# EJP RD
# European Joint Programme on Rare Diseases

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# Del 16.2
# Content of the first five online modules

**Organisation name of lead beneficiary for this deliverable:**
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Public

# Overview

# 1. Overview of the MOOCs development

WP16 aims at developing a streamlined academic online programme on rare diseases research. The 10-12 modules envisioned at the incipit of the project were challenged by outputs of activity 16.1 (in 2019), ranked by priority order and narrowed to 5 MOOCs (covering most topics envisioned at first) (see analysis of the survey carried out in 2019 in D16.1).
These 5 MOOCs cover the following topics:

- #1 Diagnosing Rare Diseases: from the Clinic to Research and back (delivered April 2021)
- #2 Innovative personalized therapies (expected launch: Sept. 2022)
- #3 Translational research applied to rare diseases (expected launch: April 2022)
- #4 Clinical Trials methodologies – co-developed with EJP RD WP20 (expected launch: Early 2023)
- #5 Rare Diseases data: ethics & regulatory challenges (expected launch: 2023)

Each course is built with Key Opinion Leaders and experts, incl. European Reference Networks representatives. MOOCs are freely accessed and hosted by the FutureLearn platform. The online platform was chosen after a thorough benchmarking as well as internal discussions in the EJP RD consortium at the EJP RD first General Assembly in September 2019 (M9).
The present deliverable is focusing on the three first MOOCs for which a detailed overview is available. It also includes the preliminary outline of the MOOC#4. As of M35, the detailed outline of MOOC#5 is not yet available even though initial conference calls and discussions have been held with the co-coordinators of the MOOC in 2021 to identify key topics. The full content of the MOOC#4 and the MOOC#5 content will be detailed in the D16.3 "Content of the full online course" due in December 2022."

# 2. MOOC#1 - Diagnosing Rare Diseases: from the clinic to research and back

## 2.1. MOOC#1 Working Group, timeline & structure

The MOOC#1 is coordinated by FFRD (Roseline Favresse) and has been co-developed with two representatives from ERN Ithaca (Laurence Faivre) and ERN Genturis (Chrystelle Colas) together with EURORDIS (Virginie Bros-Facer) who contributed all along the way by providing writing support, reviewing successive versions of the text and matchmaking with contributors, especially from PAOs.
The MOOC#1 was first delivered in April 2021 (M28).
Enrollment is free and currently open twice a year (Spring and Autumn) for an 11-week-period. Access is granted to each learner for a 7 week-period. The MOOC is totally asynchronous. The content is spread over 5 weeks, for a total volume of circa 15 hours. The course is made up of 118 steps that address the different aspects of the rare disease diagnostic pathway, both from a clinical and research perspective. 30 videos were produced specifically for this course, including eight "motion" videos. 14 international experts were interviewed, including seven patient representatives. The course is interactive, with nearly one-third of the steps requiring learner engagement.

Nine exercises have been created and more than 65 publications referenced. As of December 17th, 2021, two runs have been held (from 26 April till mid-July and from 4 October till 20 December),. 2985 learners have enrolled, from 130 countries. 3000 comments have been generated. [see the upcoming Deliverable 16.4 "First Impact assessment of the online academic course" for further information on the impact assessment of the two first runs of the MOOC#1].

## 2.2. MOOC#1 Course overview

The content detailed below is currently available online through the FutureLearn platform here as the MOOC#1 is now active and running twice a year.
This content will be reviewed and updated on a regular basis based on: (i) comments from learners that may lead to the inclusion of new contents and updates, (ii) the review of the impact assessment studies performed by task 16.3 leader, (iii) any other major scientific developments that would need to be considered.
Two upcoming developments are foreseen for 2022: i) interviews from a clinician with specific background and expertise on ethics will be added at different stages of the MOOC to open up further on ethical issues –a topic that is currently not comprehensively addressed; ii) a series of motion design videos will be created to explain the most recent advances on "Omics" technologies that are relevant for diagnosing rare diseases.

