Editorial – “Do not harm!”

Research is a strange thing. Some people think research is too slow and too complicated. Others are sceptical and wouldn’t like to be the guinea pig. From the point of a clinician the most important goal in doing research is: Do not harm!

This issue of the OIFE Magazine is dedicated to research and future perspectives, even if this will take a lot of time and money. And it is true that research is sometimes slow. Many of the currently investigated drugs and therapeutic options will only be “Standard of care” in many years from now. Precise investigation and evaluation of side effects are needed to offer a treatment, which is accepted by people with OI and follow the guidance: Do not harm!

But changes have happened in the past, and they did improve the care for people with OI. Many adults never received bisphosphonates during childhood, because this treatment, which is now standard of care, was not available at that time. At the beginning of the “bisphosphonate-era” the drug was used more restrictive than today, and a lot of
additional investigations (blood draws, biopsies etc) have been performed to make sure that researchers and clinicians do not harm with their treatments. Another huge improvement of care that most of the adult readers are too old to benefit from, was the development of telescopic rods. Today we know that they reduce the total number of surgeries. They also improve mobility and self-care of people with OI. Nonetheless, at the beginning there was extensive discussions if the long surgeries and the risk of dislocation would be acceptable to justify the use of telescopic rods. Other inventions like bone marrow transplantations, have not turned out to be beneficial. After treatment of a few patients, the trials with this kind of therapy have been stopped.

The development of new drugs was simplified by the authorities (EMA and FDA) a few years ago by implementing the so-called “Orphan disease status”. This encouraged some companies to develop drugs specific for OI or at least to investigate the effect of drugs already approved in other indications in proper clinical trials for the use in OI. Even with this orphan disease status, the process of developing new treatments and therapies is still slow. A clinical trial takes years. You need to find the required number of volunteers to participate, but this is completely necessary. In the end we aim for a drug which is hopefully effective, but without severe side effects. The importance of close monitoring of drugs which are under development is indispensable because some side effects might only occur after some time of treatment.

Currently more ideas are being researched than ever before, to improve the situation of people with OI. New drugs as antiscloerostin and new antiresorptives are being investigated. Additionally, completely new therapeutic pathways are considered, such as stem cell treatment or gene therapies. These are promising approaches, at least in basic research and in animal models. Time is needed to assess the safety and efficacy of these new agents to make sure that we do not harm patients.

During the last years an additional change in therapeutic strategies has happened, which is definitely safe, will not harm anybody and will speed up improvements in the care of people with OI. The cooperation between researchers has changed and improved dramatically. 20-30 years ago, every OI-researcher was working on his own, competing with other researchers, hiding the results until they were published. Today many (maybe too many) networks have been established to connect clinicians, clinical and basic researchers. Some are also including patients themselves, people from health care providers, authorities and ethical committees. This is an extremely promising approach, especially because patient organizations can play an active role in these networks. OI-organizations are not only commenting on initiatives presented by researchers anymore, but have the opportunity to guide these networks and to prioritize areas of special interest.

To conclude - we live in very exciting times, in which more research on OI is done than ever before. Nonetheless many people think that research is still too slow. Different approaches are currently being investigated. And research must be accurate and reliable, so that patients can trust their clinicians, when new treatments become available. This issue will give you a glimpse of what is going on in the world of OI-research. I hope you will enjoy reading.

Oliver Semler
Chair of the Medical Advisory Board of OIFE (OIFE MAB)
What is the OIFE doing?

By Ingunn Westerheim, OIFE President

Since the last OIFE magazine, most of our time has been used to catch up on other OIFE activities that suffered somewhat because of the IMPACT survey. Catching up included a reestablishment of the Pain & OI project and the creation of a first draft of our new long term strategy (2022-2026).

We have also caught up with important collaborators like the OIFE MAB, EuRR-Bone, EURORDIS and the organizers of OI2022. We have participated in events relevant for OI and rare bone conditions and we have established new connections to federations similar to OIFE. This in order to learn and exchange experiences. In the beginning of December, we also did our biannual expanded OIFE EC-meeting, where we made plans for 2022 and discussed possibilities of a Topical Meeting in Sweden in 2023. More information to come!

These are some of the virtual meetings we have attended since the last OIFE-magazine:

- OIFE EC-meetings Dec 5th (expanded) and Dec 21st
- MoCA-meeting, Oct 15th (TvW)
- OIF webinar “Leveraging Virtual Communication to Advance PCOR Adoption”, Oct 21st (IMPS)
- OI Foundation’s Town Hall, Oct 28th (IMPS)
- IPSEN & Costello Medical, Rare Bone Disorders – meeting on literature search Nov 3rd (IW)
- Mereo & Ultragenyx monthly meeting with OIFE, Nov 4th and Dec 13th (IW)
- Student Voice – student interview, Nov 5th (IW)
- Webinar on registries organized by George Reynolds, Nov 5th (IW)
- Aparito webinar on Patient Group Accelerator Programme, Nov 8th (IW)
- ECTS webinar on OI, Nov 10th (IW and more)
- Dr. Richard Keene about adult clinics & OI in the UK, Nov 16th (IW)
- SMA Europe – knowledge exchange with OIFE, Nov 18th (IW)
- Rare Diseases International (RDI)- introduction, Nov 19th (IW)
- OI2022 Sheffield planning, Nov 19th (IW, Patricia Osborne & Tracy Hart)
- Sanofi update on OI research, Nov 30th (IW)
- Cystic Fibrosis Europe knowledge exchange with OIFE, Dec 10th (IW)
- Kyowa Kirin International, Dec 14th (IW and BvD)
- BOOST Pharma – intro meeting, Dec 16th (IW and BvD)

IMPACT SURVEY
The IMPACT survey was closed on September 30th and the steering committee met on November 12th to discuss future plans. Taco van Welzenis and Ingunn Westerheim represented the OIFE. The preparation work to produce the scientific articles based on the survey is ongoing, but first the data must be cleaned. And because of all the language versions (incl. free text fields) it is a big job to make sure there is consistency and no bugs or duplicates in the data material.

We have updated our resource page on IMPACT if you want to stay up to date on the developments: www.oife.org/impact
PAIN & OI PROJECT REESTABLISHED
In April 2021 we announced that the OIFE was interested in getting in touch with professionals (PTs, OTs, psychologists, medical doctors, researchers, pain specialists etc.) who had experience on pain & pain management in OI (or related bone diseases). We have gathered a multidisciplinary group of more than 20 professionals with interest and knowledge on the topic of OI and pain. In January the expert group will have its kick-off and a brainstorming to see if there are some recommendations, we could make to improve pain treatment and pain management for people with OI. At the moment we are trying to uncover the unmet needs and patient priorities by asking the OI-community for advice and input through our various channels.

EURORDIS COUNCIL OF FEDERATIONS
On November 9th and 10th OIFE was represented at the Council of Federations (CEF) meeting of EURORDIS. CEF is a forum where umbrella organizations and federations for rare conditions in Europe come together to learn about news in the rare disease field and to provide input to EURORDIS in policy questions. Topics for this edition of the meeting where OIFE attended included:

- Revision of the general European pharmaceutical legislation (public consultation)
- A new EURORDIS programme for Community Advisory Boards (CABs)
- A new training by EURORDIS on how patients can take part in Health Technology Assessments (HTA)
- How federations can prepare themselves for a new pilot at the European Medicines Agency (EMA), when the evaluation of a new medicine starts
- Status on access to orphan medicines

Many of the topics were very relevant to activities that OIFE are involved in these days, and we gathered important knowledge that will hopefully make our work easier.
EUNETHTA STAKEHOLDER MEETING
The EUnetHTA was established to create an effective and sustainable network for health technology assessment (HTA) across Europe. HTA is a process where the authorities in a country look at the cost/benefit of paying for a new drug/surgery method or continuing with existing treatments. The EUnetHTA supports collaboration between European HTA organisations that brings value at the European, national, and regional level through:
- The facilitation of efficient HTA resource use.
- The creation of a sustainable system of HTA knowledge sharing.
- The promotion of good practice in HTA methods and processes.

On Friday 3rd of December OIFE was represented at the EUnetHTA 21 Stakeholder Kick-Off meeting. The objectives of the meeting were the introduction of the ‘new’ EUnetHTA 21 Consortium. The slides of the meeting can now be found here. The OIFE has also signed up for the EUnetHTA stakeholder repository.

