinar called "Unlocking innovation and access for rare disease patients in Europe". Reuters described it as a "high-level policy debate that will address the future of European collaboration on rare diseases, to reimagine and transform rare disease policy through access, awareness, and innovation. We will bring together the European rare disease community to tackle this area of great unmet medical need." The event included sessions which examined important rare disease issues from various perspectives; the conversation and debate involved policy makers, innovators, academia, industry, medical professionals, and patient organizations. In advance of the event, we sent an email to several of the panelists. A Member of European Parliament, Ms. Dolors Montserrat, was one of the panelists; the message below is what we wrote to her, and to the other experts invited to speak at the event:

> From: Philippe Pakter
> Date: Fri, Feb 19, 2021
> Subject: Innovation and access to care, rare disease patients: Monday Policy Event
> To: [Member of European Parliament, Ms. Dolors Montserrat]
>
> Dear MEP Montserrat,
>
> I hope this email finds you well.
>
> On Monday you have been invited as an official participant in the "Innovation and access to care for rare disease patients in Europe" policy debate. I am a rare disease parent and patient advocate currently working on a PhD in law: "Access to healthcare in Europe: the effectiveness of EU legislation in the context of rare disease patients". Based on personal experience and doctoral research, I know that there is an ongoing and heart-rending gap – a gap between Europe's aspirations for rare disease patients, and the obstacles we continue facing when trying to access innovative, medically proven rare disease care.
>
> In December 2019 my organization sent a letter to EU Health Commissioner Stella Kyriakides drawing attention to the problems. The letter placed my own family's rare disease campaign into a broader context, explaining its significance for over 30 million rare disease patients living throughout Europe. At the end of the letter, 30 highly respected signatories added their names to express official support for this rare disease access to care campaign. The signatories: Members of European Parliament from every major political party in the EU, including John Bowis and Françoise Grossetête, who served as the 2011 Directive's Special Rapporteurs, MEP Frédérique Ries, MEP Tilly

Metz, MEP Evelyne Gebhardt, MEP Petra De Sutter, MD, and others; the Executive Directors of the two largest patient organizations in Europe, the European Patients' Forum, and Yann Le Cam at EURORDIS; Professors of EU law, human rights law, health care policy, and medical ethics, from the Sorbonne, Sciences Po, Erasmus, Oxford, New York University etc., including Prof. Scott L. Greer, Prof. Andre den Exter, Prof. Olivier De Schutter and others; as well as physicians, medical researchers and patient advocates, including Dr. Holm Graessner, Alastair Kent, Dr. Durhane Wong-Rieger, Nick Sireau, Lene Jensen... a rare disease "access to care" coalition transcending political and professional and national boundaries.

I would greatly appreciate it if you would be willing to kindly review the letter we sent to EU Health Commissioner Kyriakides, attached, and consider raising the issues involved during the policy debate. Thank you very much.

Kind regards,

Philippe Pakter
Pierre Robin Europe, chairman and attorney
Gerard Terborgstraat 51 II, 1071TL Amsterdam, The Netherlands
Member, EURORDIS, The European Organisation for Rare Diseases
Member, VSOP, Vereniging Samenwerkende Ouder-en Patiëntenorganisaties
European Reference Network ERN-Cranio, ePAG Representative

We are happy to report that during the event, the speakers did discuss the issues we raised in our letter. After the event was over, we at Stichting Pierre Robin Europe maintained contact with two of the thought leaders who participated in the conference: Mr. Dave deBronkart, popularly known as "ePatient Dave", who has written several excellent books on effective patient advocacy; and Dr. Bertalan Meskó, a thought leader in healthcare technology.

Our correspondence with Mr. deBronkart has been particularly productive. Later in the year he would review an early draft of the article we submitted to Elsevier's medical journal, "Seminars in Fetal-Neonatal Medicine", and his feedback was encouraging and insightful. Details on this medical journal article will appear later on in this Annual Report.

Another important rare disease event which Stichting Pierre Robin Europe participated in took place in February 2021: the "Rare2030 Foresight in Rare Disease Policy project" conference. An engaging series of presentations was held under the title "The Future of Rare Diseases Starts Today: Recommendations from the Rare 2030 Foresight Study". High level speakers included MEP Frédérique Ries, and MEP Cristian Bușoi (Members of European Parliament); the EU Health Commissioner, Stella Kyriakides; Olivier Véran, from the French Ministry of Health; Terkel Andersen, of EURORDIS; Maroš Šefčovič, the Vice-President of the European Commission; Yann LeCam of EURORDIS; Ana Rath, the famous and incomparable force behind Orphanet; and other high-profile figures from the international rare disease movement.

In March, Rare Diseases International (RDI) organized an event describing their vision for a UN Resolution on rare diseases. During this event, "Calling for a UN Resolution on Persons

Living with a Rare Disease and their Families", RDI explained the importance of a UN resolution, and why the time for a UN resolution on rare diseases has finally come:

> RDI, EURORDIS, and the NGO Committee for Rare Diseases have joined forces to advocate towards the UN General Assembly to adopt a Resolution to Address the Challenges of PLWRD [Persons Living with a Rare Disease] and their Families. RDI has led the elaboration of a draft document for the Resolution co-authored with rare disease patient organisations around the world. The overarching goal of the UN Resolution is to permanently and firmly position PLWRD as a priority population in need of global and national policies and rare diseases as a Human Rights issue. Over the last decade, great advances have been made towards greater recognition of the needs of the rare disease community including the inclusion of rare diseases in the UN Political Declaration on Universal Health Coverage, in September 2019. However, the journey towards full inclusion and recognition is long, and much still needs to be done. The vast majority of countries do not have national strategies and frameworks to address the challenges faced by persons and families living with a rare disease. Rare diseases are often absent and ignored by public policies, which exacerbates the dearth of research and expertise, and ultimately fosters social exclusion and discrimination. Rare diseases have an impact on multiple aspects on persons' lives throughout a lifetime. Diseases are often chronic, complex, heavily debilitating and life threatening, and PLWRD confront a lack of public awareness as well as the consequences of scarcity of expertise and knowledge on rare diseases. This exposes the rare disease community to greater social, health and economic vulnerability.

This March RDI event on a proposed UN Resolution made it clear that the rare disease movement is becoming more internationally visible. At the same time, we still have a long way to go. For example: on 23 September 2019, UN Member States adopted a political declaration on universal health coverage (UHC) which mentioned rare diseases. From RDI's point of view, this represented major progress; during this March event, RDI stated that "This [the 2019 UN political declaration on UHC] marks a hugely significant milestone for the rare disease community, with rare diseases being included for the first time within a UN declaration adopted by all 193 Member States." However, during a panel discussion, we submitted a comment pointing out that the UN's 2019 political declaration on universal health coverage actually placed very little emphasis on the international rare disease community:

> Stichting Pierre Robin Europe's Philippe Pakter wrote:
> In the 2019 UN political declaration on universal health coverage, the UN squeezed us in – "rare diseases" – in paragraph 34. That is, after "oral health", and just before "road traffic accidents". That reflects the importance this world places on us, rare disease patients and our families. RDI, you are doing a heroic job trying to bring out the best in a tragically insensitive world. Durhane, Yann, Anders, your colleagues – thank you for your hard work, for your idealism, and for never giving up on us. I hope you achieve the UN Resolution. Philippe in Geneva, Lysiane's father.

In response, the CEO of EURORDIS, Yann Le Cam – who is one the most dedicated champions of rare disease patients in the entire world – wrote back:

Yann wrote:
Agreed Philippe. This is only the beginning of a long journey.

Perhaps the lesson in all this is that social change takes time and patience.

The European Patients' Forum (EPF) is Europe's main umbrella organization for European patients in general – not just for rare disease patients, but for all European patients. In 2021, the European Patients' Forum – the EPF – organized a "Patient Advocates' Seminar". There was a competitive process to gain admission into this program. In our application to enter the program, Stichting Pierre Robin Europe made it clear that in accordance with our organization's mandate, we had a specific interest in access to care for rare disease patients. We wrote the following:

> *Nowhere is the logic or moral imperative for planned cross-border healthcare more obvious than it is for EU rare disease patients seeking a highly specialised treatment not available in their own Member State – and yet this is the exact same patient group which is most likely to run into obstacles to cross-border care. Based on the principle that the true measure of any society can be found in how it treats its most vulnerable members, the disproportionate harm which this ongoing illegal Member State obstruction inflicts on EU rare disease patients is unacceptable.*

After a couple of weeks of anxious waiting, we received good news from the EPF: "We are delighted to inform you that you have been accepted as a participant in Patient Advocates' Seminar 2021! Congratulations! We received almost 150 applications for only 45 spots available so well done!" This EPF course was a deep dive into EU law and politics. The classes covered the following:

Module 1: Advocacy Awareness
- Introduction to lobbying as a tool for change
- Introduction to ethics and transparency in lobbying
- Discussion of how COVID-19 has impacted the lobbying sphere at an EU and national level:
  - What are the benefits of having health as a priority issue?
  - What are the negative aspects of so much energy focused on COVID-19?
  - How has this changed access to power and agenda setting?

