INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

**State of Play of Research
in the Field of Rare Diseases:
2014-2015**

IRDiRC

Table of Contents

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IRDiRC can be found at www.irdirc.org

Disclaimer:

The report is a presentation of the current literature, organised in order to identify and highlight trends and breakthroughs in research in the field of rare diseases. The report does not focus on initiatives to improve the organisation of healthcare systems or on articles covering aspects of the orphan drug market. In addition, trends and breakthroughs in genomics, and -omics in general, are not reported unless they bear specific rare disease features.

The report is based on published articles and press releases, therefore a time lapse between scientific breakthroughs and their publications is inevitable and the report may not perfectly reflect the initiatives at the time at which they are launched.

The findings and conclusions in this report are those of the contributors, who are responsible for the contents; the findings and conclusions do not necessarily represent the views of the European Commission or members of IRDiRC. Therefore, no statement in this report should be construed as an official position of the European Commission or any member of IRDiRC.

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Acronyms

ATMP	Advance therapy medicinal product
CDE	Common data element
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee of Orphan Medicinal Products
EC	European Commission
ECEGRD	European Commission Expert Group on Rare Diseases
EHR	Electronic health record
EMA	European Medicines Agency
ERN	European Reference Network
EU	European Union
EUCERD	European Union Committee of Experts on Rare Diseases
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
GO	Gene ontology
GRDR	Global Rare Diseases Patient Registry Data Repository
GWAS	Genome-wide association studies
HPO	Human Phenotype Ontology
HTA	Health Technology Assessment
ICD	International Classification of Diseases
IRD	Institutional review board
IRDiRC	International Rare Diseases Research Consortium
MTA/DTA	Material Transfer Agreements/Data Transfer Agreements
NCATS	National Center for Advancing Translational Sciences
NSG	Next-generation sequencing
NIH	National Institutes of Health
OMIM	Online Mendelian Inheritance in Man
OMP	Orphan medicinal product
ORDR	Office of Rare Diseases Research
PCORI	Patient-Centered Outcomes Research Institute
PMA	Premarket approval
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
RDCRN	Rare Diseases Clinical Research Network
RDI	Rare Diseases International
UDN	Undiagnosed Disease Network
UK	United Kingdom
USA	United States of America
WES	Whole-exome sequencing
WHO	World Health Organization

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Executive Summary

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The report aims to inform stakeholders at large of developments in the field of rare diseases research in order to support decisions of policy makers and research funders, as well as informed the rare diseases community at large of the achievements and of observed trends which shape the future of research and development for rare diseases.

It is based on a systematic survey of published articles, between July 2014 and June 2015, in scientific journals and press releases. This report does not cover initiatives to improve the organisation of healthcare systems or articles covering aspects of the orphan drug market. In addition, trends and breakthroughs in genomics, and -omics in general, are not reported unless they bear specific rare disease features.

The findings and conclusions in this report are those of the contributors, who are responsible for the contents. No statement in this report should be construed as an official position of members of IRDiRC.

Several major policy initiatives were taken during this period:

▶ The allocation of more funding for Rare Diseases Clinical Research Networks (RDCRN) by the National Institutes of Health (NIH) allowing the establishment of six new consortia;

▶ The data sharing policy adopted by the NIH applying to all NIH-funded, large-scale human and non-human projects that generate genomic data;

▶ The institution by the Food and Drug Administration (FDA) of a policy to expedite the review of certain breakthrough therapy-designated applications for the past several months;

▶ The FDA guidance on ways to use electronic media like interactive websites to help facilitate the informed consent process;

▶ The FDA new fast track programme to approve high-risk medical devices for diagnosis or treatment of serious diseases for which no technology currently exists;

▶ The US government investment into the National Institutes of Health Undiagnosed Disease Network (NIH UDN) to address diagnosis of rare and ultra-rare diseases over the next four years;

▶ The adoption by the European Commission Expert Group on Rare Diseases (ECEGRD) of a recommendation on codification for rare diseases;

▶ The EMA and FDA release of a draft joint proposal to facilitate clinical research on new medicines to treat Gaucher disease; and

▶ The funding by the Canadian Institutes of Health Research (CIHR), in partnership with Genome Canada, of the Canadian Rare Diseases Models and Mechanisms Network to investigate molecular mechanisms of rare diseases.