RARE BONE SUMMIT
On December 6th and 14th Oliver Semler, Ingunn Westerheim and Inger-Margrethe S. Paulsen represented the OIFE at the virtual Rare Bone Disease Summit. Tracy Hart represented the OIF. The Summit is a global multi-stakeholder group meeting that aims to provide a platform to enable contributors working in the rare bone disease field to collaborate towards improving the lives of people living with these conditions. It is planned to be an annual event. The Summit 2021 was led and funded by Ipsen Pharma, with Kyowa Kirin, Alexion, BioMarin, and Ultragenyx as the supporting strategic partners, in close collaboration with patient organisations, experts, and medical and scientific societies. To learn more about the 2021 RBD Summit, please visit rbdsummit.com

OIFE CO-AUTHORS ON ORPHANET ARTICLE ON DATABASES
Rebecca Tvedt Skarberg (ERN BOND ePag) and Ingunn Westerheim were co-authors on a published article in Orphanet Journal called “Patients’ priorities and expectations on an EU registry for rare bone and mineral conditions”. Based on the findings of a survey, the rare bone community (ca 500 responses) prioritised the key components for an EU-based rare bone and mineral condition research database (which the community preferred as name instead of registry). The survey demonstrated that by the patients would prefer using only specialist centre visits for data collection, however this will miss a substantial number of individuals, limiting generalisability. Combined healthcare professionals and patient platforms will be required to collect representative and complete natural history data for this patient group. Read the open access article here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8564998/
Meet the OIFE delegates

Eva Sacherer, Austria

My name is Eva Sacherer. I studied curative and special education in Vienna (today the course is called inclusive education). Subsequently, I specialized in further training as a sign language interpreter for the field of deafness and deaf blindness. All my professional activities revolve around the topic of the participation of people with disabilities and the breaking down of barriers.

Our son Jakob was born recently. He is unique, but that's what all parents say about their children, of course. Jacob knows exactly when he's hungry and stops when he's had enough. He loves it when the rays of the sun glisten through trees and plays with his cuddly blanket for hours. Some days he likes to go by car, other days he doesn't. We haven't quite figured out why, but he'll tell us at some point. Oh yes, and by the way, he also has brittle bones.

I am very happy to have been selected as the Austrian delegate for the Osteogenesis Imperfecta Federation Europe (OIFE).

The organization I represent is called OIA Osteogenesis imperfecta Austria. We have 100 members, 40 of whom are personally affected. The association is run exclusively on a voluntary basis.

Our ongoing projects are: Annual meeting with specialist lectures, Christmas party in Vienna as a cozy get-together and cooperation with the expertise centre. This is a merger of bone departments from 3 hospitals in Vienna. We’re also working on production of a new folder and developing an app that answers questions for people with rare bone diseases.

The OIA focuses on:

Being contact persons for all people who have questions about OI incl. persons affected by OI, parents, teachers, medical staff etc. We organize the annual meeting and provide financial support to members to encourage mobility (Physiotherapy, orthopedic shoes, hearing aids etc). Exchange of experiences bring interested people together. We also update our Facebook group and homepage and stay in contact with the centre of expertise.

From my professional experience, I am aware of the importance of international networking in the field of rare diseases. This is why I applied to become the Austrian delegate and that’s also the aim OIFE should focus on in my opinion.

Bringing together so-called professional experts and experts in their own life for a better understanding and treatment of all people involved is important. This includes making a strong political impact. With the existence of our son, this aspect has acquired an essential personal component.
Julia Piniella, Spain

Who are you and what is your relationship to OI?
My name is Julia Piniella and I am the director of Fundación AHUCE since 2015 and the coordinator of AHUCE association since 2020. I live in Valencia, although I was born in the Canary Islands. I studied early childhood education and psychology. Now I am doing a master’s degree in foundation management. I have mild OI (Type I). My diagnosis came very late (only 10 years ago). In relation to OI, my goal is very clear: research of the condition at a multidisciplinary level.

In what way does OI affect you personally?
Currently, I don’t have many bone fractures, but I do have a lot of muscle and ligament problems. This in addition to a lot of fatigue and chronic muscular pain. I recognize that this sometimes makes me angry. I want to do many things, but my body often does not allow me to do so. For mental health, I am learning to say: Julia, stop!

Tell us about your organization!
AHUCE and Fundación AHUCE are two entities that are currently serving about 600 people with OI plus their families. We try to provide comprehensive care that is specialized and professionalized but also close. The AHUCE association include a social worker (Belén Chavero), a psychologist (Tamara Fernández), and a physiotherapist (Miguel Rodríguez). The AHUCE Foundation is formed by a psychologist (Rubén Muñoz) and a social worker (Carlos Monfort). The board members of both entities are the same (6 people who are people with OI and family members).

I coordinate both entities. The AHUCE Foundation, in addition to some social projects finances and promotes research on OI. Since 2015 we have funded more than 10 research projects. Covid has meant an important stop in terms of fundraising for research, but we do not lose hope of resuming all our research activities in the near future.

What do you do when you’re not doing OI-work?
I love traveling, reading and good food. I am passionate about cats. I am a family person and also share time with my friends.

If you were the OIFE president for a week, what would you do?
I would not like to be the president of the OIFE, because I think Ingunn and her team are doing really well. I think that the presidency of OIFE is a great responsibility, and that the rest of the OI community should be very grateful that there are people who take on these responsibilities.

What is the most important task for the national organizations?
Sharing information is essential, both for the direct care of people and in research projects. We learn from each other and can help each other.

What should OIFE focus on?
Helping the most disadvantaged countries to create organizations that can help the people who live there. For example, the “Flying OI experts” is a very important project.

Any messages for the readers of OIFE magazine?
I would like to thank OIFE for the opportunity to talk about my work. And I would like to thank all the people who have accompanied me in these 10 years dedicated to OI. I have had a great mentor (María Barbero) and great people who, in hard times, have helped me not to move away from my goal: to investigate OI. We have to do many things for people with OI, and we can only do it if we work in a coordinated way.
New OIFE Youth Coordinator Simey Truong

*Interview with Simey Truong, Germany*

My name is Simey Truong. I am 26 years old and have OI type 3, so I am bit short (I am only 1.12m tall) and sitting in a wheelchair. During my childhood I had a lot of fractures, but they didn't stop me from experiencing a lot. I'm a member of the German OI Society DOIG since I was born. There I have learned a lot, made friends and gained self-confidence. Since 2021, I am proud to represent the OIFE as Youth Coordinator.

**Do you have a role in DOIG? What exactly?**

In the DOIG, I am active as youth coordinator in a team of six. We try to connect young people with OI in Germany and organize meetings. Since the beginning of the year, I have also been leading the DOIG’s social media team. We use Facebook and Instagram for public relations and to inform our members about what is happening in the association.

**What do you do outside OI work?**

I'm currently working at SWR. It’s a big German radio and TV station. There I work in an editorial department which shows daily portraits of people from the region on Instagram. I also work for the children's charity "Herzenssache”.

**Why did you agree to join the OIFE Youth Coordinator Team?**

I have been attending the OIFE Youth Events since I was 15 years old. At that time, I was one of the youngest participants. I have always enjoyed meeting new people and visiting foreign countries. Throughout the years I have made many friends in different parts of the world. As Youth Coordinator, I want to strengthen the connection between young people with OI. My goal is also to show how different we all are and at the same time quite similar.

How can the OI-organizations (and OIFE) be more inclusive and relevant for young people with OI?

I have often experienced that young people don't want to join an organisation because they think that we are only talking about our sufferings. But at our meetings it's not about what we can't do. It is about supporting each other, encouragement and about showing that "We can do it!" Together we are many and we can achieve a lot!

**Any messages for the readers of OIFE Magazine?**

I am glad that there is such a big organisation like OIFE. It connects people all over the world. This way we can show the world people who have become great personalities despite or just because of their disabilities.
Informal report from IntOI 2020+1

A summary by Lidiia Zhytnik, member of OIFE’s Medical Advisory Board

On September 9, 2021 the IntOI 2020+1: Virtual International Meeting Early Stage Investigators Symposium, took place. It was organized by the OI Foundation and chaired by Dr. Joan Marini. The meeting highlighted OI research, performed by young investigators all over the world. The OIFE was delighted to see so many young and enthusiastic researchers. Results from more than 40 OI research projects were carefully selected for presentation on the IntOI 2020+1 Virtual Symposium. In this short summary, OIFE would like to feature some of the knowledge shared with us.