**WEEK 1. Introduction to the course** (28 steps)

- Welcome and Introduction
  - 1.1 - Why this course? *Article*
  - 1.2 - Topics of the week *Article*
- What is a rare disease?
  - 1.3 - Rare diseases: introduction and definitions *Article*
  - 1.4 - What is a rare disease? *Article*
  - 1.5 - Are some cancers considered as rare diseases? *Article*
  - 1.6 - What is the impact of rare diseases on patients? *Article*
  - 1.7 - Glossary for Course "Diagnosing Rare Diseases: from the Clinic to Research and back" *Article*
- Are all rare genetic diseases inherited?
  - 1.8 -Genetic inheritance: introduction and definitions *Article*
  - 1.9 - Monogenic disorders inheritance patterns *Article*
  - 1.10 - Other inheritance patterns *Article*
- Challenges met when diagnosing rare diseases
  - 1.11 - Defining diagnosis *Article*
  - 1.12 - Why is it important to have a diagnosis for a rare genetic disease? *Article*
  - 1.13 - Eva's story: "At that point, I felt that either I was an extremely unlucky person, or something was really wrong with me" *Article*
  - 1.14 - Is the genetic diagnosis process similar for all rare diseases? *Video (01:27)*
  - 1.15 - Alex's diagnostic story: a testimony from a geneticist *Article*
- What do we call a diagnostic odyssey?
  - 1.16 - What is a diagnostic odyssey? What are unsolved cases? *Article*
  - 1.17 - Detailing a long patient's diagnostic odyssey *Audio*

    - 1.18 - What to expect from a genetic diagnosis? *Video (01:41)*
    - 1.19 - Joan's story: "I like to see a doctor who sees the bigger picture" *Article*
- The place of patients' groups and organizations
    - 1.20 - Kay's story *Video (04:29)*
    - 1.21 - What is SWAN? what are their objectives? *Video (07:53)*
    - 1.22 - Emily's Story - Part I *Article*
- Why is it so important to put a name to a disease?
    - 1.23 - Summarizing issues at stake around the diagnosis *Article*
    - 1.24 - Emily's story - part II *Article*
    - 1.25 - Joan's story: "How renaming the disease affected me" *Article*
    - 1.26 - Example of a patient diagnostic pathway *Video (01:51)*
- Test your knowledge
    - 1.27 - Check what you have learnt this week *Quiz*
    - 1.28 - Reflection on the week *Article*

**WEEK 2. What is the clinical diagnostic pathway for rare diseases patients?** (26 steps)

- Welcome and Introduction
    - 2.1 - Topics of the week *Article*
- How is a first genetic consultation held?
    - 2.2 - What is a genetic consultation? *Article*
    - 2.3 - Introduction to our 3 patients' cases *Video (03:05)*
    - 2.4 - The questioning patient/parent *Video (02:08)*
    - 2.5 - Collecting family history *Video (02:03)*
    - 2.6 - Exercise on family tree *Audio*
    - 2.7 - Investigating personal medical history *Video (03:04)*
    - 2.8 - Clinical examination and phenotyping *Video (02:18)*
    - 2.9 - Practice by using databases to reach a diagnosis *Article*
    - 2.10 - A few notions about psychomotor development examination *Article*
    - 2.11 - A focus on morphologic variations and dysmorphology *Article*
    - 2.12 - Prescribing paraclinical evaluations *Video (01:53)*
    - 2.13 - Proposal of genetic testing *Video (02:59)*
    - 2.14 - Results from genetic testing *Video (03:54)*
- Consenting to genetic testing - practical, ethical and research issues
    - 2.15 - What is informed consent? *Article*
    - 2.16 - What are additional data and secondary findings? *Article*
    - 2.17 - Beyond diagnosis: consenting for research studies *Article*
- Medical diagnosis and genetic diagnosis: degree of evidence and challenges
    - 2.18 - Degree of evidence of a medical diagnosis *Article*
    - 2.19 - What are the advantages and limitations of a genetic diagnosis? *Article*
    - 2.20 - The typical journey of a UK patient aiming for a diagnosis *Audio*
    - 2.21 - Is genetic diagnosis always beneficial for patients and families? *Video (02:25)*
- Diagnosing rare diseases in Europe - collaborations and realities
    - 2.22 - European Reference Networks: what are they? *Audio*
    - 2.23 - Are there differences in clinical genetic services across Europe? *Video (01:35)*
    - 2.24 - A patients' organization view on uneven access to diagnosis *Video (01:19)*