Module 2: How to influence EU policy
- Overview of the EU policymaking process
  - Pre-legislative
  - EP vs Council
  - Different channels of influence (ECI, etc.)
- How to create links between national-level and EU-level organizing
  - How can EU-level lobbying benefit national policy goals?

Module 3: Creating your lobbying plan

- Timing: deciding when and how to lobby for your cause
- Role of evidence and reliable data in building a compelling case
- More in-depth analysis of ethics and regulation in lobbying for patient issues
    - Special attention will be paid to forming new relationships and alliances between participants from various groups and countries

Module 4: Executing your lobbying plan (90 minutes)

- Creating a compelling case
    - How are patient organisations unique?
    - How can patient voices be leveraged in an empowering way?
    - Story telling as an effective public policy tool
- Securing and preparing meetings
    - How to "speak the language" of policymakers
    - How to communicate effectively during COVID times (virtual meetings)
- Monitoring progress
    - How to monitor progress, adapt your strategy, and keep attention on your cause

With the information and skills we acquired in this EPF course, we at Stichting Pierre Robin Europe decided upon and planned out a strategic lobbying plan. Our lobbying plan focused on three avenues: administrative action; legislative action; and judicial action. The administrative avenue of our lobbying plan envisioned action through the European Ombudsman. The legislative avenue of our lobbying plan encompassed two aspects: (a) submitting a petition through the European Parliament's Committee on Petitions; and (b) communicating to the European Commission through its Public Consultation "Feedback period" on the 2011 Cross-border Healthcare Directive in the first and second quarters of 2021. The judicial avenue of our lobbying plan involves strategic litigation. Specifically, we will litigate a pilot case in which a rare disease patient faced obstacles when trying to access a rare disease treatment in another EU Member State.

Having decided to pursue strategic litigation as a tool for lobbying, we at Stichting Pierre Robin Europe recognized the need for lawyers and law firms for support. We communicated the following message to candidate law firms:

> There are over 7,000 rare diseases that we know of; most have no approved treatment or cure. Half of the patients are children; the mortality rate is unspeakably high. Rare disease patients are in desperate need of more research, treatments, and support.
>
> EU cross-border healthcare is crucial for rare disease patients, because highly specialised treatments are often only available in distant EU Member States. Reports on the 2011 Cross-border Healthcare Directive from the EU Commission, EU Parliament, and the European Court of Auditors, indicate that the Directive is being used very little… and when EU citizens do try to use it, Member States continuing raising unjustified obstacles to get in the way. One example of this is the abuse by Member States of the prior authorisation procedure.

> According to the European Patients' Forum, the "prior authorisation seems to be by far the normal practice for rare disease patients, perhaps because in most cases the care required falls under the prior authorisation requirements." Since rare disease patients are far more likely to require prior authorisation, obstacles placed in the way of prior authorisation have a disproportionate impact on EU citizens who are already struggling with a rare disease. We seek to change this through strategic litigation.

Two international law firms agreed to provide us with legal services on a pro bono basis: one international law firm headquartered in Europe; and another international law firm headquartered in America. Both of these international law firms have lawyers and offices all around the world. These two international law firms will represent us in the judicial avenue of Stichting Pierre Robin Europe's lobbying plan, and will provide effective legal counsel whenever Stichting Pierre Robin Europe is in need of aggressive legal support.

To sum things up: this outstanding EPF course brought home for us the dramatic difference between "awareness raising" on the one hand, and "lobbying" on the other. It also demonstrated the crucial importance of lawyers and law firms, and the role lawyers and law firms play, in effective lobbying. As a result, we at Stichting Pierre Robin Europe took the necessary steps to obtain the legal support we will need for the upcoming years. This will help us as we pursue Stichting Pierre Robin Europe's fourth organizational goal, which appears in the beginning of this Annual Report, and which also appears in our organization's Articles of Incorporation:

> *To provide information about various legal tools and resources which can be used by Pierre Robin Sequence patients and their families for the purpose of facilitating access to highly specialised Pierre Robin Sequence treatments which may not be available within their own state of residence. Examples of such legal tools include the EU's 2011 Cross-border Healthcare Directive, Regulation 883 on the Coordination of Social Security Systems, the fundamental principle of the freedom to provide and receive services in the EU under Article 56 of the Treaty on the Functioning of the European Union, and the established caselaw of the Court of Justice of the European Union; to engage with lawyers, academics and patients' rights organizations regarding the use of these laws, and foster their continued development; to engage in public outreach, advocacy efforts, and possible legal action, when such laws are not respected.*

The EPF's 2021 Patients' Advocacy Seminar took Stichting Pierre Robin Europe a big step forward as a rare disease patient advocacy organization.

On 12-14 May 2021, EURORDIS held an organization-wide Membership Meeting. Due to COVID-19, the meeting, presentations and workshops were all organized virtually. The theme of this online conference was the future. Mr. Yann Le Cam, CEO of EURORDIS, wrote the following:

> It is time to reset Europe's rare disease focus for the next decade: we need a policy framework in Europe adapted to today's realities, to embed excellence and bring policies in line with new technologies, values and infrastructures. Europe's efforts since 2009 have shown how much progress can be made when national plans and strategies

for rare diseases are coordinated across countries and integrated at EU level. We cannot lose momentum now: the Rare 2030 recommendations set the direction we need to go.

Workshops and discussions were held on a number of themes, including the following: innovative strategies and initiatives for advocating on a specific issue; advocating at a national level; advocating on an EU level; and shaping the next 10 years of rare disease policies as part of Europe's Action Plan for Rare Diseases.

In June 2021, Stichting Pierre Robin Europe participated in two General Assembly meetings, from two separate rare disease patient umbrella organizations: the Dutch rare disease umbrella group, Vereniging Samenwerkende Ouder-en Patiëntenorganisaties (VSOP); and the European rare disease umbrella group, EURORDIS. For the most part we listened and learned about new developments in these organizations. During the EURORDIS General Assembly meeting however we brought up Stichting Pierre Robin Europe's plan to engage in strategic litigation:

> From Philippe Pakter to Everyone:
> In the USA, the African-American woman, Ms. Rosa Parks, refused to give up her seat and walk to the back of the bus. She took her case to court; "strategic litigation". The Rosa Parks lawsuit created momentum and led to progress which went way, way beyond public transportation. I believe EURORDIS should take infringements of our rights, our rights as rare disease patients, our rights as European citizens, our rights as human beings, to court. No more walking to the back of the bus. Strategic litigation. Example: many of us rare disease patients want improved access to care... and yet in our struggle to access highly specialised rare disease treatments, we continue facing obstacles, in spite of EU law:
> https://pierrerobineurope.com/kyriakides
> EURORDIS, please let us know what you think. Philippe Pakter, Stichting Pierre Robin Europe, the Netherlands.
>
> From Yann LE CAM to Everyone:
> Yes, Philippe, let's explore that. Thank you very much. We will follow up with you.

We found this response from the CEO of EURORDIS to be encouraging.

On 7 June 2021 EURORDIS organized a webinar on the evaluation of the EU's 2011 Cross-border Healthcare Directive. In advance of the webinar, EURORDIS shared with us, the webinar participants, a message which EURORDIS was drafting to the European Commission on the 2011 Cross-border Healthcare Directive:

> Going forward, the EU needs a more innovative and ambitious approach to meet the needs of the RD patient population. The right to cross-border healthcare will remain an empty promise for rare disease patients as long as there is no further EU action to fully define the cross-border healthcare services, regardless of the delivery channel, and ensure timely access for all RD patients living in the EU.
> …

> Evidence shows that healthcare outcomes improve with increasing experience of the clinicians, in other words volume significantly increases quality for most procedures/conditions. In practice this means that any patient living in the EU with a disease that affects fewer than 500 people across the EU, as well as patients that require complex services where fewer than 500 procedures are undertaken each year across the EU, should be treated in a few centres recognised as 'rare disease lighthouses' that maintain a volume high enough to maintain excellent outcomes. It also means that MS that lack the minimum volume standard required to develop competent and safe services (typically 70-110 cases per year) should have a mechanism to aggregate demand for joint procurement It is clear that scarcity of expertise and low volume of cases call for more innovative and ambitious EU-wide approach to meet the needs of the rare disease patient population.

We at Stichting Pierre Robin Europe greatly appreciate it when a respected international rare disease group like EURORDIS makes an important public statement like the one above. In this statement EURORDIS is addressing the same facts and issues which we at Stichting Pierre Robin Europe consider to be so important, and which form the basis for much of our action as an organization. What it comes down to is this: for patients suffering from a complex rare disease, a rare disease Center of Expertise with high patient volume offers the most promising chance of obtaining the best possible outcomes. For rare disease patients, patient volume is absolutely critical.