New technologies in bone research
The honour of a basic keynote talk was given to Prof Natalie A. Sims from St Vincent's Institute of Medical Research, Australia who communicated six new technologies and their application in bone research. According to one of the studies, intravital imaging, used to observe cells inside a living mouse helped to identify new bone cell – osteomorphs. Ostomorphs fuse together to form an osteoclast – a well-known bone cell for everyone with OI. Moreover, scientists could identify this new cell type in the skeleton, by looking at activity of our genes in one single cell (single cell RNAseq). Some of these genes are specially interesting, as they are regulating bone structure, which means they can be used to develop new therapy targets for bone disorders. These and other papers cited by Prof Sims in her talk can be accessed in her Twitter @NathalieASims.

New OI gene KIF5B
Many new things are happening in both basic and clinical research. First of all, a new OI gene is coming (yep, more and more are added to the list). It means that OI gene panels might become longer, but some OI people will finally get their genetic diagnosis. The KIF5B gene apparently causes moderate OI, with full range of typical OI symptoms: fractures, low BMD, short stature, scoliosis, brittle teeth, hearing loss. The defect leading to OI might be connected to transport of collagen. The work was performed by Ronit Marom, Baylor College of Medicine, US.

Variability of OI clinical pictures
Nadia Garibaldi from the University of Pavia, Italy, explored variability of OI clinical pictures. She took a genetic defect, which in some cases lead to lethal, but in other cases to non-lethal OI in mice. Nadia looked on gene activity in mouse cells with this gene defect. According to the study, mice who have lethal OI have more problems with cell skeleton and cell nuclei skeleton. Our bodies have not only a big skeleton, but also tiny protein „skeletons“ inside every cells, which seem to have problems too.
3D bioprinting of bone organoids
In University of Zürich, Switzerland, Timothée Ndarugendamwo with colleagues perform 3D bioprinting of bone organoids (fancy!). An organoid is a simplified mini-copy of an organ, which can be used to test therapies and hopefully substitute mouse experiments in the future, and study disease mechanisms. Scientists take bone cells of people with OI and print them with a 3D printer, layer-by-layer together with a polymer, until a mini-copy of a bone is formed. Bone cells in the mini-bone piece felt fine and could produce collagen.

Development of joint deformation
Joohyun Lim, Baylor College of Medicine, US activated FKBP10 (attention, those with genetic OI type XI) mutations in parts of mice tendons and ligaments and studied development of joint deformations. After exploration of activity of genes involved in formation of joint deformities, researchers were able to affect a network of these genes and partially recover joint deformities.

From skin cells to bone cells
Researchers from Amsterdam UMC, The Netherlands, are working on a cell model for OI. Lauria Claeyys has found a way to make bone cells more available for research - just from skin cells. She took skin cells and turned them into stem cells (basically back to the times before birth), and then brought them through different stages to bone cells. According to Lauria: „It will help to test therapies and study OI mechanisms on bone cells without actually needing to take a bone biopsy“.

Bone toughness of young and old mice
Anxhela Docaj, The City College of New York, US studied bone toughness of mice with OI. Scientists looked at the ability of bone to resist fracture and compared it between young mice and older ones. Although bones of adults are tougher, they did not have toughening mechanisms, which younger bones have. Researchers think that this understanding of differences between young and adult bone fracturing will help to prepare special clinical therapies for children and for adults with OI.

Impact of neuraxial anesthesia
At the clinical part of the symposium, Nicholas Bohannon, University of Nebraska Medical Center, US reported results from a study on post-operative pain in OI kids and neuraxial (spinal) anaesthesia. Researchers looked through 611 surgery cases in 194 OI children during 2000-2020. Scientists wanted to compare effect of neuraxial anaesthesia and complex anaesthesia for surgeries on legs. According to the presented results, the use of neuraxial anaesthesia (spinal one) improved pain control, and lead to decreased intake of opioid painkillers. Also, they claim that no adverse events happened in all of the spinal anaesthesia cases during 20 years.
Optical spectroscopy
William Querido, Temple University, US studies ways to look at bone quality without irradiation (like DXA and X-rays we are used to). The researcher assessed bone quality in OI people using optical spectroscopy in the visible and infrared range. It could provide information about bone quality similarly to usual DXA scanning and X-rays used in clinic nowadays.

When to start bisphosphonate therapy?
A study of Marie-Eve Robinson, Shriners Hospital for Children, Canada showed that starting bisphosphonates at an earlier age will help to gain more height for those with severe OI (type 3) and moderate OI (type 4), but not for mild OI (type 1). Sorry, mild OI-ers, you still have to go for high heels.

Risk of eye problems in OI
Researchers from University of Southern Denmark, Denmark investigated risks of eye problems in OI people. Marie Louise Lyster has studied records of 907 OI people, from 1977 to 2018. According to the results, people with OI have higher risks of eye diseases compared to non-OI people - it appears that we have to keep an eye on our eyes, guys. Read an interview with Marie Louise in this magazine.

Inclusion of students with OI
McGill University/Shriners Hospital for Children, Canada presented by Jessica Chemtov shared a creation of a tool which will help for optimal inclusion of students with OI. Jessica created guidelines and recommendations for integration of OI kids in primary and secondary school. Important items of the guidelines for inclusion of OI students are listed here: general information about the student, fracture response protocol, student inclusion recommendation, mobility considerations, transfer consideration, toileting protocol, physical education class recommendations, fieldtrip information, transportation considerations, evacuation plan, seating and scholarly considerations, consent and authorization forms and an annual renewal document. Researchers concluded that there should be a collaboration and partnership between school and health care centre of the child.

Information about the rest of OI research projects performed by young professionals and presented on the event can be found in the abstract book of the symposium. We would like to express our kind support and admiration to everyone who work on OI and advances OI research. You can watch the whole recording of the conference on YouTube.
Key4OI – past, present and future

Interview with Dagmar Mekking, director of Care4BrittleBones

Who are you and what is your relationship to OI?
I am Dagmar Mekking from the Netherlands. I am a mother of a 15 year old daughter with OI. Also I am the director of Foundation Care4BrittleBones. The purpose of the foundation is to improve quality of life for people with OI through research.

What was the background for Key4OI in the first phase?
You may have heard the sentence “What gets measured, gets done” or “You can’t really improve anything, unless you measure it”. Businesses are all using these concepts to drive business performance. In the last 10 years, healthcare around the world started to go into this direction too. It turned out that the focus of healthcare measures was mostly on “process”, as in “how often does someone receive physiotherapy” or “how often does someone get medication X and how much”. This was easy to measure, it was important for safety, for healthcare insurance and for the billing system.

Across healthcare (not just OI) it turned out that relatively little attention went to the outcomes in the person that was treated. We knew what treatment was administered, but if it actually worked was often not known. The key is really to consider what the value is that a patient gets from undergoing any kind of treatment. Foundation Care4BrittleBones has picked up this general trend and coordinated the development and implementation of this “idea” for the OI community.

Why was there a need for this project?
OI is complex and everyone is different. There are potentially > 100 of things we could be measuring. Did you know that each year about 200 articles are being published about OI? There is a lot of dedicated people out there and that’s absolutely amazing! We would like to argue though that the activity levels and the “local insights” somehow don’t translate into improvements for everyone with OI. We believe we can do better in sharing knowledge and doing research together to really improve quality of life. For any rare disease we see that it is critical to determine the most important topics to focus on and then to “organise” ourselves to make progress in this area. This is what Key4OI can do.

FROM
• > 600 different measures for OI in healthcare & research literature
• Inconsistent data. Limitation for healthcare and research
• No prioritization
• Slow progress on Quality of Life for OI

TO
• > 15 domains underpinned with validated measures
• Better, more and consistent data for healthcare and research
• Focus on the most important areas
• Faster progress on Quality of Life for OI (Learning system)
So what is an outcome measure?
Traditionally healthcare measures focused on process measures. Key4OI focuses on outcome measures. They measure the result in people with OI, regardless of the treatment. If we all measure the same areas (for example: fractures, pain, fatigue, mobility, emotional wellbeing etc) and we measure with the same measuring stick, this will open up a world of new insights about OI and which interventions are effective for which patients (for instance for which types of OI).