- Test your knowledge
  - 2.25 - Check what you have learnt this week *Quiz*
  - 2.26 - Reflection on the week *Article*

**WEEK 3. Diving into analysis and interpretation of genetic results** (34 steps)

- Welcome and Introduction
  - 3.1 - Topics of the week *Article*
- What are the available tests to diagnose a rare disease?
  - 3.2 - Introduction *Article*
  - 3.3 - Chromosomal genetic tests *Article*
  - 3.4 - Sanger Sequencing *Article*
  - 3.5 - Next generation sequencing (NGS) *Article*
  - 3.6 - Defining "coverage" and "depth" *Article*
  - 3.7 - Targeted gene panels *Article*
  - 3.8 - Targeted gene sequencing - a patient's case *Article*
  - 3.9 - Exome Sequencing *Article*
  - 3.10 - Genome Sequencing *Article*
  - 3.11 - Other genetic tests for specific hypotheses Article
- Genetic testing in practice
  - 3.12 - What does the future hold in terms of advances in genetic diagnosis in the clinic? *Video (01:30)*
  - 3.13 - Defining utility and validity *Article*
  - 3.14 - Which test for which suspected disease? *Quiz*
- How NGS techniques have been a game-changer in clinical genetic services?
  - 3.15 - What has changed in the last 10 years? *Video (03:01)*
  - 3.16 - What are the current main issues and opportunities in this field? *Video (01:41)*
  - 3.17 - Technological advances and patients' feelings *Video (02:05)*
- Explanation of the human genome variability and the challenges met when interpreting data
  - 3.18 - The variability of the human genome *Article*
  - 3.19 - Difficulties in interpreting data *Article*
  - 3.20 - Interview with Prof Han Brunner *Video (05:37)*
- What are prediction tools?
  - 3.21 - Pathogenicity prediction tools *Article*
- Basic principles of bioinformatics and biological analysis
  - 3.22 - Introduction to Bioinformatics *Article*
  - 3.23 - Bioinformatics applications to genetic analysis *Article*
  - 3.24 - Data interpretation *Article*
- Multidisciplinarity is the key
  - 3.25 - Why multidisciplinary collaboration is highly needed? *Article*
  - 3.26 - Has your clinical practice changed with the rapid uptake of NGS? *Video (01:34)*
- Reporting results to patients
  - 3.27 - The presumed diagnosis is confirmed *Article*
  - 3.28 - The diagnosis is an ultra-rare disease *Article*
  - 3.29 - The diagnosis is unexpected *Article*
  - 3.30 - The diagnosis is uncertain *Article*
  - 3.31 - No diagnosis could be found *Article*
  - 3.32 -Summary *Article*

- Test your knowledge
  - 3.33 - Check what you have learnt on genetic testing and results *Quiz*
  - 3.34 - Reflection on the week *Article*