Also, for rare disease patients, cross-border healthcare is absolutely critical. Since each rare disease only affects a relatively small number of patients, and since those patients are spread out over large areas, a rare disease patient may have to travel across one or more national borders in order to reach a high-volume Center of Expertise specializing in their particular condition. This explains why cross-border healthcare is so crucial for rare disease patients; rare disease patients have to rely on cross-border healthcare in a way that other patients do not.

During this 7 June 2021 EURORDIS webinar on the evaluation of the EU's 2011 Cross-border Healthcare Directive, Stichting Pierre Robin Europe posted the following comment. Our comment concerned one of the enduring obstacles to cross-border healthcare, lack of a referral.

> Regarding referrals: a rare disease patient in the EU seeking a highly specialised rare disease treatment only available in another EU Member State must essentially ask his or her local doctors to formally admit in writing that the medical treatment they offer is clinically inferior to the medical treatment which has been developed by competing doctors just next door in that "other" European nation. If the treatment is time sensitive, then this letter has to be obtained now, right now, not later. Based on simple human nature, pride, and based on practical considerations as well – a doctor's understandable reluctance to lose patients to other doctors – this can be a disaster waiting to happen, for an EU citizen who is already struggling with a rare disease.

This comment elicited numerous public responses and private messages from other rare disease patients who confirmed that they too have faced difficulties getting the referral they needed, from local doctors, in order to access a rare disease treatment in another EU Member State.

Indeed, in an official report published by EURORDIS calling for a mature ERN system, EURORDIS pointed out that "lack of referral" is one of the greatest barriers which rare disease patients face when we try to access care:
http://download2.eurordis.org/documents/pdf/EURORDIS_vision_on_mature_ERNs_FINAL.pdf
A referral could take the form of a direct introduction to an appropriate rare disease expert. This would make sense if the rare disease patient did not know who to turn to for help, but the patient's general practitioner did know, and decided to help the patient along by sending the patient directly to that expert. A referral could also take the form of a letter from a local physician to a third party. For example, a local physician might address a letter to the patient's national healthcare fund, recommending that the healthcare fund authorize the patient to undergo a highly specialized rare disease treatment which is only available at a certain rare disease Center of Expertise. Without this referral letter, an application for prior authorisation is almost certain to be refused. As pointed out by EURORDIS, and as discussed during this 2011 Cross-border Healthcare Directive webinar, "lack of referral" can be a major obstacle for a rare disease patient who is trying to access safe and medically proven rare disease care.

On 7 July 2021, Rare Diseases International hosted a High-Level Side Event at the United Nations High-Level Political Forum on Sustainable Development. This UN event was co-hosted by Spain, Brazil and Qatar – the Core Group of Member States promoting the call for a UN Resolution on Addressing the Challenges of Persons Living with a Rare Disease and their Families. Also involved in this July event was the NGO Committee for Rare Diseases, Rare Diseases International, and EURORDIS.

One of the main figures behind Rare Diseases International is Dr. Durhane Wong-Rieger; in order to explain the importance of a UN Resolution on rare diseases, Dr. Wong-Rieger write the following:

> The more than 300 million persons living with one of over 6000 identified rare diseases – often chronic, complex, heavily disabling and life threatening – deserve recognition and visibility within the UN's agenda towards inclusive sustainable development. This has been recognised by a number of UN Member States and agencies and bodies (WHO, UNICEF, UNDP, ECOSOC) at the two High Level Events of the NGO Committee for Rare Diseases. First in 2016, at the 'Global Gathering for Rare Diseases' and then in 2019 at the Second High Level Event organised to mark the occasion of Rare Disease Day and co-hosted by 15 Member States.
>
> Indeed, living with a rare disease has an impact on all aspects of a person's life, including the social, economic, health, educational and employment dimensions. This means that the issue is not only a sustainable development and equity priority, but it also represents a human rights priority. In fact, the 2018 Report of the Special Rapporteur on the rights of persons with disabilities to 73rd Session of the UNGA Member States were encouraged to consider developing and implementing policies and practices targeting the most marginalized groups of persons with disabilities such as persons living with a rare disease. And the 2019 Report of the United Nations High Commissioner for Human Rights to the session of the ECOSOC recognised the need to

> protect the rights of persons living with rare diseases as a particularly vulnerable population.
>
> The side-event to the High Level Political Forum 2021 has the objective to showcase how addressing the challenges of persons living with a rare disease, recognising their rights, needs and priorities, as well as promoting their active participation, and harnessing the opportunities for their inclusion in society is essential to the realisation of the 2030 Agenda and to the sustainable recovery from the COVID-19 pandemic. The rare disease civil society community (represented by the NGO Committee for Rare Diseases, Rare Diseases International and EURORDIS-Rare Diseases Europe) with the support of a number of UN Member States including Spain, Brazil and the State of Qatar, proposes to discuss, at the event, the adoption of a UN General Assembly Resolution that can act as a catalyst and provide a constructive and consensual intergovernmental vision on the issue.

Sometimes it can be difficult to recognize the link between what we as a rare disease patient advocacy organization do, and policy work at the UN level – for instance, the campaign to pass a UN resolution on rare diseases. However when Dr. Wong-Rieger and her colleagues in Rare Diseases International present the basis for this type of high-level UN action, the connection becomes more clear. When a high-level political instrument exists alongside grass roots action, then both become more meaningful and effective.

On 7 September 2021 Reuters organized an event titled "Treatment without borders: the EU case for equitable patient access to advanced therapies". The intersection between highly specialized rare disease treatments, and EU cross-border healthcare, made the event particularly important for Stichting Pierre Robin Europe. Reuters introduced the event as follows:

> The EU Pharmaceutical Strategy is looking to improve patients' access to therapies for challenging and rare conditions. The EU legislation on cross-border healthcare is an important instrument to ensure patient access to the best available care. There is urgent need to revise this legislation to enable EU patients to access novel advanced therapies and medicines for rare diseases when these are not available in their home country. EuropaBio's Advanced Therapies Series continues with a virtual discussion on avenues for enhancing the access of EU patients to novel biotechnology-derived treatments. A panel of EU, national and industry representatives will attempt to put forward solutions for securing equitable access to both specialised centres and to treatment for all EU patients in need.

Presentations were made by a number of internationally respected experts, including Jana Popova, Executive Committee Member of the European Alliance of Neuromuscular Disorders Associations & EUPATI Patient Engagement Training Coordinator; Martin Dorazil, Deputy Head of Unit Digital Health, DG Health, European Commission; Irina Grossenbacher, Region Europe Patient Access Director at Novartis Rare Diseases; Brieuc Van Damme, Director General, RIZIV/INAMI, the National Institute for Health and Disability Insurance; Tomislav

Sokol, Member of European Parliament; and Dirk Vander Mijnsbrugge, Vice President, Medical Affairs Lead, Rare Diseases International Developed Markets, Pfizer.

During the event, Stichting Pierre Robin Europe actively posted questions and shared comments with the panel, including the following.

> Let us imagine a young child in Bulgaria suffering from a life-threatening rare disease. An advanced gene therapy is available in Germany. However in Bulgaria, the Bulgarian social security fund's basket of healthcare benefits does not include gene therapy as a covered medical treatment. Regardless of Regulation 883... regardless of the 2011 Directive... and regardless of the ERN system... this Bulgarian child is stuck – unless he/she is rich, and can afford to pay for the advanced gene therapy in Germany out of pocket. Panelists: can you please provide an honest and workable solution to this problem?

For this question there are no easy answers – and the panelists admitted it. Indeed the opening keynote presentation for this event posed the following core question: "Is EU cross-border access to advanced treatments a reality, or a goal for the future?" The unfortunate truth is that for now, EU cross-border access to advanced treatments remains a goal for the future.

Later on in the event, a Member of European Parliament gave a presentation which addressed the issue of equitable access to advanced treatments in a cross-border context. Stichting Pierre Robin Europe is familiar with this particular MEP, so we decided to present him with a challenging question.

> Most European citizens view cross-border healthcare as an opportunity, particularly EU citizens who suffer from a rare disease. Others see it as a potential threat: "To protect the stability of social security systems, especially those less technically modern and not financially strong, it is essential to give, by means of EU legislation, freedom to Member States to clearly define treatments which will not be covered, even if they are more effective than the treatments available on their own territory." This particular EU healthcare expert believes that Member States should have the right to obstruct patients from accessing cross-border healthcare, even if the treatment they seek abroad is more effective than the treatment which is available at home. In practice, if an effective treatment has been developed, in the EU, for a rare disease – but the treatment is expensive – then new Member States should have the right, under EU law, to cut the patient loose – including that Bulgarian child suffering from a life-threatening rare disease. The expert in question is our panelist today, MEP Tomislav Sokol. Could you kindly comment MEP Sokol?