A new set of guidelines and recommendations are likely to benefit RD research:

- ▶ Guidelines to standardise the citation of bioresources in journal articles;
- ▶ Practical guidance on informed consent for paediatric participants in a biorepository; and
- ▶ International Charter of principles for sharing bio-specimens and data.

Reports on outcomes of previous major initiatives demonstrate the productivity of these projects:

- ▶ Canada's national rare disease gene discovery consortium (FORGE) project;
- ▶ The Deciphering Developmental Disorders (DDD) project in UK;
- ▶ The FDA's Orphan Products Grants Program; and
- ▶ The EMA's adaptive licensing pilot project.

Several strong trends were identified:

- ▶ Patient-centred approaches are now widely recommended;
- ▶ Clouds over the orphan drug market due to high prices, which are generating initiatives to find innovative alternative models of research and development;
- ▶ Repurposing of drugs and finding new targets in general are the focus of many research teams;
- ▶ Revisiting Health Technology Assessment (HTA) approach for orphan drugs is perceived as a necessity;
- ▶ Optimising access to already generated clinical and biological data becomes the priority, as well as easing data collection;
- ▶ Data sharing is the leitmotif, especially for genomics data; and
- ▶ Adaptive design is the model for rare diseases trials.

Two breakthroughs in therapy have to be acknowledged:

- ▶ The progress of targeted delivery of silencing RNA (siRNA) therapeutics; and
- ▶ The first stem-cell therapy recommended for conditional marketing approval in the EU.

1. Introduction and Methods

Introduction

The International Rare Diseases Research Consortium (IRDiRC) was established in 2010 to associate researchers and organisations invested in rare diseases research in order to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases.

Methods

This report is a compilation of information published in scientific journals and press releases over the period of July 2014 to June 2015. The scientific literature was systematically scanned using the key words "rare diseases" and "orphan drugs" and their synonyms. In addition, the summary tables of eighty top ranking journals in various fields were systematically scanned. Only the articles tackling a general issue, not disease specific, were retained for this report.

All the selected articles describing major initiatives or major research outcomes were highlighted in an electronic newsletter, OrphaNews, which also publishes news about specific rare diseases. This material was organised under two main topics: Initiatives and Trends & Gaps. The focus remains on the two IRDiRC goals, therefore, initiatives to improve the organisation of healthcare systems and articles dealing with the economic aspects of the orphan drug market were not considered.

The report does not necessarily reflect the opinion of the IRDiRC members, but the analysis of the Scientific Secretariat through the conducted literature survey.

2.   New Policy Initiatives (July 2014-June 2015)

2.1   Recent Policy Initiatives in Europe

2.1.1   Launch of a process to establish European Reference Networks

At the invitation of the European Commission (EC), a conference on European Reference Networks (ERNs) was held on 23 June 2014 in Brussels, Belgium.[1] The conference aimed to discuss the organisation of specialised networks across the European Union (EU) and examine the next steps of the deployment process in preparation of the forthcoming call for ERNs in the fourth quarter of 2015. The establishment of ERNs lays in accordance with Directive 2011/24/EU on patients' rights to cross-border healthcare.[2] In the directive, along with low prevalence complex diseases or conditions, rare diseases are mentioned explicitly as an area in particular need of European clinical entity networks. Regardless of the region, the network must provide highly specialised, affordable, high-quality and cost-effective care. The idea of linking centres of expertise throughout Europe in an effort to pool expertise and concentrate knowledge and resources is, of course, very attractive. The principles of such an approach were explored in depth by the Rare Disease Task Force and, subsequently, by the EU Committee of Experts on Rare Diseases (EUCERD) who published reports and recommendations.[3]

2.1.2   Public consultation on guidelines to aid developers of gene therapy through the regulatory process

Gene therapy holds great potential for the cure of many diseases, particularly in rare diseases, and is an exciting and innovative field. However, bringing gene therapy to the market can be challenging as most of its developers are very small companies or come from academia, and are not familiar with the regulatory environment. The European Medicines Agency (EMA) has released a draft guideline on quality, non-clinical and clinical aspects of gene therapies for a three-month public consultation, starting 20 May 2015.[4] The draft guideline provides detailed guidance on both the scientific and development aspects of this type of medicines, and on the regulatory requirements that companies need to fulfil, including good manufacturing practices.