In Key4OI we focus on CROMS and PROMS. Clinically reported outcome measures (CROMS) are measures that a hospital/doctor will need to generate. Examples: a DEXA scan, an X-Ray, a Lung function test etc. Patient reported outcome measures (PROMS) are measures reported by the person with OI. Examples: the level of pain or fatigue, the ability to participate in society or emotional wellbeing. The last 10 years it has become widely accepted that the perception of the patient is probably what matters most. We have to know how the people with the condition experience quality of life.

Which methods were used in Key4OI and who were engaged in the project?
First we engaged with the patient organisations that have a big international footprint, OIFE and OIF and made sure they supported the project. Both were in the steering committee that oversaw the project of developing Key4OI 2018-2019. We formed a project lead team which consisted of 5 healthcare providers in the Netherlands and Care4BrittleBones. The decisions were all taken by an expert team of 25 people of which 20% had OI themselves.

Can you explain the different steps in the process?
1. **Determine vision**
   We determined our vision to develop an outcome set as “broad as life”, useful for routine clinical care of any multidisciplinary team and beneficial for every person with OI.

2. **Convene the project and expert team**
   It was critical to have the right mix of expertise in this group: geographically diverse, experienced in children and in adults with OI and multidisciplinary and with strong representation of the OI community (ca 20% of the group were experts with OI). We consulted a lot with OIFE and OIF to have experts involved that really understand OI and that we as a community trust a lot.
3. Literature search
The project team dived into the literature and clinical trials to understand the topic of outcome measures of OI “today”. We had great help from the specialised NGO ICHOM (International Consortium of Health Outcome Measures) and a professor for epidemiology and outcome measurements, Prof. C. Terwee, who advised us.

4. Methodology
We then determined the methodology to develop a formal agreement on a set of outcome measures for OI (so called “consensus”), selecting the ICHOM standard due to its strong international reputation. ICHOM is an NGO which has developed a strong scientific approach how to investigate a condition with regard to the impact it has on the individual patient (eg lung cancer, depression, arthritis) leveraging the voices of patients and experts. They are also providing a structured process on how to prioritize the findings using the ICF framework and measure the outcomes in the identified priority areas in a scientifically strong (“validated”) way. They provide a quality control for any ICHOM accredited set. We are proud that Key4OI has achieved the accreditation in 2021.

5. Focus groups to determine domains
Domains can be translated to “topics” or “areas”. The method behind it is based on the International Framework for Functional outcomes (“ICF – framework”). The framework applies worldwide and is also used by the World Health Organisation (WHO). It describes all the “domains”/“topics” we need to think about for “any humans”. This way we made sure we didn’t forget anything. Each domain is described in a precise scientific way that is understood in the same way in every country. The choice of domains was done by the
Expert team and based on input from focus groups of people with OI and many discussions withing the Expert team. We looked for countries willing to organise focus groups for adolescents and adults. We translated the material and helped to prepare their local facilitators. The discussions were held in local languages, recorded, transcribed and translated by a scientific translation service provider for the medical sector.

6. Find the best possible, validated measures
Once the domains were selected and we knew what was relevant per domain, we worked within the team to find the best possible, validated measures to capture what was going on in this area. We collected “all possible measuring tools” available for the topic and made sure we understood them in detail (eg some are only for certain age groups or have costs attached etc). We then made the best possible content validated match between the list of validated measures and what the OI community and experts were looking for.

We used a Delphi process to take decisions within the Expert group. A Delphi process is a scientific anonymous survey which is used to finalise a discussion and ensure that a consensus has been achieved without any kind of pressure. This is important to make sure the decision is objective, clear and unbiased by “who said what”. For example, we used Delphi to determine which domains would be measured in Key4OI and which areas not. We also used it to determine the measurement tool that is most appropriate to use based on the input we have for this domain.

7. Summary, recommendation and scientific article
We bundled it all together to ensure it covered all aspects and no overlaps and described this in a way that every hospital is theoretically able to work with it. This summary was then published in the OrphaNet Journal of Rare Diseases.

Were there any surprises along the way?
Many! Let me mention one: We discussed thoroughly if we should include pulmonary function into Key4OI. At the time the experts felt this topic was primarily relevant for people with a severe form of OI and not for all people with OI. Thanks to the great work of the OI Foundation in particular, the thinking has turned around and we are now discussing to include it into Key4OI after all. The Key4OI set is as “smart” or “not smart” as the state of our scientific insight.

Why did you establish Key4OIPlus?
Key4OIPlus was developed since the three areas (cardiopulmonary, dental and ENT) were not covered in Key4OI. There was a lot of feedback that these 3 areas are of very high importance for quality of life for (at least) some people with OI. There were enough experts and people with OI interested in bottoming these topics out with a separate small outcome set that could be added to the base set whenever needed. Two of the three areas may end up in Key4OI after all, as the working group has been able to make a strong case for this. But this discussion is still ongoing. We have used the exact same method as for Key4OI.

What is the role of the pilots?
We established pilots because we knew there was a lot of “teething problems” to deal with to be able to implement Key4OI in routine healthcare. We assumed that we would learn things that would also lead to changes in the basic outcome set. We therefore limited the use to a handful of countries as pilot locations. They have worked intensely over a 2-year period and learned together how to implement Key4OI. The pilot locations are HongKong SAR, Shenzhen China, Norway, Isala and UMC Utrecht in the Netherlands, Nemours hospital Wilmington USA and the Shriners Children’s Hospital in Montreal Canada. The pilots are implementing the set into their routine healthcare. We will also test satisfaction of patients and healthcare providers and seek to improve on the feedback we receive.
Which products have come out of Key4OI in total?
All the products can be found on www.key4oi.org. It includes the Orphanet article, the reference guide with a data dictionary and 2 patient tools, a checklist for preparing for a visit to a multidisciplinary team and a 1 page health action plan called “compass”. We will translate the patient tools into different languages to support the use of Key4OI worldwide. More tools and more support will become available over time.

The purpose of these tools was to boil the available information down to something that is practical and useful for people with OI, when managing their health. Both the compass and the checklist were predominantly developed with and through the OI community “end users”. But of course, we also had professionals providing input and feedback.

How can Key4OI play a role in clinical practise and clinical trials?
Key4OI can be used in routine clinical practice. Some locations may just use the patient tools, but may over time choose to capture the underlying data too. This will benefit the individual patient with OI as it helps healthcare providers with and without experience with OI to focus on the needs of the individual person with OI (not just the “bones”). Key4OI promotes multidisciplinary care throughout a lifetime. In the future, it may also serve to improve clinical practice. For example, healthcare providers could choose to compare how they are approaching psychosocial care for OI or pain and learn from each other, using 1 language and 1 consistent data set.

Ideally Key4OI would also be used in clinical trials. The simple thought is that clinical trials need to demonstrate that they make a significant difference to the health outcomes of people with OI. By using Key4OI it will become easier and faster to demonstrate the difference (as historical data will have built up already) and to compare across clinical trials. It would also be beneficial that the data that is collected, is collected for the long term benefit for the patient and OI and not just for the sake of the trial as such. It could also be used in regulatory processes with the same logic. It’s however important to say that Key4OI is not firmly linked to a registry. We are not collecting any data. We think that this needs to be managed by professional institutions.

What are the future plans?
All the tools are freely available for everyone without a licence. Every country who wants to benefit from the knowledge exchange and being part of the Key4OI Learning Community needs to demonstrate that they are actually going to implement a significant part of Key4OI in a sustainable way. If they can demonstrate this, we will mention them on our website as a “Key4OI location”. There is no commercial model involved. Only if used by commercial parties a fee may apply. We will discuss and agree on this together with our stakeholders.

Would it be an idea to develop OI specific outcome measures?
Everything we do should be sustainable. Having a basic “demographic set” of outcome measures that is identical with other diseases makes sense. Having a disease specific set also makes sense as the outcomes in OI will be different from cancer. The most critical is that the measures used within the outcome set should be generic! The desire to develop measures from scratch for OI is very understandable, however extremely
challenging as the measure would need to be validated across languages, different types of OI and age groups. This is the reason why we have chosen many PROMIS measurement tools. PROMIS has a strong scientific basis and has been widely used for many years. PROMIS is not perfect, but is proven effective in many conditions, it has been used with OI already in various hospitals, it is available for free, and for some areas available in more than 50 different languages.