There was no response from the Member of European Parliament, MEP Sokol. However the point of our intervention was to get both the panelists and the attendees to reflect upon and discuss these important matters. These questions have a strong bearing on us rare disease patients, and they will continue to have a strong bearing on us for years to come.

In September 2021 Stichting Pierre Robin Europe was invited to deliver a presentation as part of a medical symposium coordinated by the Amsterdam University Medical Center. The opportunity emerged in the following way. Professor Dr. Corstiaan Breugem is an internationally recognized Pierre Robin Sequence expert. In the past, Dr. Breugem has provided Stichting Pierre Robin Europe with invaluable support when we as an organization produced an information document for Pierre Robin Sequence parents. In the winter of 2021, Dr. Breugem was scheduled to give an inaugural lecture as a newly appointed full Professor in Plastic and Reconstructive Surgery at the University of Amsterdam. The subject of his inaugural lecture was "Crossing borders to improve treatment in Plastic Surgery". The September symposium, which we were invited to participate in, preceded his inaugural lecture, and focused on the same topic: crossing borders to improve care. Dr. Breugem asked Stichting Pierre Robin Europe to deliver a presentation with the title, "Legal aspects of helping children in different countries in Europe". We worked very hard on the presentation, and the presentation was well received by the clinicians who attended the symposium. Our presentation was recorded and can be viewed on YouTube: https://youtu.be/aKrW9F9wT-E

Amsterdam UMC
University Medical Center

Stichting INTERPLAST HOLLAND

Amsterdam UMC Department of Plastic Surgery, & Interplast Holland
Symposium, 30 September 2021

Crossing Borders to Improve Global Treatment in Plastic Surgery

Presentation:
Legal Aspects of Helping Children in Different Countries in Europe
Philippe Pakter, chairman, Pierre Robin Europe; PhD student, law

In 2021 we learned of an educational/training opportunity offered by EURORDIS to patient organizations in the international rare disease patient community: the "EURORDIS Leadership School 2021". We applied to join the program and we were happy to learn that we were accepted. The EURORDIS Leadership School 2021 course ran for several months, from mid-summer through the end of November 2021. The webinars included:

- 360 Degree Self-awareness & Emotional Leadership
- Maximising your communication & impact
- Conflict Resolution
- Negotiation
- Reflection session (to help us integrate what we have learned)

Training topics included:

- Power and Influence
- Insightful Influencing
- Physiology of Status and Authority
- Psychology of Status and Authority
- Applying a framework to difficult situations
- Emotionality of Status and Authority
- Relational Dynamics
- Practising Influencing Presenting with impact
- Working on Speeches: Emotions & Characters
- How to give & receive feedback
- Presentation of speeches and feedback
- Awareness exercise
- Review of selected speeches & presentation in plenary

It is remarkable that such a high-quality course happens to be accessible to rare disease patient advocates, free of charge, allowing rare disease patient organizations to acquire new skills and increase their impact in the rare disease movement.

In October 2021 a rare disease patient organization we have been connected with for years, the Cambridge Rare Disease Network, contacted Stichting Pierre Robin Europe and informed us about an opportunity which was being offered by Costello Medical Consulting Limited:

> Founded in 2008, Costello Medical provides scientific support to the healthcare industry in the analysis, interpretation and communication of clinical and health economic data. Alongside supporting pharmaceutical and MedTech companies, we provide our services and offer support to non-profit organisations on a pro bono basis. This year Costello Medical is pleased to be running a programme for eight patient organisations and charities that support rare disease patients and families. This programme will help organisations that want to learn how to develop materials to communicate with patients, funders, clinicians and other stakeholders in the rare disease community.

We immediately applied to join this training program, and we were happy to learn that we had been accepted. The program was led by communications experts who have experience working with rare disease patient advocates, and who are experts at effective communication and content promotion. The Costello Medical "Patient Group Skills Programme" was another one of the valuable educational programs we at Stichting Pierre Robin Europe benefitted from this year, alongside other educational programs we completed in 2021 – the program organized by the European Patients' Forum, and the program organized by EURORDIS, as discussed above.

Another exciting event for Stichting Pierre Robin Europe in 2021 was that the highly respected Elsevier medical journal, "Seminars in Fetal-Neonatal Medicine", decided to devote a full edition of their journal to Pierre Robin Sequence. All 15 articles in their December 2021 edition

(volume 26, issue 6, 101288) would focus on this one rare disease. The editors presented Stichting Pierre Robin Europe with an unexpected honor; they formally invited Stichting Pierre Robin Europe to contribute an article with the title: "A parent's view on the care of their baby with Robin Sequence". We saw this as a promising opportunity to bring visibility to the interests and concerns of Pierre Robin Sequence patients – which is necessary for providing patient centered care – which in turn contributes to better patient outcomes. We shared a draft of the paper with a physician we know and with whom we have collaborated in the past: Professor Dr. Peter A. Mossey. Dr. Mossey is a Professor and Personal Chair of Craniofacial Development & Dentofacial Orthopaeds at the University of Dundee; he is the Associate Dean for Research; and he is the Director of the WHO Collaborating Centre for Craniofacial Anomalies and Technology Transfer. Dr. Mossey wrote the following about our draft paper:

> Thanks, Philippe – this is tremendous and it emphasises the need or should I say absolute imperative that we obtain and heed the patient / parent perspective in the approach to rare diseases. This certainly provides aspects that we do not read about in the textbooks.

We received positive feedback on our draft article from other physicians and patient advocates as well.

After submitting our final draft to Elsevier, we received an encouraging response from Elsevier's CEO, Ms. Kumsal Bayazit. Ms. Bayazit was so impressed with the quality of our article that she personally waived the $4,100 Gold Open Access fee which Elsevier normally charges for Open Access in this particular medical journal. Ms. Bayazit emailed us the following message:

> I am so very grateful you took the time and made the effort to write the paper from a rare disease patient and parent perspective. As you state it is critical that the vantage points and experiences of patients and parents are included in the literature to improve care and treatment… My very best wishes to Lysiane and if I can be of any further assistance, please feel free to reach out to me.
>
> Best regards,
>
> Kumsal
>
> Kumsal Bayazit
> Chief Executive Officer
> Elsevier

At Stichting Pierre Robin Europe we believe that this rare disease patient perspective article reflects well on the rare disease patient movement, and demonstrates the high quality work which we as rare disease patient advocates can contribute to rare disease research. What follows is a copy of the article, which contains, in the Acknowledgments section, a special thank you to Elsevier's CEO, Ms. Kumsal Bayazit:

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A parent's view on the care of their baby with Robin sequence

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ABSTRACT

A Robin sequence parent presents the view that Robin sequence healthcare providers are engaging in practices which may be outdated, excessively invasive, and unnecessarily detrimental to quality of life, and proposes possible areas of research to improve patient outcomes.

1. Introduction

I am the parent of a child named Lysiane who was born in France in 2017 and diagnosed with Robin sequence (RS). I am the chairman of Pierre Robin Europe, an RS patient advocacy organization based in the Netherlands. I am currently earning a PhD in cross-border healthcare law at the University of Geneva.

In this article I will present thoughts and suggestions concerning RS care, based upon my own experience as an RS parent. I will then conclude with five general recommendations, which may be applied more broadly to all rare disease care.

RS is a rare disease affecting approximately 1 in 10 000 babies. It is characterized by micrognathia, glossoptosis, and Upper Airway Obstruction (UAO). RS presents two main symptoms, of varying severity: UAO, and feeding difficulties. Treatment options include both non-surgical and surgical techniques.

1.1. Prenatal diagnosis and counseling

A prenatal diagnosis of RS can reduce trauma, improve care, and save lives; however the prenatal warning signs of RS are sometimes missed. Prenatal ultrasound (US) images showed that my daughter had severe micrognathia; this went unnoticed by the US team. The US team did however make note of polyhydramnios, over multiple screening sessions. Micrognathia and polyhydramnios are known potential warning signs of RS – but no RS flags were raised. This was at a tertiary care hospital in a major European city. Based on my ongoing contact with hundreds of other RS parents across Europe and America, this situation is not uncommon, and suggests that we need better criteria on how RS can be identified during prenatal US.

As a parent I am greatly encouraged by the promising research which is being carried out to improve the prenatal diagnosis of RS [1]. An early diagnosis of any disease benefits healthcare providers, patients and families in multiple ways. Also, many RS babies suffer from one or more associated conditions; a red flag for RS would alert clinicians of the need to vigilantly search for these associated conditions. Finally, the mandible is "a common site for defects associated with genetic conditions, a good number of which can be recognized prenatally" [2]. Additional time invested in studying the mandible, for instance by measuring the inferior facial angle, would not only yield potential warning signs of RS, and by extension various conditions commonly associated with RS; it would also help raise red flags about numerous other potential problems wholly unrelated to RS.