**WEEK 4. What are the research steps to reach a diagnosis?** (20 steps)

- Welcome and Introduction
  - 4.1 - Topics of the week *Article*
- Specific research challenges of cases without diagnosis
  - 4.2 - Introduction *Article*
  - 4.3 - Cases without a diagnosis: what to propose to patients? *Audio*
  - 4.4 - Interview with Prof Han Brunner *Video (05:12)*
- Reclassification of Variants of Uncertain Significance
  - 4.5 - Introduction to what VUS are *Article*
  - 4.6 - A few more definitions *Article*
  - 4.7 - Classifying a variant as pathogenic *Audio*
- Family co-segregation
  - 4.8 - Understand family co-segregation *Article*
  - 4.9 - Family co-segregation: Exercise *Quiz*
- What is clinical and functional reassessment?
  - 4.10 - Defining clinical and functional reassessment *Article*
  - 4.11 - Genotype or phenotype first? *Video (01:20)*
- How to overcome negative exomes?
  - 4.12 - Why are some exomes negative? *Article*
  - 4.13 - Research options to overcome negative exomes *Article*
  - 4.14 - Additional techniques: ultra-deep sequencing & other tools *Article*
  - 4.15 - Additional techniques: other -omics technologies *Article*
- Importance of international collaborations
  - 4.16 - International initiatives to tackle undiagnosed rare diseases *Article*
  - 4.17 - Undiagnosed patients' networks *Video (03:43)*
  - 4.18 - Solving the unsolved - A research project *Article*
- Test your knowledge
  - 4.19 - Check what you have learnt so far *Quiz*
  - 4.20 - Reflection on the week *Article*

**WEEK 5. What's next after the search for a diagnosis?** (24 steps)

- Welcome and Introduction
  - 5.1 - Topics of the week *Article*
- How basic pathophysiological research can improve a diagnosis?
  - 5.2 - Basic research contribution to diagnosis – introduction *Article*
  - 5.3 - In vitro assays to assess the pathogenicity of a variant *Article*
  - 5.4 - How in vivo experimental model organisms can help in the diagnosis of a rare disease? *Article*
  - 5.5 -Using patient-specific induced pluripotent stem cells to improve diagnosis *Article*
  - 5.6 - Development of biomarkers *Article*
  - 5.7 - A case study: Amyotrophic Lateral Sclerosis (ALS) *Article*
- Towards multifactorial inheritance
  - 5.8 - Estimating risks and assessing the role of the environment *Article*
  - 5.9 - Risk prediction models and tools *Video (07:26)*

    - 5.10 - Genetic and environmental risk factors *Video (09:16)*
- Next Generation Sequencing: from Diagnosis to Prevention
    - 5.11 - A brief introduction to pharmacogenetics *Article*
- Why are rare diseases registries and databases especially important?
    - 5.12 - Registries and databases: some definitions *Article*
    - 5.13 - GenIDA: A database organized in the form of a social media *Article*
    - 5.14 - IAMRARE™ Registry Program & Undiagnosed Rare Disease Registry *Article*
- How Social Sciences can help better understand challenges surrounding rare disease diagnosis?
    - 5.15 - Why applying Social Sciences and Humanities to better understand rare disease diagnostic pathways? *Article*
    - 5.16 - Testimony from a Social Science Researcher *Article*
    - 5.17 - What does a diagnosis entail for patients' rights and recognition? *Article*
    - 5.18 - Does a genetic diagnosis impact on social support rare diseases patients and families can benefit from? *Audio*
    - 5.19 - How to deal with uncertainty? *Article*
    - 5.20 - Naming rare genetic diseases: gene or syndrome? Article
    - 5.21 - How to deal with additional findings? *Article*
- Next Generation Sequencing in medical practice: can we afford it?
    - 5.22 - A health economics perspective *Article*
- Wrap up and next steps
    - 5.23 - Check what you have learned this week and before *Quiz*
    - 5.24 - Reflect on what you have learned in this course *Article*

# 3. MOOC#2 - Innovative personalized therapies for rare diseases

## 3.1. MOOC#2 Working Group & Timeline

The MOOC#2 is focused on the Innovative Personalized Therapies for the treatment of rare diseases. A dedicated working group, led by FFRD (Magda Granata & Roseline Favresse) has been created and includes two scientific coordinators from ERN TransplantChild (Eduardo Lopéz Granados) and CVBF (Consorzio per Valutazioni Biologiche e Farmacologiche) (Giovanni Migliaccio). As of December 2021 (M35), further external contributors from relevant European scientific institutes and Patient Organizations are being contacted to collaborate on the development of this course. MOOC#2 is expected to be launched in September 2022 (M45).