Are there costs connected to some of the recommended tools?
There is no cost for the use of Key4OI for non-commercial purposes. PROMIS is free of costs for all the existing translations. Costs are only involved when a translation needs to be generated. It would be a once off fee.

OI in children and adults - same thing or 2 different planets?
Key4OI started out with developing a version for children and one for adults, as we were convinced that they would be very different planets. Throughout the process we found ca. 80% overlap and it became clear that many “adult issues” that don’t seem to play a key role for children, actually do start at a younger age. It will be tremendously useful to take a “lifelong perspective” for achieving the best outcomes for people with OI.

Any messages to the readers of OIFE Magazine?
There is just one advice: Please start using Key4OI!

- Download the checklist to support your next appointment if you are person with OI or a parent!
- Discuss Key4OI with your expertise centre if you are a patient organization. They are welcome to use it!
- Consider working with the Key4OI approach if you are a healthcare provider!
- Use the data that will eventually become available, if you are a researcher!
- Talk to us if you are an industry representative and you want to link up with Key4OI!

More information can be found on www.key4OI.org.

If you have any questions, please contact us on info@key4OI.org and join us in the virtual www.qualityoflife4oi.org conference on 12 February, which includes Key4OI as one of the information streams.

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<th>Basic Science Survey – deadline February 1st</th>
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<td>Are you involved in basic science? Then we would like to make you aware of the OI Basic Science Survey. The Survey is initiated by the Care4BrittleBones Foundation. The purpose of this survey is to explore the Basic Science Research activities related to OI in the widest sense. Care4BrittleBones would like to identify common challenges and opportunities in order to work together on solutions going forward. The information provided will be treated confidentially. An anonymized and aggregated version of the survey will be shared more broadly and be discussed in the Basic Science workshop during the Conference QualityofLife4OI on 12th of February 2022: <a href="http://www.qualityoflife4oi.org">www.qualityoflife4oi.org</a></td>
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Link to the survey for Basic Scientists interested in OI: https://www.surveymonkey.com/r/RX63D58
About mice, zebrafish and chemical chaperones

Interview with Antonella Forlino, professor of Professor of Biochemistry at the Department of Molecular Medicine at the University of Pavia, in Italy

Who are you & what is your relationship to OI?
I am a Full Professor of Biochemistry at the Department of Molecular Medicine at the University of Pavia, in Italy. I dedicated my research activity to OI and I developed a long-standing expertise on this field along the years. I started during my Master Degree working with primary patients’ cells, I continued during my PhD studying OI extracellular matrix in vitro. During my post-doctoral training at the NIH in Bethesda I generated the first non-lethal murine (mouse) model and finally I focused on OI in my independent research activity when I established my own laboratory in 2001 in Pavia. I am interested to investigate the molecular basis of dominant and recessive OI forms, especially the ones causing abnormal collagen structure, aiming to identify new targets for innovative therapies. My lab is now focused on pharmacological approaches, but we are aware of the relevance of gene therapy to cure the disease and we will love to work on that in the future as well.

What project are you working on at the moment?
In my lab we have several projects running. Most of them are centred on translational approaches focused on OI. One of our projects is involving murine (mouse) models of dominant OI and another dominant and recessive OI zebrafish models. Both are addressing the testing of new pharmacological therapies based on targeting Endoplasmic reticulum stress (ER stress), a key modulator of disease severity, recently proved by us, to be a valid target to treat OI in preclinical studies. ER stress occurs when proteins are not properly folded or conformed (misfolded protein).

What is the project about?
Using dominant murine models for OI we are employing different approaches to improve the effect of the chemical chaperone 4PBA either by combining anabolic and antiresorptive therapies, by using new modified molecules designed by molecular modelling and attempting several administration routes. Using dominant and recessive OI zebrafish models we are performing drug screening to test new molecules targeting ER stress as well as other intracellular pathways and evaluating their effect on bone structure and composition.

Who is behind the project and how is it financed?
The projects are carried out by my group that includes a young researcher, three PhD students, two postdoctoral fellows and several Master students. The availability of grants in the field of rare diseases is challenging. We are at the moment supported by OI associations (OIF and ASITOI), a national grant an R-21 NIH grant. We are continuously applying for grants both at national and international levels, often in collaboration with other OI labs. It is a great community to be part of!

How many/which types of animal models are there in OI?
The research community have several animal models to investigate molecular basis of OI as well as to attempt translational investigation. Both dominant and most of the recessive OI forms have been reproduced in animal models, now available and providing unique tools for preclinical investigations. The most used are mice followed in the recent years, by zebrafish.
How can you learn about bone structure in OI by studying fish?
Indeed, zebrafish do not have limbs! Nevertheless, all the bone cell types: the bone forming osteoblasts, the bone resorptive osteoclasts and the bone mecanosensor osteocytes are present in zebrafish bones; both endochondral and membranous ossification (bone formation) are present and, due to the swimming mode, the vertebral compression and fractures are better reproduced in fish than in murine models. Cell differentiation and intracellular pathways are highly conserved.

Also the availability of several transgenic lines expressing fluorescent dyes under bone cell specific promoters and the transparency of embryos and juvenile fish allow to follow in vivo bone cell differentiation. The tail regeneration ability of zebrafish allows to investigate bone formation in adults. Finally taking into consideration size, cost and amount of drugs needed, zebrafish definitely allow large drug screening investigation at low cost and quicker time compared to other animal models.

Do you have any findings/results yet?
In the last years we published four studies proving the goodness for OI of targeting ER stress using the chemical chaperone 4-phenylbutyrate. This already approved drug was effective in ameliorating cell homeostasis in primary fibroblasts from dominant and recessive OI patients, in primary osteoblasts from dominant OI murine models and also 4PBA ameliorated skeletal properties in the dominant OI Chihuahua zebrafish model.

In which way can the results from your project be used in clinical research?
The identification of molecules able to ameliorate cell homeostasis and/or bone properties in vitro and in vivo could be translated to patients. Of course the timing will depend on their approval by FDA and EMA and it will generally be quicker if the drugs are already approved for other disorders. This is the reason why my lab is selecting a repurposing drug approach.

Were patient organizations involved?
My research has always seen the involvement of patient associations, especially ASITOI, but also, BBS, OIF and OIFE. I strongly believe it is fundamental to have a close contact with the patient community, since overall my research is strongly motivated by them and their demand. To contribute to health in OI has moved my activity since the beginning. I participate in the patient’s meetings and I am member of the OIFE Medical Advisory Board, trying to be available whenever my expertise could be of support. Often they support my grant applications.

What do you do when you don’t study fish?
I study mice. Hehe. Besides research, I love to bike and I try to do that as soon as I have some free time. I also love to read, especially thriller stories! I love music as well. I cannot live without it, and I do not go to bed before I have watched a movie.

Do you have any messages for the readers of OIFE Magazine?
Be part of the OI community, support it, contribute to it, and be motivated to enlarge it beyond national borders!
Why does Denmark have so much registry research?

My name is Lars Folkestad. I am an associate professor and staff specialist at the department of endocrinology at Odense University Hospital. There I am part of the team that follows and cares for adults with OI. We are aiming towards a multi-disciplinary approach to our outpatient OI clinic visits, but most of our efforts have been halted due to this horrendous COVID situation.

Which research projects related to OI are you currently working on?
Funding clinical research related to rare diseases can be difficult in today’s climate. We are currently trying (and failing) to finance a nationwide clinical study to elaborate on the extra skeletal aspects of OI. Luckily, we have been able to fund epidemiological studies using the Danish health registers. I am currently working with these data and hope to be able to share them with you shortly. Denmark is a rather small country and adult OI care is situated at 3 University centres. We are very set on collaborating and sharing knowledge to ensure the best care of our patients. Did you read the interviews with Emilie and Marie-Louise? I cannot stress how impressed I have been working with them.

Why is there so much registry research coming out of Denmark?
The Danish health registers are unique data sources intended for governance - where almost everything is registered about everybody all the time. Furthermore, data collection is mandatory by law and for the most part done automatically using the clinical database that we use in everyday work in all aspects of the society from schools to hospitals. In Denmark every inhabitant is given a unique personal identifier that can be used for record and register linkage. This makes it possible for long-term follow-up literally without any missing data. The coverage of the registers is above 99%. Time and time again they have been shown to be valid regarding accuracy of the data. During my PhD studies, one of my supervisors – Professor Bo Abrahamson - introduced me to the method. We then worked together on using the registers for rare bone diseases such as OI. We have been lucky to be able to update our data and have many more questions to answer.