Anatomy does not correlate very well with severity when it comes to RS symptoms; a baby with moderate micrognathia can suffer from severe UAO, and vice-versa. However in carrying out prenatal screening for RS, the goal is not to predict severity; the goal is simply to identify a high risk that the baby will be born with RS. In such cases clinicians can advise the mother to give birth in an RS Center of Expertise, at a hospital offering tertiary level or comprehensive care, rather than at home.

Improving our ability to prenatally diagnose RS is one challenge, but what happens next? What type of counseling should be provided, who should provide it, and what form should it take? In a retrospective analysis of 1530 Dutch babies born with a cleft, the infant mortality rate of RS babies was found to be eight times higher than the infant mortality rate of the general Dutch population [3]. Stark figures like these are likely to horrify the average parent or parent-to-be, but making things even more complicated is RS's dramatic heterogeneity. RS babies with certain associated conditions will face even higher infant mortality rates, while RS babies with isolated RS will face lower infant mortality rates. What kind of RS counseling is appropriate in the face of such great uncertainty? Further research to develop RS counseling practices, in partnership with the RS patient community, could help to improve patient outcomes.

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Abbreviations

AHI	Apnoea Hypopnoea Index
CPAP	Continuous Positive Airway Pressure
ICU	Intensive Care Unit
MDO	Mandibular Distraction Osteogenesis
OA	Obstructive Apnoea
RS	Robin sequence
SIDS	Sudden Infant Death Syndrome
TLA	Tongue Lip Adhesion
TPP	Tübingen Palatal Plate
UAO	Upper Airway Obstruction
US	Ultrasound

1.2. Postnatal treatment: conventional cleft care versus RS care

Several years ago an international consensus was reached concerning the diagnostic criteria for RS – micrognathia, glossoptosis, and UAO; while most RS babies are born with a cleft palate, a cleft is not required for an RS diagnosis [4]. From my perspective as an RS parent, it seems logical to omit the cleft as a diagnostic criterion; below I will explain why.

In the Intensive Care Unit (ICU) our daughter was desaturating on a regular basis. The flashing red light, the urgent beeping sound, the doctors and nurses rushing over to silence the terrifying electronic alarms, our knowledge that repeated instances of oxygen desaturation cause brain damage – this was our day to day experience when we visited Lysiane in the ICU. In addition to her breathing difficulties, Lysiane was unable to drink sufficient quantities of milk; in the ICU she never once drank even 20 ml of milk in a single feeding, in spite of the fact that a specialist was doing her best to help her along. Lysiane required machines to meet two of her most basic needs, respiration and nutrition. Her cleft palate, which we knew had to be closed at or around the end of her first year of life, was low on our list of concerns.

While the RS baby's cleft may be a part of the sequence, a possible result of the RS baby's tongue position during the prenatal period, the cleft's importance in the context of actual RS care seems limited. The functional difficulties these babies face, the breathing difficulties and the feeding difficulties, are not primarily a result of the cleft palate; the functional difficulties are more closely associated with glossoptosis and in some cases neurological problems. These are not issues which physicians typically have to address in the context of conventional cleft care, and indeed the breathing and feeding difficulties which we associate with RS can exist even if the baby has no cleft at all. Another characteristic of RS treatment which sets it apart from conventional cleft care is that among RS babies there is a pronounced risk of associated conditions, which can greatly exacerbate the RS baby's immediate health problems and long term prospects. Taking all of this into account, it seems to make sense that a cleft palate is no longer required as an RS diagnostic criterion.

2. RS care

2.1. The RS baby's need for multidisciplinary care

An RS baby is not a baby with a cleft who happens to have a small chin; an RS baby is a baby with a complex rare disease who happens to have a cleft. Some RS parents do not understand this, or have a hard time accepting it. It is important however that healthcare providers get this message across. Not only is RS rare, and complex, but the dizzying number of conditions which commonly arise in association with RS make it even more complicated and challenging [5]. Through a basic understanding of the complexity of this rare disease, parents may better appreciate the importance of the full multidisciplinary team of experts which RS care requires. Healthcare providers may consider actively engaging RS parents by explaining the role which each expert will play in their baby's ongoing care.

The RS baby's feeding difficulties can result not only in a failure to thrive; the feeding difficulties can also be profoundly demoralizing for RS parents. Since the RS baby's feeding problems are not the same as those of a baby with a conventional cleft, the RS baby's multidisciplinary team should include highly specialized nurses and speech therapists who have worked specifically with RS babies.

For parents, the RS baby's feeding difficulties can be demoralizing; the breathing difficulties, terrifying. To treat the RS baby's UAO, options include both non-surgical and surgical techniques. I will discuss some of these treatments below, from the RS parents' perspective.

2.2. Prone sleeping

Prone sleeping was proposed for RS babies in the early 1900s, half a century before the term Sudden Infant Death Syndrome (SIDS) was ever mentioned in the medical literature. Today prone sleeping is condemned by healthcare providers throughout the entire modern world. This sets the stage for an enduring tension in RS care.

Every time we visited our hospital's maternity ward for prenatal care, we saw a large poster in the waiting room reminding us: *"Couché sur le ventre, votre bébé court un risque mortel. Ne faites pas cette erreur. Couchez toujours votre bébé sur le dos"* (in English: "A baby sleeping on her stomach runs a mortal risk. Do not make this mistake. Your baby should always sleep on her back"). After our daughter Lysiane was diagnosed with RS, however, our physicians told us that stomach sleeping was suitable. As parents we were torn. Prone sleeping increases a baby's risk of SIDS by a factor of five, ten, and possibly more [6]. As RS parents we kept asking ourselves, "if Lysiane's UAO poses an even greater threat than SIDS, *un risque mortel*, then shouldn't her healthcare providers be providing her with some kind of a healthcare treatment?" It seemed to us that with prone sleeping, Lysiane's physicians were asking us to swap one known danger for another – to resign ourselves and our newborn baby to the lesser of two evils.

In 2019 I attended an RS Symposium at the European Cleft Palate Craniofacial Association's International Congress. During a period of open discussion between clinicians, one of the physicians insisted that if it were her own baby, she would not place the baby to sleep in the prone position; she therefore refused to recommend this practice to RS parents. I suddenly realized that as RS parents, our serious concerns about prone sleeping had not been unreasonable; the tension between this century old "prone sleeping for RS babies" protocol, and current medical knowledge, is very, very real.

Medical studies which looked at "side sleeping" ("lateral sleeping") found that it too significantly increased the risk of SIDS [7]. Babies move when they sleep, and when placed on their sides, fall easily into the prone position; exhausted parents cannot stay up all night watching them. Given the notoriety of prone sleeping, the term "side sleeping" may serve to some extent as a polite euphemism for prone sleeping; in practice however this may be a distinction without a difference.

If there were a convincing body of RS medical research demonstrating, with polysomnography, that the clinical benefits of prone sleeping significantly outweighed the risks, then this entire analysis would be different. But the evidence-based research on prone sleeping for RS babies is scarce [8]. Based on its known risks, prone sleeping cannot properly be described as "conservative"; based on its questionable benefits, it may be ambitious to call it a "treatment".

Years ago the American Academy of Pediatrics, which strongly advises parents to always place babies to sleep on their backs, warned Fisher-Price about the design of its "Rock 'n Play Sleeper". The reason: this sleeper was designed in such a way that made it easy for a baby to roll over onto her stomach and fall asleep, in the prone position. Fisher-Price sold the product anyway, all over America, and in Europe as well –

and a number of babies did indeed die in these sleepers. Eventually Fisher-Price issued an international recall of over 4.7 million units, at tremendous cost [9]. Here however, in the context of RS care, healthcare providers are actually *recommending* prone sleeping – at home, without a pulse oximeter, and without any parental training in cardiopulmonary resuscitation. Can this century-old "prone sleeping for RS babies" protocol be reconciled with 21st century medical knowledge? This question seems to call for both evidence-based research, and careful reflection.

2.3. Mechanical ventilation assistance

In the COVID-19 era many non-healthcare practitioners have gained at least some passing familiarity with Continuous Positive Airway Pressure (CPAP) and other forms of mechanical ventilation assistance. In CPAP we see a desperate attempt to maintain life, in the absence of any readily available treatment or cure. No COVID-19 patient wants to be hooked up to a breathing machine, but the patient accepts the burden of care – the ongoing hospitalisation, the substantially reduced mobility, the considerable sacrifice in quality of life – because the patient, who wants to live, has no other choice. Most COVID-19 patients receiving CPAP ventilation assistance have indeed lived life to some extent, up to adulthood, and many into their senior years. For RS babies on the other hand life is just beginning; CPAP's burden of care is particularly painful for the entire RS family.