## 3.2. MOOC#2 Course overview

Below is the final outline for MOOC#2. This MOOC will span over five weeks with approximately 3 hours of content each week. As for MOOC#1, the content is scalable with increasing levels of difficulty each week, enabling non-experts to attend the first week(s) of the course and more advanced learners to go through the whole course.

**WEEK 1. Getting into Innovative Personalized Therapies – Introduction to the subject and recap of basic knowledge**

- Sub-Activity - Welcome & Introduction
  - Why has this course been created?
  - Learning objectives of the course
  - Topics of Week 1
- Sub-Activity: The rare disease landscape
  - Rare diseases: introduction and definitions
  - Specific issues related to the treatment of rare diseases – data & numbers
  - Specific issues related to the treatment of rare diseases – Patient testimony
  - Glossary for Rare Disease -
- Sub-Activity: Recap of some basic knowledge
  - Recap of some mol bio concepts – part 1
  - Recap of some mol bio concepts – part 2
  - Recap of some key concepts in immunology – part 1
  - Recap of some key concepts in immunology – part 2
  - What is a biomarker? Why is it used in therapy?
- Sub-Activity – Introduction to innovative therapies
  - What is an innovative therapy?
  - Introduction to gene & cell therapy
  - Introduction to protein-based therapeutics
  - Introduction to transplantation
  - Introduction to tissue engineering
- Sub-Activity – Innovative therapies and rare diseases
  - Current approaches to rare diseases
  - The place of innovative therapies in treating rare diseases - a testimony from a clinician?
- Sub-Activity - Test your knowledge
  - Summary of main topics and issues
  - Check what you have learnt this week - Quiz

**WEEK 2. Innovative therapies: cell& gene therapy, gene editing, protein-based approaches**

- Sub-Activity - Introduction to the Week 2
  - Topics of Week 2
- Sub-Activity – Cell therapy: different approaches
  - Autologous, allogenic and xenogenic approaches
  - Different types of cell therapy: overview
  - Cell-based therapy testing in animal models and in vitro studies
  - Approved cell therapy products
  - Challenges and limits of the cell therapy approach
- Sub-Activity – Gene-based therapies
  - Different types of vectors used in gene-based therapy
  - Different approaches used in gene-based therapy
  - Gene therapy products pathway
  - Aprroved gene therapy products
  - Limits and challenges of gene therapy
  - Current status and future developments of gene therapy

    - Example of a gene therapy for the treatment of a neuromuscular or immune disorder

- Sub-Activity – Genome editing
    - Genome editing approaches
    - Genome editing clinical trials: current status and future development
- Sub-Activity – Protein-based therapeutics
    - Antibody therapies
    - Protein replacement therapies
    - Protein-based therapies: current status and future developments
- Sub-Activity - Check your knowledge
    - Summary of main topics and issues
    - Check what you have learnt this week - Quiz

**WEEK 3. Innovative therapies – regenerative medicine**

- Sub-Activity - Introduction to Week 3
    - Topics of Week 2
- Sub-Activity – Regenerative medicine
    - What is regenerative medicine? Definition and history
- Sub-Activity – Transplantation
    - Definition and types of transplants
    - Which are the organs and tissues transplantable?
    - Types of donors
    - Current status of transplantation in the treatment of rare diseases
    - Cell therapy applications in transplantation
    - Regulations surrounding organ donation
    - Ethical issues introduced by the use of transplantation
    - Current bottlenecks of transplantation approaches
    - Role of Next Generation Sequencing and nanotechnology platforms in addressing the current limits of transplantation
- Sub-Activity – Tissue engineering
    - Tissue engineering: introduction and history
    - Cell sources and isolation
    - Scaffolds used in tissue engineering
    - Examples of tissue engineering
    - Current status and future development of tissue engineering products
    - Tissue engineering regulatory regimes throughout the world
- Sub-Activity – Wrap up
    - Role of regenerative medicine therapies in treating rare diseases
- Sub-Activity - Check your knowledge
    - Check what you have learnt this week - Quiz –
    - Reflection on the week