What are the benefits and limitations of registry research as a method?
The benefits, if you ask me, are obvious. We are dealing with a rare condition and collecting clinical data on all patients in Denmark would be difficult to say the least. Using the registers, we have nationwide and population-based data on for example contacts to the health care system. This can be used as markers of diseases associated with OI, and we can even compare the OI population with the general population if this is of interest.

The limitation of the registry data is that it’s just that, register based. We have little or no clinical data. For example, I can tell you what the risk of asthma is in the OI population and drug use related to asthma, but I cannot tell you anything about pulmonary function.

Furthermore, the clinical spectrum of OI is as you know quite wide or in other words OI is not just OI. The register data will give us information about who has OI but not what genetic background or clinical severity. We are however working to overcome this limitation, but we are not there yet.
Any messages to the OIFE Magazine readers?
I hope that 2022 is the year where we get to meet up, discuss and develop new ideas for new projects face to face. I really hope that the International OI conference will take place in Sheffield this year. Zoom and other online meetings are great and a way to stay updated and keep in touch. But nothing beats sitting down talking to people, after a long day at a conference. This is where the best networks are formed, and the best ideas come to life. Fingers crossed. See you all soon!

Risk of eye diseases in OI

Interview with Marie Louise Lyster, medical student from University of Southern Denmark in Odense

My name is Marie Louise Lyster. I am a 26-year-old medical student from University of Southern Denmark in Odense, graduating in January 2022. In the beginning of 2021, I started working on my research project about risk of eye diseases in OI as my master’s project with my supervisor, Lars Folkestad, MD. Together with the rest of the team we published the article in *Bone* in November. This was my first time working with an OI related topic and I found it very interesting!

Who was behind your project?
I did the formal analysis, visualization, writing of original draft, editing and review with help and guidance from my supervisor, Lars Folkestad, who also did the investigation, funding acquisition and conceptualization. Jannie Dahl Hald, Malin Lundberg Rasmussen, and Jakob Grauslund helped with review, editing and conceptualization. The study is a nationwide register-based open cohort study based on data from The Danish National Patient Register. We included all patients registered with an ICD-8 or ICD-10 code for OI between 1st of January 1977 and 31st of December 2018. Each OI patient was matched with 5 reference individuals. A list of different eye diseases related to parts of the eye rich in collagen I were included, and we compared the risk of each eye disease between the OI cohort and the reference population. Funding sources are Odense University Hospital, Free Research Fond, Region of Southern Denmark, Grant for continued clinical research and Jascha Fonden, Research Grant.

What was your research project about?
Our project is about risk of eye diseases in OI. Collagen I plays an important role and is an essential structural component in different compartments of the eye. Due to the qualitative defects in collagen I in OI we hypothesized that patients with OI are likely to have an increased risk of ocular diseases related to parts of the eye rich in collagen I.

What were your most interesting findings?
Our results showed an increased risk of eye diseases in OI compared to the general population. We also found that most of the included eye diseases were diagnosed at an earlier age in patients with OI compared to the reference population. It is possible that eye diseases are discovered sooner and more frequent in OI patients due to specialist follow-up and care (surveillance bias). Our results indicated some degree of surveillance bias, however, the effects on the risk estimates were negligible.

What is the take home message for clinical work?
There is an important ocular aspect of OI. Some of the included eye diseases can potentially be sight threatening. Thus, regular examinations by ophthalmologists could be considered to detect these diseases at an earlier age in OI patients. It is necessary with further research to understand the role and severity of eye diseases in OI.

Marie Louise:
“The most important take home message is that ocular diseases may play a significant role in OI. I think that more attention should be centred around the risk of eye diseases in OI.”
Fracture risk after pregnancy in women with OI

Interview with Emilie Karense Lykking, newly graduate doctor from University of Southern Denmark

I am a newly graduate doctor from University of Southern Denmark, who found interest in OI during my final year of Med. School. At the moment I am working at the department of endocrinology at Bispebjerg Hospital in Copenhagen.

I wrote my thesis on Fractures following pregnancy among women with OI through supervision from Dr. Lars Folkestad. I found a special motivation in investigating this further since few studies have evaluated the risk of fractures related to pregnancy in OI.

Who was behind the project?
We are a group of researchers from different European countries. The team consists of Emilie Karense Lykking, Heidi Kammerlander, Fleur S van Dijk, Daniel Prieto-Alhambra, Bo Abrahamsen, and Lars Folkestad. In cooperation with Lars Folkestad, I designed the study, analysed data, and wrote the main draft of the article. The project used a self-controlled-case series (SCCS) method, based on register data from the Danish National Patient Register.

Emilie: “When a woman with OI has a desire to become pregnant the risks advocating against should be properly investigated.”

The SCCS method is an epidemiological study design in which individuals act as their own control where only cases are included, and a comparison is made between incidence rates in time windows before and after the exposure of interest. In this case pregnancy.

I received government financed education support, which all Danish students receive each month. Apart from that, we received no funding.

What was your research project about?
The project evaluates the fracture risk 12- and 19-months prior to conception compared to a period of 12- and 19 months following childbirth. The study is based on data from the Danish National Patient Register collected between 1995 and 2018. We included all women who gave birth between 1995 and 2018 and compared their fracture rate 12 and 19 months before and 12 and 19 months after pregnancy. It is known that non-OI women loose bone mass in relation to pregnancy and breastfeeding. It is also known that the BMD fully recovers 19 months postpartum (after childbirth). Few studies have evaluated the risk of fractures related to pregnancy in OI. Our hypothesis was that women with OI would experience a higher incidence of fractures during pregnancy and postpartum due to a fall in bone mineral density.

What were your most interesting findings?
Using a 12-month window of observation we identified a total of 20 fractures; ten fractures in the pre-conception period and ten fractures related to pregnancy and postpartum.
Amounting to an Incidence Rate Ratio of 0.8 with a 95% confidence interval (0.3-2.0). This indicates that there is no difference in fracture rates in relation to pregnancy. This stayed true when adjusting for age at delivery and we found similar results when using a 19-month window of observation.

It is important to mention that we had no data on OI phenotype. We had data on height that indicates that most women in our population have a milder phenotype. It was a surprise to find that based on our data we could not identify any increased risk of fractures when comparing fracture rates 12 or 19 months prior to conception to fracture rates during pregnancy and 12 or 19 months postpartum in women with OI.

**What is the most important take home message for clinical work?**

When giving advice to women with OI who have a desire to become pregnant it is important not to create a bugbear. I have come by some patient societies advising women with OI to think twice about becoming pregnant due to the possible increased risk of fractures during pregnancy and post-partum. Our study shows that this might not be the case. I urge doctors to do more research in this area, so we can document the actual risks and possible complications and not base our clinical work on conjectures.

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**Osteoarthritis in OI**

*Interview with Jane Dahl Andersen, MD with specialty in Endocrinology and Internal Medicine at Lillebælt Hospital, Denmark*

My name is Jane, I am a MD with specialty in Endocrinology and Internal medicine. My specific interest is in bone and calcium metabolism, in particular the rare disease OI. In the Bente Langdahl group at Aarhus University Hospital, DK, I had the opportunity to see OI patients in research projects and to some extent in the out clinic too.

However, I am now working in the southern part of Denmark, at Lillebælt Hospital with more general bone and calcium metabolism. But I still have a profound interest in OI and at the moment I am working with Lars Folkestad, on another OI project.

**Who was behind the project?**

The idea for this project arose at Merton College in Oxford, UK, where I was at a Clinical Training course on Osteoporosis and other Metabolic Bone Diseases arranged by the Bone Research Society, having lunch with Bo Abrahamsen among other colleagues, back in April 2017. It seems a long time ago. The challenge has been that all involved authors have taken time out of their free time/ spare time as most of us working in the clinic, not fulltime researchers.

**What was your research project about?**

The project was built on an idea from clinical experience, a question arose: Is osteoarthritis (OA) more frequent in osteogenesis imperfecta? What is the risk of osteoarthritis in OI?