In addition to its considerable burden of care and reduced quality of life, CPAP has also been shown to create a significant risk of causing facial deformities in children, due to the constant pressure which the CPAP mask exerts on the growing facial structures of the child's face. "Global facial flattening was observed in 68% of the patients and concerned the forehead (43%), malar area (38%), and maxilla (28%). One or two anatomical regions were concerned in 37% and 18% of the patients, respectively. A concave face was observed in 12% of the patients … This observational study underlines the high prevalence of facial side effects of nasal mask use in children" [10].

The known risk of facial deformities is understated in certain studies proposing CPAP for RS babies. One such study suggests that the risks are minimal, and can be constrained, based upon the relatively short treatment duration required. The authors write, "This relatively short period restricts the potential side effects of long-term noninvasive continuous positive airway pressure such as facial flattening and maxillary retrusion" [11]. To support this conclusion, this CPAP study cites another CPAP study for support [12]. However the study which is cited indicates that the mean duration of treatment was not in fact short; the treatment periods for the observed patients were all at least seven months long, and the majority of patients received ventilation assistance well beyond the one year mark [12].

Furthermore the above-mentioned study on CPAP and facial deformities underscored the fact that maxillary retrusion ("maxillary retrusion was observed in 37% of the patients") did not correlate with treatment duration at all; "In univariate and multivariate analyses only daily use (>10 h per day) was associated with maxillary retrusion" [10]. The substantial risk of maxillary retrusion was triggered not by months and months of use, but rather by daily use which exceeded 10 h per day. RS babies suffering from UAO require ventilation assistance when they sleep; babies sleep more than 10 h per day. Unless the baby is prevented from falling asleep, the risk of maxillary retrusion seems inescapable. At issue here are facial deformities, among babies who already suffer from facial deformities. "This relatively short period restricts the potential side effects of long-term noninvasive continuous positive airway pressure such as facial flattening and maxillary retrusion" [11]. Such a problematic statement should have raised serious questions during the process of peer review.

High flow nasal cannula exerts less pressure on the baby's face, but like CPAP, high flow nasal cannula calls for substantial medical equipment, and often requires long term hospitalisation. In the event that the mechanical ventilation equipment is transported into the home, major challenges remain. Even when the baby is not sleeping, the ventilation equipment must be on stand-by, because babies tend to take unscheduled daytime naps; this makes it difficult for the mother to put her baby into a baby carriage and take a quick trip to the supermarket, or take the baby for a stroll in a nearby park.

Lysiane began her life receiving mechanical ventilation assistance, so my family and I know its arduous burdens first hand. Eventually we transferred Lysiane from the French ICU to Tübingen Germany to undergo the Tübingen Palatal Plate (TPP) treatment. The TPP ended Lysiane's dependance on mechanical ventilation assistance, eliminated the need for prone sleeping, and allowed us to finally leave the hospital, and bring Lysiane home.

2.4. Surgery

The majority of RS babies are born with a cleft, so surgery for RS babies is in most cases a given. There seems however to be an increasingly strong push to subject these babies to additional surgeries, to resolve the baby's UAO. These surgeries are generally performed in the first few months, or even the first few weeks of the baby's life. How effective are these surgical procedures?

The effectiveness of Tongue Lip Adhesion (TLA) is particularly difficult to gauge. To begin with, TLA studies produce noticeably different results, depending upon which healthcare provider published the study. Furthermore studies published on TLA often present vague and subjective assessments, which can be difficult to understand. Virtually everyone agrees on the importance of practicing evidence-based medicine, using objective criteria. Virtually everyone agrees that polysomnography is the gold standard for measuring the severity of UAO. Nevertheless many TLA studies simply ignore polysomnography altogether.

Some of the more recent TLA studies do mention polysomnography, and emphasize its singular importance in the context of RS research and care. "Tongue-lip adhesion is a surgical technique proposed in the treatment of airway obstruction related to glossoptosis, but few published studies have been based on objective criteria. The purpose of this study was to evaluate the efficacy of tongue-lip adhesion, as determined by polysomnography, in children with Pierre Robin sequence … Preoperative assessment was based on nap polysomnography in the sleep laboratory when the child was stable … Follow-up polysomnography was performed an average of 1 month after tongue-lip adhesion" [13]. These explicit references to polysomnography are reassuring, and this study's conclusions make TLA appear quite promising: "The postoperative clinical assessment revealed resolution of signs of respiratory distress in 30 cases (81%)," and in the group of 37 babies who underwent the procedure, TLA "resolved obstructive sleep apnoea in 29 patients" [13].

What data did the polysomnography yield? "The apnoea-hypopnoea index (AHI) decreased in all patients. The median postoperative AHI was 27 events per hour (range: 5–65) ($P < 0.0001$)" [13].

At issue here is a surgical procedure which is being proposed for newborn babies with a rare disease. How can a median postoperative AHI of 27 events per hour support a finding that TLA "revealed resolution of signs of respiratory distress in 30 cases (81%)" and "resolved obstructive sleep apnoea in 29 patients" out of this group of 37? [13] It cannot. Serious questions should have been raised during the process of peer review.

Another study, carried out by Harvard/Boston Children's Hospital, which looked at both TLA and Mandibular Distraction Osteogenesis (MDO), and which focused on the exact same variable – pre- and postoperative AHI – indicated that TLA failed to do its job over half of the time: "Successful resolution of OA [Obstructive Apnoea] occurred in 9 patients (47%) in the TLA group and 22 patients (92%) in the MDO group" [14]. Given the inconsistent results across the various TLA studies, and the inconsistent ways in which the researchers arrived at their conclusions, it is not easy for an RS parent to have faith in this

particular procedure. An RS mother does not want to send her newborn baby into two rounds of TLA surgery, three rounds or more in the event of dehiscence, if she knows that the odds of success are at about the same level as a coin toss.

The studies on MDO tend to show a greater reliance on polysomnography than the studies on TLA. Also, MDO's success rate, based upon pre- and post-intervention AHI, appears to be higher, and also more consistent from one study to the next. However compared with TLA, MDO is a more aggressive surgical procedure; even the physicians who express enthusiasm for MDO readily admit that this invasive procedure is associated with various risks, and various unknowns, some of which are long-term.

As pointed out by the President of the International Confederation of Cleft Lip and Palate and Related Craniofacial Anomalies, Dr. Felicity Mehendale, "surgery is trauma; it is always good to remember that" (presentation at the 2019 European Cleft and Craniofacial Initiative for Equality in Care COST Action). When the surgery is performed on a newborn baby, then the surgery is not just traumatic for the patient, it is also traumatic for the parents as well. Surgery on newborn babies should only be performed when reasonably necessary. An emergency decision to carry out tracheostomy to save a baby's life stands out as a relatively straightforward call, based upon the necessity and proportionality of the intervention. The rationale for MDO is less clear, because the TPP treatment offers, in most cases, a completely viable non-surgical alternative [15]. MDO is perhaps most questionable for RS babies in the European Union; in the EU, patients have a legal right to access cross-border healthcare in another EU Member State. The parents of an RS baby in France, wishing to avoid TLA and/or MDO, have a legal right, under EU cross-border healthcare law, to travel to Germany, and receive the non-surgical TPP treatment in Tübingen.

2.5. Access to rare disease care – Lysiane's patient journey

Lysiane did not have the benefit of a prenatal diagnosis; as a result she was born in a hospital which was not an RS Center of Expertise. Every single day we would go to the ICU in order to spend time with her. When visiting hours were over we had to leave the ICU and go home without her, a difficult separation which we were forced to repeat every single evening. Lysiane remained in that French ICU for five straight weeks, receiving mechanical ventilation assistance; there was no release date in sight. The ICU became our second home. It would be difficult to adequately convey the boundless pain of that time period.

After five weeks in the ICU, we submitted an application to the French healthcare authorities requesting prior authorisation for Lysiane to receive the TPP treatment in Tübingen Germany. That is, we asked that Lysiane be transferred from her hospital in Lyon, which was not a Center of Expertise for RS, and which could offer her nothing more than to keep her in the ICU indefinitely, connected to a mechanical breathing machine – to a hospital in Tübingen, which was a Center of Expertise for RS, and which offered a highly specialized, medically proven, safe, non-surgical, cost-effective treatment for her rare disease. In our application we included a letter from the coordinator of the Tübingen RS Center of Expertise, translated to French, distinguishing the TPP from other RS treatments. We also included four internationally peer reviewed medical studies, all evidence-based (with pre- and post-intervention polysomnography data, and weight gain data), demonstrating the safety and efficacy of the TPP treatment [16,17,18,19].