**WEEK 4. Personalized/precision medicine**

- Sub-Activity - Introduction to the Week 4 -
    - Topics of Week 4
- Sub-Activity – Introduction to personalized medicine
    - Definition of personalized/precision medicine

  - "Omics" technologies at the service of personalized medicine
  - Personalized medicine vs "one fits all" approach
  - Why personalized medicine is important in the field of rare diseases
- Sub-Activity – At the heart of personalized medicine
  - Workflow/strategies of personalized medicine for rare diseases
  - Role of Artificial Intelligence and predictive tool in the evaluation of health risk and in the design of personalized therapies
  - Personalized medicine in rare diseases – a real example (testimony?)
  - Introduction to pharmacogenomics -
  - Introduction to "toxgnostics"
- Sub-Activity - Check your knowledge
  - Check what you have learnt this week - Quiz
  - Reflection on the week

**WEEK 5. Implementation of Innovative Personalized Therapies: challenges and future developments**

- Sub-Activity - Introduction to the Week 5
  - Topics of Week 4 –
- Sub-Activity – Challenges in implementing Innovative Personalized Therapies
  - Integration of big data
  - Design of clinical trials
  - Regulatory implications
  - Access to the market – Intellectual Property issues
  - Financing and reimbursing mechanisms
  - Developing awareness around Innovative Personalized Therapies – the actors involved in the Innovative Personalized Therapies – landscape -
  - Ethical issues – Patient privacy and data sharing and confidentiality
  - Ethical issues – Cost of the treatment/reimbursement of the cost of the therapy
  - Ethical issues – Equal access and equity
- Sub-Activity - Check your knowledge
  - Check what you have learnt this week - Quiz
  - Reflection on what you have learned in this course

# 4. MOOC#3 - Translational Research on rare diseases

## 4.1. MOOC#3 Working Group & Timeline

The EJP RD MOOC#3 is focused on translational research applied to rare diseases. The working group is coordinated by FFRD (Roseline Favresse) and includes representatives from ERN EURO-NMD (Teresinha Evangelista, Annemieke Aartsma-Rus, Carla d'Angelo), EATRIS (Rebecca Ludwig, Anita Kavlie and Agustin Aransaz-Duque) and FFRD (Célia Mercier, Magda Granata). As of M35, the course design has been defined (as a 5-week online course, 3 hours a week), contributors have been identified and contacted and half of the contributions have been duly received. The MOOC#3 will be launched by the end of April 2022 (M40).

## 4.2. MOOC#3 Course overview

**WEEK 1. "Getting into the Translational Medicine"**

- Sub-Activity - Welcome & Introduction
  - 1.1. Why this course?
  - 1.2. Topics of week 1
  - 1.3. Learning objectives for Week 1
- Sub-Activity: Setting the scene
  - 1.4. Rare diseases: definitions & context
  - 1.5. Introduction to the case study on TK2
  - 1.6. Drug Discovery Process and R&D pipeline
  - 1.7. Rare disease: Natural history
- Sub-Activity - Introduction to preclinical research
  - 1.8. What is preclinical research?
  - 1.9. What preclinical models to use?
  - 1.10. Case study: preclinical models used in TK2 deficiency
- Sub-Activity - Introduction to clinical research
  - 1.11. Clinical Phase
- Sub-Activity – Introduction to regulatory and marketing authorization issues
  - 1.12. Regulatory & Marketing Authorization
- Sub-Activity - Translational research in rare diseases: specificities and challenges
  - 1.13. Rare disease landscape: main contributors and stakeholders
  - 1.14. Opportunities: patients' involvement and role in translating discoveries into treatments
- Sub-Activity - Check your knowledge
  - 1.15. Check what you have learnt this week - Quiz
  - 1.16. Reflection on the week