**What was your most interesting findings?**

We found that OA is more frequent in OI and at a younger age, compared to the background population. Our findings are based on registers, which of course have some limitations, and for sure more clinical studies need to be conducted, I still however, find it very satisfying, that my assumption from clinical work with OI is supported by the results of this project.
A Roadmap to Surgery in OI

Interview with
Ralph J.B. Sakkers, MD, PhD, Paediatric Orthopaedic Surgeon,
Department of Orthopaedic Surgery, University Medical Center Utrecht, The Netherlands
& Simona Paveri and Leonardo Panzeri, Italian OI-association As.It.OI

What was the purpose of the project “Roadmap to Surgery in OI”?

Dr. Sakkers: The purpose of the project Roadmap to Surgery in OI was to create a roadmap for a standardized, integrated approach for optimal outcomes of surgery in OI, not only from a surgical view, but also from the patient’s perspective, that can be used in all infrastructures and cultures. The roadmap has been endorsed by the Study Group Genetics & Metabolic Diseases of the European Paediatric Orthopaedic Society and by the Executive Committee of the Osteogenesis Imperfecta Federation Europe and the Care4BrittleBones Foundation.

The article is open access and can be found here: https://pubmed.ncbi.nlm.nih.gov/34180749/

How did you work?

Dr. Sakkers: The international interdisciplinary task force included members from European patient organizations and 12 healthcare professionals (HCPs) in orthopedic surgery, rehabilitation medicine, and nursing from centres recognized worldwide as leaders in the interdisciplinary care of OI. The task force developed a survey on issues around OI surgery (defined and discussed by the members) who then consulted other experts worldwide. All the responses, and the subsequent group discussions among the task force members via 9 conference calls, formed the consensus expert opinion. A set of recommendations for surgical care was then drafted and discussed at a day-long workshop during the International Conference for Quality of Life for Osteogenesis Imperfecta in Amsterdam, the Netherlands in November 2019. The recommendations were subsequently circulated to members of the Study Group on Genetics and Metabolic Diseases of the European Paediatric Orthopaedic Society and the OIFE for endorsement.

What did the people with OI contribute with vs. the professionals?

Dr. Sakkers: The collaboration between people with OI and professionals was very good, not only during the group discussions in the task force, but especially also in the day-long workshop during the International Conference for Quality of Life for Osteogenesis Imperfecta in Amsterdam where many patients from many different countries and different continents were present. One of the very important contributions from the patients among other contributions were the descriptions of the different socio-cultural environments and the descriptions on how these differences influence the possibilities for, and needs and personal experiences of the different patients.
Leonardo and Simona: A specific strategy was adopted by us to represent the patient perspective. During a 10 year period, lots of OIers (both adolescents and adults) and/or their families have contacted the Italian organization ASITOI to prepare themselves of surgery. Especially surgery of the long bones or the spine. Most of their questions, fears, problems, expectations have been deeply discussed both with them and with professionals.

The discussions held with professionals has been made both on an individual basis but also on a more generic level. This on issues common to many OIers, taking into account the age, type of OI as well as other factors. We have collected the various questions and expectations to try and provide the most comfortable and comprehensive environment for OIers in hospitals, rehabilitation centres and at home as for the pre-surgery, surgery and post-surgery phases.

We used this background and experience in the discussions to establish the roadmap. And we compared our input with the comments and observations by professionals from other countries. It was a very good experience.

What are the biggest challenges in OI surgery today?

Dr. Sakkers: That is not an easy question to answer. In general, the surgical management of the brittle bone in all types of surgery in OI remains a challenge.

Simona and Leonardo: The biggest challenge is the maintenance of good interactions with surgeons in addition to increasing the skills of the persons with OI in order for them to interact with surgeons. What do we mean by this? Well, it’s important to have a good enough understanding of OI surgery including a knowledge of those technical words which are often used by surgeons and specialists. This in order to be in a position to understand what is happening, etc. On this background it is important to continue to speak about these topics during national conventions and meetings with OIers in order to increase their skills and understanding of terminology in this field.
What are the biggest knowledge gaps?

**Dr: Sakkers:** The biggest knowledge gap in OI is the still existing considerable lack of knowledge on the multifactorial process and interactions that take place from the gene to the formation of the actual bone/skeleton. For example, in families with OI, the same mutation in the cells can lead to large differences in severity of OI among the family members that have the same mutation.

This meaning that the mutation in the coding for collagen only starts an interaction process of which the subsequent components and their interactions and effects are still largely unknown, not only for OI bone, but also for normal bone. This subject is not directly addressed in the Roadmap, since the surgery can be helpful for the patient as a support, but is not the solution for the brittleness of the bone.

**Simona and Leonardo:** Most surgeons still have no knowledge at all on OI, which is natural since it is a rare disorder. But more importantly—a big challenge is due to the fact that there still are surgeons who decide to do surgery on or treat OI patients, even if they have no knowledge or experience in OI, without seeking advice from someone who has experience. For this reason, it is important for patients to have a good basic knowledge package. Another gap is the lack of unified measurements of outcomes in surgery. In this context, the Key4OI project seems promising or at least a good starting point.

A more general knowledge gap in OI - we lack knowledge on basic research. More focus on this could lead us to an effective treatment for OI in future. However, the continuous interaction with institutions, pharma companies, ministries of health, etc. is of great importance for patient organizations. We need to be involved at the time when new treatments/drugs are tested and we need to take a more active role in the risk evaluations of new treatments and methods.

**Were there any surprises during the process?**

**Simona and Leonardo:** During the process of the surgery roadmap, we were really surprised about the fact that in some countries, especially Canada, the patient’s point of view and the one of the family members, was already part of an integrated approach. We were really impressed by this, in a very positive way. Apart from this, we have been really impressed by the positive reactions from adolescents who have actively participated and have played an active role to discussions, being able to speak about themselves and the problems they must face.

**Can you give a very short summary of the recommendations?**

Consensus on recommendations was reached within 4 themes:

- the interdisciplinary approach
- the surgical decision-making conversation
- surgical technique guidelines for OI
- the feedback loop after surgery

The interdisciplinary approach was subdivided in the topics “Patient view” and “Health Care Professional checklist”. The surgical decision-making conversation focused on shared decision making and an individual approach for each case, taking into account cultural variations and values, the role of the decision maker and local regulations. Surgical technique guidelines were subdivided in the topics General, Lower Extremity, Upper Extremity and Spine. The feedback loop after surgery explained the importance of the evaluation of both clinical and patient-reported outcomes by using core outcome measurement tools that can be used globally such as the Key4OI Standard Set of Core Outcome Measurements for OI.
Artists & activists with OI: Benjamin Mejía
Interview with Benjamin Mejía, El Salvador

Who are you and what is your relationship with OI?
I am Benjamin Mejía, I am 28 years old, I live in the City of San Salvador, Capital of the Republic of El Salvador, Central America; I am currently a Fourth Year Student of the Architecture Degree at the University of El Salvador. I have OI type I.

When I was born, my parents were told I would never walk. But thank God, at the age of 28, I can walk without the help of orthopedic devices, even if I have some walking problems due to previous fractures. For a couple of years, I received Fosamax, to strengthen my bones. And Fortunately, I have recovered from all my fractures. At the age of 14 I began to have hearing loss, which progressed. Currently I use intracranial hearing aids, which I can control with an app on the phone.

How is the situation of people with OI in El Salvador?
Unfortunately, most people with OI in El Salvador have low income. The majority of people with OI are excluded from society because of their disabilities. In El Salvador there are few people with OI who manage to study, complete high school or a university career. There is no registry of people with OI in the country, nor demographic data of people with OI or other disabilities in general. The only thing that exists is a group of children who receive intravenous medicine from time to time at the Benjamin Bloom National Children’s Hospital, in San Salvador. Most of these children have few economic resources, and sometimes they receive donations to pay for the medicine. But I am sure there are many cases, to which the support does not reach.

Do you have an OI-organization or group in El Salvador?
There is only a group on Facebook called Osteogenesis Imperfecta El Salvador, but it is made up of parents of children with OI. Personally, I only know two adults with OI. I tried writing something in the newspaper to create awareness on Wishbone Day. But the newspaper chose a completely different angle which didn’t focus on OI at all, something which made me both angry and disappointed. This made me give up on projects related to OI for the time being. But I can try again if there are other adults with OI in El Salvador who would be willing to help. In the meantime, I am involved in general disability activism promoting human rights for people with all kinds of disabilities.