France's main RS Center of Expertise in Paris, which does not offer the TPP treatment, would not support the transfer to Tübingen. Instead of providing the medical referral letter we required as part of our application, they instead issued a statement suggesting that France's treatment, CPAP, and Germany's treatment, the TPP, are equally effective.

The French healthcare authorities subsequently refused our request for prior authorisation. The basis of the refusal was that France's treatment is equally effective as Germany's treatment, echoing France's main RS Center of Expertise in Paris. My father took out a bank loan, using his home as security for the loan; we transferred Lysiane to Tübingen and paid for the TPP treatment ourselves, using the borrowed funds. The TPP did its job; it resolved Lysiane's breathing difficulties, liberated Lysiane from the breathing machine, and permitted us to finally take Lysiane home, changing her life, and changing our lives too. We documented our rare disease patient journey in meticulous detail in an open letter to the President of the French Republic Emmanuel Macron [20].

The European Commission's SOLVIT Network, after carefully analyzing Lysiane's case, formally concluded that France, in refusing Lysiane's application for the TPP treatment in Germany, violated EU cross-border healthcare law (SOLVIT Case Number 2569/17/DE). We, Lysiane's parents, are now engaged in an appeal procedure to reverse France's refusal. Our supporters and allies include Members of European Parliament from every major EU political party; the executive directors of the two largest patient organizations in Europe, the European Patients' Forum and EURORDIS; professors of EU law, human rights law, health care policy, and medical ethics, from the Sorbonne, Sciences Po, Erasmus University, Oxford, New York University, and elsewhere; a major international law firm supporting our case on a pro-bono basis; as well as physicians, medical researchers, patient organizations and patient advocates, demonstrating a consensus that crosses all political, professional and national boundaries [21].

2.6. Tübingen Palatal Plate: international uptake of the TPP treatment

RS was named after a stomatologist, Dr. Pierre Robin, who studied the condition almost a century ago. It is perhaps fitting that RS care has now been transformed by an orthodontist, Dr. Margit Bacher, who invented a safe and effective way to save these babies from their breathing difficulties, and facilitate feeding, without machines or surgery. A prospective multicenter study as well as a retrospective study analyzing longitudinal data from 307 RS babies admitted to the Tübingen University Hospital both demonstrated that the TPP not only resolves UAO, but also improves weight gain in RS babies [16,22]. In addition to its safety and efficacy, the TPP comes with a relatively low burden of care, and improved quality of life: limited hospitalisation, unrestricted mobility, no cumbersome equipment, and no surgery. Babies from around Europe and Russia and even America have been transferred to Tübingen to benefit from the TPP treatment, which is now administered by multiple healthcare providers in Germany. Recent advances have rendered this already economical treatment even more economical to administer [23,24].

In most of Europe's RS Centers of Expertise, however, the TPP remains unavailable. As an RS parent who has seen the remarkable effectiveness of the TPP treatment first hand, I sometimes wonder why this is the case. The European Union is supposed to function as a union. In medicine in particular, the European Reference Network system was established, and receives EU funding, precisely in order to promote collaboration and pooling of rare disease knowledge and expertise. In practice, the TPP treatment will likely have to travel from Tübingen, across the Atlantic ocean to America, and then back across the Atlantic ocean to Europe once again, before babies in major EU Member States outside of Germany can expect to benefit from the breakthrough TPP. What can explain this inertia?

The English author and philosopher Gilbert Keith Chesterton wrote: "It isn't that they can't see the solution. It is that they can't see the problem" [25]. As an RS parent I believe this strange situation applies in the world of RS care. Every healthcare provider in the international community of RS experts knows about the efficacy, safety, and quality of life benefits which the TPP treatment provides. Even physicians lacking any familiarity with RS can readily learn about the TPP's medically proven ability to resolve UAO and increase weight gain by accessing the numerous, peer-reviewed, evidence-based medical studies which have been published on this highly effective technique [15,16,17,18,19,22,

23,24,26,27].

However, RS experts *are* familiar with the TPP, they *do* see it; but they do not see the *problems* inherent in their own RS treatments of choice. They do not see that parents are terrified about placing their baby to sleep in the notorious prone position. They do not see that parents do not want their baby to depend upon and remain attached to a mechanical breathing machine, turning the hospital into a second home, or the home into a second hospital. Parents do not want their baby to undergo Tongue Lip Adhesion, a hideous procedure first proposed a century ago, whose benefits remain in question. Parents do not want to send their newborn baby into even more aggressive surgery, such as MDO, unless there really are no other good options.

3. Conclusion

Using Lysiane's experience as a case study, what useful lessons can be drawn? First, as noted in the beginning of this article, an improved RS prenatal screening protocol could reduce trauma, improve care, and save lives. At the same time, there seems to be a need for further research to determine what kind of pre- and postnatal RS counseling would be appropriate in the face of this complex and heterogenous rare disease [28].

Second: by actively involving rare disease patients and parents as engaged participants and stakeholders in a collaborative rare disease care team which includes researchers, clinicians, genetic counsellors, psychosocial counsellors, and other healthcare providers, we may gain greater visibility on patients' needs and concerns, and produce better patient outcomes.

Third: the vast majority of rare diseases lack any approved treatment or cure. Lysiane's case may serve as a useful reminder that when a safe, medically proven, economical rare disease treatment has been developed, healthcare providers should facilitate access to that treatment. Unless there is a strong justification for denying access to a particular treatment – danger, questionable efficacy, excessive cost – a family should not have to take out a personal bank loan as a condition for accessing safe and medically proven rare disease care [29].

Fourth: Lysiane's experience demonstrates that in Europe there is a promising opportunity to facilitate access to cross-border healthcare for rare disease patients, through a properly designed program of education and training. In the EU, prior authorisation for cross-border healthcare is subject to strict legal scrutiny. EU law states that "individual decisions of refusal to grant prior authorisation shall be restricted to what is necessary and proportionate to the objective to be achieved, and may not constitute a means of arbitrary discrimination or an unjustified obstacle to the free movement of patients" (Directive 2011/24/EU on the application of patients' rights in cross-border healthcare). The EU Court of Justice specifies that every refusal to grant prior authorisation must be justified by "an overriding reason in the public interest" (Case C-173/09 *Georgi Ivanov Elchinov v Natsionalna zdravnoosiguritelna kasa* [2010] ECR I-08889). These standards for refusal are high and very difficult to meet, because by EU design, refusals should be exceptional events. In order for rare disease patients to benefit from meaningful access to care, these rules must be respected – but in order for healthcare administrators to respect these rules, they must first understand them. How can the legal standards governing EU cross-border healthcare be clearly and effectively explained to Europe's numerous and diverse healthcare funds and administrators? Who should provide the training? What form should it take? And how can this information be communicated to EU citizens, including those from socially and economically disadvantaged backgrounds, so that they too can benefit from European advances in rare disease care? These questions call for further research and action, preferably on an EU level.

Fifth: Lysiane's case demonstrates the limits of digital healthcare, and the idea that "information and knowledge should travel, so the patient doesn't have to." Sometimes the patient *does* have to travel. The patient has to travel to receive treatment at a light ion hadron therapy facility; likewise, the patient has to travel to receive a highly specialized rare disease treatment such as the TPP. The TPP treatment requires a relatively large team of individuals and disciplines and concentrated expertise, including neonatologists trained in upper airway nasopharyngeal fiber optic endoscopy, pediatric sleep medicine, orthodontics, cranio-maxillofacial surgery, neonatal nursing, and speech therapy. A treatment like the TPP cannot be offered in every hospital, or even in every country, and it does not need to be. The important point though is that if the patient *does* have to travel to access one of these highly specialized treatments, then the patient, especially the rare disease patient, should be helped, not hindered.

I appreciate this opportunity to contribute the patients' perspective, and I hope that it fosters useful dialogue. A healthcare provider's work can be extremely difficult. The responsibility you have taken on is profound. I wish you strength and courage as you face the tremendous moral challenges which constitute such a routine part of your day-to-day job.