**WEEK 2. Why do we need preclinical models for rare diseases?**

- Sub-Activity - Introduction to the Week 2
  - 2.1. Topics of Week 2
  - 2.2. Learning objectives for Week 2
- Sub-Activity - Animal models: why and when
  - 2.3. Why do we need animal models?
  - 2.4. Limitations of model systems
  - 2.5. How to optimally use your model
- Sub-Activity - Which types of animal models?
  - 2.6. Different and main preclinical models (cells, animals, organoids, etc.)
  - 2.7. When to use which model
- Sub-Activity - Dos and donts
  - 2.8. 'Dos and donts' on animal models' systems
  - 2.9. Challenges of modelling in rare diseases
- Sub-Activity - New models
  - 2.10. CRISPR and new avenues
- Sub-Activity – Wrap up
  - 2.11. Key messages
- Sub-Activity - Check your knowledge

- 2.12. Check what you have learnt this week - Quiz
- 2.13. Reflection on the week

**Week 3. Targeted discoveries and lead compounds for rare diseases therapies**

- Sub-Activity - Introduction to the Week
  - 3.1. Topics of Week 3
  - 3.2. Learning objectives for Week 3
- Sub-Activity - Target product profile
  - 3.3. Identifying the right targets
- Sub-Activity - From hits to leads
  - 3.4. Hight Throughput Screening
  - 3.5. Leads' optimization
  - 3.6. Formulation
  - 3.7. Informatics and Data mining approaches
- Sub-Activity - Biomarkers development
- Sub-Activity - A clinical trial: when to go for it and how?
  - 3.8. TACT Example (TREAT-NMD Advisory Committee for Therapeutics)
  - 3.9. How to access sponsoring of clinical trials?
  - 3.10. Best practices when collaborating with Industry
- Sub-Activity - Specific case of drug repurposing studies
  - 3.11. Specific case of drug repurposing studies
- Sub-Activity - New/Advanced therapies
  - 3.12. New therapies not based on drug development (ATMP incl. cell/gene therapies)

Sub-Activity – Wrap up – Avoiding common mistakes moving from preclinical to clinical

- 3.13. Learning from mistakes – case example
- 3.14. Best way forward – ideal scenario

- Sub-Activity - Check your knowledge
  - 3.15. Check what you have learnt this week - Quiz
  - 3.16. Reflection on the week

**WEEK 4. Clinical trials and market authorization, patients' experience in trials**

- Sub-Activity - Introduction to the Week 4
  - 4.1. Topics of Week 4
  - 4.2. Learning objectives for Week 4
- Sub-Activity From Pre-clinical to clinical
  - 4.3. From pre-clinical to first-in-man
  - 4.4. Safety studies
  - 4.5. Clinical trial design - Defining endpoints
- Sub-Activity
  - 4.6. Regulatory issues and early access
  - 4.7. Patient engagement
  - 4.8. Defining relevant and appropriate Patient Centered Outcome Measures
- Sub-Activity – Ethical aspects
  - 4.9. Ethical issues
- Sub-Activity - Check your knowledge
  - 4.10. Check what you have learnt this week

- 4.11. Reflection on the week

**WEEK 5. Life cycle of a therapy post-marketing, patients' experience in trials**

- Sub-Activity - Introduction to the Week 5
  - 5.1. Topics of Week 5
  - 5.2. Learning objectives for Week 5
- Sub-Activity Post-marketing life cycle
  - 5.3. Challenges & trends (incl. reimbursement and pricing)

Sub-Activity - Artificial Intelligence & drug discovery
  - 5.4. Focus on Artificial Intelligence to speed up drug discovery
- Sub-Activity – Different perspectives
  - 5.5. Experience from ERN stakeholders involved in post marketing authorization studies
  - 5.6. Patients' perspective on drug access and post marketing studies
  - 5.7. Testimony from a Social Science study on this subject
- Sub-Activity - Check your knowledge
  - 5.8. Check what you have learnt this week - Quiz
  - 5.9. Reflection on the week