We have heard that you have been involved in disability advocacy lately?
In November 2019 I graduated from the first training in Politics, Public Policy and Governance given to young people with various disabilities. The purpose of this training was to train leaders who would be agents of change for the benefit of people with disabilities, thus enforcing Article 32 (Right to Participation in Political and Public Life) " in the Special Law of Inclusion of Persons with Disabilities of El Salvador which has been in force since 1 January 2021.

Unfortunately to date, our Law, although it is already in force, does not have an assigned budget to be executed or an implementation plan, to secure the fundamental human rights of people with disabilities in El Salvador. In December 2020, I graduated from a training in public policies and Sustainable Development Goals of the
2030 Agenda (SDG 2030), which at the global level, nations and states parties intend to meet by 2030. It was a training for young people who are involved in political and social advocacy, and I represented the voice of disabled students together with one other person. Leave No one Behind! In June 2021, I obtained a scholarship to study Human Rights and Advocacy, from which I successfully graduated on December 3 of this year 2021.

What do you do as an artist?
Art is more of a hobby of mine. But I do practice a Pencil-Based Sculpture Technique. This means I cut and paste coloured pencils and create small sculptures from them. I was part of an art contest in 2012, where the use of BIC products was requested. In the Creativity Category we had to create a sculpture with any product of that brand, based on the theme of the contest, which on that occasion was: My Country El Salvador. The next year the topic was My Family. I won the first prize both years. After that I have created various sculptures, some with a patriotic character, and others with a character of awareness and Inclusion of people with Disabilities. You can follow me on Instagram @bengi_mjart

What kind of artwork do you like to make the most?
Those that leave a message of awareness, and those that recreate objects of Nature.

What role does the artist have in society?
An Important role, because through art we can express emotions, transmit positive messages, social awareness and leave a legacy to society.

Do you have a message for the readers of the OIFE Magazine or for OIFE?
A phrase that I want to share with you is the following: “People like birds are different in flight, but the same in their right to fly”. Let us remember that the most democratic states are those that respect human rights. People with disabilities in general are subject to rights, therefore, everyone's job is to respect, raise awareness, and fulfil the human rights of people with disabilities.
YOUTH WEEKEND BELGIUM
From May 5 to May 8, 2022 the youth weekend will take place in Bruges, Belgium. Registration is open now and will close February 1st: forms.gle/tGH2ZeMkPyPVc8o89

SECOND OPINION SERVICE IN SPAIN
Have you ever wished that you had the opportunity to ask for a second opinion after receiving medical advice from your doctor? The Spanish OI-organization is now offering a second opinion service, where people with OI and other rare bone conditions can get a second opinion from experts in the field. The process is coordinated by the social worker Belén Ahuce.

NEW MEMBERS IN ERN BOND
On 1st of January 2022, 620 new members will join the European Reference Networks, as unanimously approved by the ERN Board of Member States. 22 new healthcare providers have been accepted by the EU as full members of ERN BOND from the following countries: Austria, Germany, Denmark, Spain, Finland, France, Ireland, Italy, The Netherlands, Norway and Portugal. See a full list on oife.org

DO YOU KNOW WHAT A PATIENT REGISTRY IS?
Do you know what a patient registry is? Our role is to ensure that patients' perspectives are included in the development and use of such systems. Are you interested in learning more? Join the NEW Open Academy online course created by EURORDIS. Enrol here: l.eurordis.org/6rag

GOOD NEWS FOR EUROPEAN NGOs
We are happy to announce that thanks to the campaign #BringBackOperatingGrants and Members of the EU Parliament (MEPs) who care about rare conditions, the operating grants for health NGOs in Europe are back! Health NGOs include the larger organizations like the European Patients’ Forum and EURORDIS, which OIFE is very much dependent on in our policy work.
NEW OIFE MEMBER - ZERO ONE
We welcome the Chinese foundation Zero One as new associate member of OIFE. The Zero One Rare Bone Disease Foundation was established on February 28th, 2019 and became a special foundation in January 2020. They are based in Shenzhen in the South of China and are currently in touch with more than 1750 people with OI. We wish them a very warm welcome to our international OI-network! You can read more about them on this webpage.

GREETINGS FROM PERU
On December 10th, children with OI received their second dose of treatment in 2021. It was held at the Pediatric Service of Antonio Lorena del Cusco Hospital, directed by Dr. Javier Cuno Vera. The organization Asociación Osteogénesis Imperfecta del Perú calls on their health authorities for approval of "The Technical Guide for Care of Patients with OI" so that more hospitals in Peru’s provinces can replicate the initiative of Cusco.

UN RESOLUTION ON RARE CONDITIONS
ON December 16th the first ever UN Resolution on Persons Living with a rare condition was adopted by consensus. It was supported by all 193 Member States of the United Nations. We congratulate Rare Diseases International and collaborators with this huge victory. Let’s all hope it will make a difference for people living with a rare condition!

SUBMIT YOUR PHOTO TO EURORDIS PHOTO AWARD!
Can we once again manage to get a photo of (or by) a person with OI reach the top 3 podium in the photo award of EURORDIS?

Find your cameras and shoot a photo representing life with a rare condition. Submit your photos here: 1eurordis.org/xeZQ

TRANSITION FROM CHILD TO ADULT
What are the important aspects to think about when a child is about to transfer from pediatric to adult care? When do you start planning? What is important to think about? This article about transition from pediatric care to adult care of people with XLH could just as well have been written for people with osteogenesis imperfecta. It is open access, so anyone can download and read the entire article.
Research announcements

Romosozumab Trial for OI

The company Amgen is sponsoring a multicenter clinical trial to study the safety, pharmacokinetics, and pharmacodynamics of the investigational drug romosozumab in children and adolescents who have OI. Currently the study is open to eligible children ages 5 to less than 18 years of age who have a diagnosis of OI Type I through IV. The study has sites participating in this clinical research in the following countries: Germany, Hungary, Italy, Spain, Greece, Turkey, Russia, Austria, Netherlands and Switzerland. For more information, please visit the clinical trial registry page at: https://www.amgentrials.com/study/?id=20160227

If you have any additional questions, please contact the Amgen Call Center at +1 (866) 572-6436 or send email to medinfo@amgen.com. A Customer Service Representative will be able to find a study site near you and provide you with the site study contacts who can tell you more about the clinical research study.

DISCLAIMER

The OIFE is not involved in the design or management of research studies we announce and as such, is neither endorsing nor supporting these studies. The mission of the OIFE is to keep the OI community informed of all relevant studies. This information is made available as a service to the OI community. We are available to answer questions on this or any other research announcements. Please contact the OIFE at office@oife.org if you have any questions.
Save the (new) date OIFE Investigator Meeting!

OIFE INVESTIGATOR MEETING NOV 18TH 2022

OIFE is together with members from our Medical Advisory Board inviting you to save the date for the very first virtual European Investigator Meeting for osteogenesis imperfecta (OI).

Date
November 18th 2022 (on Zoom)

Time
2 PM – 7 PM Central European Time
8AM – 1PM Eastern Standard Time

Programme committee
The programme committee of the 2022 edition consist of the following European researchers and members of the OIFE MAB: Claire Hill (UK), Antonella Forlino (IT), Lars Folkestad (DK), Liidia Zhytnik (EE)

What is the aim of the event?
Our aim is to present an overview of current OI-research (basic and clinical) in Europe and beyond. Presenters will include both experienced OI-researchers and new investigators.

Target group
The target group is primarily researchers and clinicians working with OI, but anyone interested in OI-research can join.

Invited speakers
The following invited speakers have been confirmed: Frank Rauch (CA), Brendan Lee (US), Nick Bishop (UK), Oliver Semler (DE)

Further information & updates
For further information, please contact the event coordinator Ingunn Westerheim on office@oife.org

To receive updates about the event – sign up here.
Contact

Ingunn Westerheim (President): president@oife.org
Ute Wallentin (Coord. Social Network): socialnetwork@oife.org
Stefanie Wagner (newsletter editor and secretary): secretary@oife.org
Stephanie Claeyys and Simey Truong (Youth Coordinators): youth@oife.org

Website: http://www.oife.org
Facebook: www.facebook.com/OIFEPAGE
Twitter: @OIFE_OI
Instagram: oioife
LinkedIn: https://www.linkedin.com/company/oife
YouTube: OifeOrg