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References

[1] Nguyen JQN, et al. Can Robin sequence Be predicted from prenatal ultrasonography? J Oral Maxillofac Surg 2020;78.
[2] Paladini D. Fetal micrognathia: almost always an ominous finding. Ultrasound Obstet Gynecol 2010;35.
[3] van Nunen DPF, et al. Elevated infant mortality rate among Dutch oral cleft cases: a retrospective analysis from 1997 to 2011. Front Surgery 2014;1.
[4] Breugem CC, et al. Best practices for the diagnosis and evaluation of infants with Robin sequence. JAMA Pediatrics 2016;170.
[5] Logjes RJH, et al. The ontogeny of Robin sequence. Am J Med Genet 2018;176.
[6] Carpenter R, et al. Sudden unexplained infant death in 20 regions in Europe: case control study. Lancet 2004;363.
[7] Moon RY. SIDS and other sleep-related infant deaths: evidence base for 2016 updated recommendations for a safe infant sleeping environment. Pediatrics 2016;138.
[8] Poets CF, Wiechers C. Reappraising prone positioning for infants with Robin sequence: a cautionary tale. Arch Dis Child 2021;106.
[9] U.S. Consumer Product Safety Commission. Fisher-Price Recalls Rock 'n Play Sleepers Due to Reports of Deaths. CPSC.gov.; 2019. https://www.cpsc.gov/Recalls/2019/Fisher-Price-Recalls-Rock-n-Play-Sleepers-Due-to-Reports-of-Deaths/.
[10] Fauroux B, et al. Facial side effects during noninvasive positive pressure ventilation in children. Intensive Care Med 2005;31.
[11] Amaddeo A, et al. Continuous positive airway pressure for upper airway obstruction in infants with Pierre Robin sequence. Plast Reconstr Surg 2016;137.
[12] Leboulanger N, et al. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. Pediatrics 2010;126.
[13] Broucqsault H, Lamblin M-D, Hosana G, Fayoux P. Evaluation of the efficacy of tongue-lip adhesion in Pierre Robin sequence. Euro Annals Otorhinolaryngol Head Neck Disease 2018;135.
[14] Resnick CM, Calabrese CE, Sahdev R, Padwa BL. Is tongue-lip adhesion or mandibular distraction more effective in relieving obstructive apnea in infants with Robin sequence? J Oral Maxillofac Surg 2019;77.
[15] Poets CF, Koos B, Reinert S, Wiechers C. The Tübingen palatal plate approach to Robin sequence: summary of current evidence. J Cranio-Maxillofacial Surg 2019;47.

[16] Poets CF, et al. Multicenter study on the effectiveness of the pre-epiglottic baton plate for airway obstruction and feeding problems in Robin sequence. Orphanet J Rare Dis 2017;12.
[17] Müller-Hagedorn S, Buchenau W, Arand J, Bacher M, Poets CF. Treatment of infants with Syndromic Robin sequence with modified palatal plates: a minimally invasive treatment option. Head Face Med 2017;13.
[18] Buchenau W, et al. Functional treatment of airway obstruction and feeding problems in infants with Robin sequence. Arch Dis Child Fetal Neonatal Ed 2017; 102.
[19] Maas C, Poets CF. Initial treatment and early weight gain of children with Robin Sequence in Germany: a prospective epidemiological study. Arch Dis Child Fetal Neonatal Ed 2014;99.
[20] Pakter P. Letter to French President Emmanuel Macron, "Lysiane - French baby with a rare disease". Pierre Robin Europe; 2018. https://pierrerobineurope.com/letter-to-macron/pdf/.
[21] Pakter P. Letter to EU Health Commissioner Stella Kyriakides, "Rare Disease Patients and Access to Care". Pierre Robin Europe; 2019. https://pierrerobineurope.com/kyriakides-pdf/.
[22] Wiechers C, et al. Retrospective study on growth in infants with isolated Robin sequence treated with the Tuebingen Palate Plate. Orphanet J Rare Dis 2021;16.
[23] Müller-Hagedorn S, Arand J, Scholz T, Poets CF, Wiechers C. An innovative method for manufacturing the Tuebingen palatal plate for infants with Robin sequence. BMC Pediatr 2020;20.
[24] Xepapadeas AB, et al. Technical note on introducing a digital workflow for newborns with craniofacial anomalies based on intraoral scans - part II: 3D printed Tübingen palatal plate prototype for newborns with Robin sequence. BMC Oral Health 2020;20.
[25] Chesterton GK. The collected works of G.K. Chesterton. Ignatius Press; 1986.
[26] Wiechers C, et al. Mandibular growth in infants with Robin sequence treated with the Tübingen palatal plate. Head Face Med 2019;15.
[27] Naros A, et al. Perioperative complications in cleft palate repair with Robin sequence following Tuebingen palatal plate treatment. J Cranio-Maxillofacial Surg 2021;49.
[28] Sandow R, Kilpatrick NM, Tan TY, Raj S, Forrest LE. Parental experiences and genetic counsellor roles in Pierre Robin sequence. J Commun Genetics 2020;11.
[29] Pakter P, Sadek J, Miller N. Rare Revolution Magazine: "Crossing Borders to Access Rare Disease Care, Lysiane's Story". Pierre Robin Europe; 2020. https://pierrerobineurope.com/rare-revolution-pdf/.

In spite of the continuing challenges created by COVID-19, we made substantial progress pursuing Stichting Pierre Robin Europe's goals in the year 2021.

We look forward to continuing our efforts in 2022.

Chairman: _____
(signature, Philippe Pakter)

Secretary: _____
(signature, Neil Russell)

Treasurer: _____
(signature, Lisa-Beth Harris)

PIERRE ROBIN EUROPE

Board Members

The Board Members of Stichting Pierre Robin Europe are:

Chairman	–	Jean-Phillippe Pakter
Secretary	–	Neil Russell
Treasurer	–	Lisa-Beth Harris

Stichting Pierre Robin Europe
Gerard Terborgstraat 51 2, 1071TL Amsterdam, the Netherlands
www.PierreRobinEurope.com

Stichting Pierre Robin Europe - Income and Expenses, 2021

Details on 2021 line items and exchange rates
Exchange Rate: $1 = €0.8434 (1 July 2021)
Exchange Rate: CHF1 = €0.9117 (1 July 2021)

Operating Income (Euros)		
Type	**2021**	**2020**
Grants and legacies	0.00	0.00
Investment income	0.00	0.00
Membership fees	0.00	0.00
Merchandise sales	0.00	0.00
Other revenues	0.00	0.00
Partnership	0.00	0.00
Public subsidies	0.00	0.00
Services	0.00	0.00
TOTAL/REVENUES	**0.00**	**0.00**

Operating Expenses (Euros)			
Type	**2021**	**2020**	
Communication	0.00	0.00	
Desktop computer software	0.00	0.00	
Domain name	7.14	6.91	$8.47 x 1 year
Email services	198.34	191.92	$235.17 x 1 year
Hosting services, website	126.51	122.40	$150 x 1 year
Insurance	0.00	0.00	
Maintainance/repairs	0.00	0.00	
Office supplies, business cards	0.00	0.00	
Other (Legal/Membership fees)	166.17	167.40	EURORDIS, VSOP, ProRaris
Postal charges and telephone	0.00	0.00	
Project expenses	0.00	0.00	
Publication	0.00	0.00	
Rent and utilities	0.00	0.00	
Representation expenses	0.00	0.00	
Salaries	0.00	0.00	
Social security charges	0.00	0.00	
Training fees	0.00	0.00	
Translation fees	0.00	188.90	
Travel, int'l conferences	0.00	255.10	
Various purchases	0.00	0.00	
Website, software	129.84	182.91	
TOTAL/ EXPENSES	**628.00**	**1115.54**	

Income less Expenses (Euros)		
	2020	**2020**
Income	0.00	0
Expenses	628.00	1115.54
Income less Expenses (Euros)	**-628.00**	**-1115.54**

Philippe Pakter

Chairman, Philippe Pakter

Secretary, Neil Russell

Lisa-Beth Harris

Treasurer, Lisa-Beth Harris

Stichting Pierre Robin Europe - Balance Sheet, 2021

Assets (Euros)		
Type	**2021**	**2020**
CURRENT ASSETS		
Cashflow		
Liquidities	0	0
Cash	0	0
Bank account	0	0
Postal account	0	0
Total liquidities	0	0
Operating assets		
Debts	0	0
Stocks in reserve	0	0
Outstanding income	0	0
Other current assets	0	0
Total current assets	0	0
FIXED ASSETS		
Tangible fixed assets (furniture, IT equipment, vehicle, etc)	0	0
Intangible assets (Formation/Startup Costs)	6610.73	5982.73
Royalties	0	0
Depreciation	0	0
Capital assets (loans, ownership titles, bonds, etc)	0	0
Fixed assets total	6610.73	5982.73
TOTAL ASSETS	**6610.73**	**5982.73**

Liabilities (Euros)		
Type	**2021**	**2020**
LIABILITIES		
SHORT TERM FOREIGN CAPITAL		
Cashflow debt		
Bank overdraft	0	0
Operating debts		
Suppliers' debts	0	0
Outstanding expenses	0	0
Reserves	0	0
PERMANENT ASSETS / CAPITAL		
Long term debts		
Loans (Loan to cover Formation/Startup costs)	6610.73	5982.73
EQUITIES		
Allocated funds		
Funds allocated for projects	0	0
Unallocated funds		
Capital	0	0
Reserve	0	0
Retained Earnings	0	0
TOTAL LIABILITIES	**6610.73**	**5982.73**

Philippe Pakter

Chairman, Philippe Pakter

Secretary, Neil Russell

Lisa-Beth Harris

Treasurer, Lisa-Beth Harris