# 5. MOOC#4 - Rare Diseases Clinical Trials methodologies

## 5.1. MOOC#4 Working Group & Timeline

MOOC#4 is co-developed with the EJP RD WP20. WP20 (Rima Nabbout, Ralf-Dieter Hilgers, Luca Sangiorgi, Marta del Alamo, Tanja Bülow-Berger) is coordinating the content development while WP16 will be in charge of its implementation within the FutureLearn platform as well as developing the most suitable pedagogical structure and tools. The co-development of this MOOC emerged as an opportunity at the 2nd EJP RD General Assembly when WP16 and WP20 realized that both of them were aiming at developing MOOCs. One of the WP16 objectives is to implement MOOCs that are in line with the RD community needs. WP16 is also providing an online efficient opportunity through its contract with the FutureLearn platform. Pulling efforts from WP20 and WP16 then appeared as the most efficient way to address that specific training need. Several calls were held in 2021 to initiate the process. EJP RD MOOC#4 is meant to be developed in 2022 and available online in early 2023. As of December 2021, the general outline is available, chairs have been tentatively identified for each week as well as a first list of potential contributors.

## 5.2. MOOC#4 Preliminary outline

MOOC#4 will span over 6 weeks, each of them being 2,5 to 3 hours long.

**Week 1. Introduction and Repetition**

- **Learning objective:** Learn how to formulate specific research questions and statistical hypotheses related to rare disease problems
- **Content:**
  - a. Including learning objectives and necessary background knowledge (45 min).
  - b. Common/Recurrent rare disease trial problems (45 min) 2 examples to show the process of an academic driven/repurposing trial

- c. Research question and hypotheses development based on the given examples (80-85 min)

**Week 2. Using the right endpoint in RD clinical trials**

- **Learning objective:** Learn about different types and characteristics of clinical and/or primary endpoints. Understand the consequences for statistical analysis when choosing a specific endpoint.
  - Examples from EJP RD clinicians for each endpoint type – to explain definition of primary endpoint expressing several features of the disease
- **Content:**
  - a. brief refresher of "clinical endpoints" from week 1
  - b. brief presentation of specific work performed by IRDiRC on those issues
  - c. examples to explain the definition of a primary endpoint expressing several features of the disease
    - Composite endpoints (? Duet between patient expert and clinician)
    - Multiple primary endpoints (strategies to analyze)
    - Time to event (cardiac/pulmonary diseases: time to transplant/failure - time to renal failure)
    - Surrogate/biomarker

**Week 3. Phase II: Typical designs in small population groups**

- **Learning objective:** Learn about typical rare disease trial designs for Phase II (definition EMA, ICH E8) trials.
- **Content:**
  - a. Early Phase trials
  - b. Simon Design, Randomized Simon Design (binary/continuous endpoint; with/without stop for futility; stochastic curtailment)
  - c. Dose-finding: Group-up-and-down
  - d. Continuous monitoring for toxicity
  - e. Single subject trials
    - What it is
    - Different n-of-1 trial layouts
    - Aggregated n-of-1 trials
  - f. Platform Trials

**Week 4. Phase III: Typical designs in small population groups**

- **Learning objective:** Learn about useful techniques to design rare disease Phase III trials (definition EMA, ICH E8).
- **Content:**
  - a. What are relevant aspects of Phase III CT (presentation/introduction by EMA)
  - b. Sample Size estimation (sample size re-assessment techniques)
  - c. Multicenter trials and stratification
  - d. Use of historical/external control data (incl. extrapolation techniques)

**Week 5. Design Extensions**

- **Learning objective:** Understand the diversity of the specialized tools to design rare disease trials.
- **Content**
  - a. Bayesian, adaptive, and sequential designs (interim analysis)

- b. Randomization techniques
- c. Enrichment design (FDA Guideline)
- d. PCOMs

**Week 6. Wrap-Up**

- **Learning objective:** Understand the value of having various design techniques to adequately tackle RD research questions.