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[1] European Reference Networks for Rare Diseases portal
http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm#
[2] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF
[3] EUCERD Recommendations on Rare Disease European Reference Networks (RD ERNs)
http://www.eucerd.eu/?post_type=document&p=2207
[4] EMA/Committee for Advanced Therapies, 23 March 2015: Draft Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/05/WC500187020.pdf

2.1.3   Adoption of recommendations to code rare diseases with Orphacodes

The European Commission Expert Group on Rare Diseases (ECEGRD) adopted its first recommendation on codification for rare diseases on 12 November 2014.[5] Addressed to the EC and its Member States, it outlines the state of play in the field and provides the rationale for the use of Orphacodes as a complementary coding system when no specific code exists for a rare disease. Six recommendations are proposed to improve the codification of rare diseases in health information systems. These include the need to consider a complementary approach whilst rare diseases are incorporated into International Classification of Diseases (ICD) and Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT); the importance of exchanging experiences on the use of Orphacodes at national level through a working group to be established in a future EU Joint Action on rare diseases; and the further promotion of Orphacodes within the ICD-11 revision process taking place at the World Health Organization (WHO). Member States are encouraged to consider and explore the feasibility of the use of Orphacodes at national level and to include the codification of rare diseases as an area of their national plans/strategies for rare diseases. The recommendation concludes with a strong encouragement for the EC and its Member States to seek possibilities to support the implementation of identified solutions.

2.1.4   EMA announcement that clinical trial data will be shared

After a lengthy debate over access of clinical trial data, the EMA have released a press statement confirming that clinical trial data of medicinal products with marketing authorisation in Europe will be made public.[6] This policy takes effect for all products to be submitted after 1 January 2015, while sponsors of previously authorised products are required to release their data by June 2015. Data can be viewed and downloaded to ensure that it can be analysed and re-evaluated as required. Companies may be allowed to suggest redaction of certain proprietary information; however the final decision will remain at the discretion of the EMA. While Europe is the first to implement this landmark decision, it is hoped that other regulatory agencies would follow suit.

2.2   Recent Policy Initiatives in the USA

2.2.1   More funding for Rare Diseases Clinical Research Network

Rare Diseases Clinical Research Network (RDCRN) in the USA, dedicated to furthering translational research and investigating new treatments for patients with rare diseases, was awarded USD29 million

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[5] European Commission Expert Group on Rare Diseases: Recommendation on Ways to Improve Codification for Rare Diseases in Health Information Systems; adopted at the 3rd meeting on 12-13 November 2014
http://ec.europa.eu/health/rare_diseases/docs/recommendation_coding_cegrd_en.pdf

[6] Press release, 2 October 2014: EMA adopts landmark policy to take effect on 1 January 2015
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/10/news_detail_002181.jsp&mid=WC0b01ac058004d5c1

to study more than 200 rare diseases by the National Institutes of Health (NIH).[7] Established in 2003 by the NIH Office of Rare Diseases Research (ORDR), RDCRN currently comprises of 2,600 researchers and is overseen by the National Center for Advancing Translational Sciences (NCATS) to work towards advancing medical research on rare diseases by facilitating collaboration, study enrolment and data sharing. RDCRN is made up of 22 distinctive consortia and a Data Management and Coordinating Center that work collaboratively to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert doctors, and clinical research opportunities. This new NIH funding will establish six new RDCRN consortia, including bone diseases, lung diseases, food allergy disorders, and three separate neurological diseases concentration areas – amyotrophic lateral sclerosis and related disorders, autism and intellectual disabilities, and frontotemporal lobar degeneration.

2.2.2 New NIH genome data sharing policy

The NIH has issued the data sharing policy replacing the previous genome-wide association studies (GWAS) data sharing policy issued in 2007.[8] It will apply to all NIH-funded, large-scale human and non-human projects that generate genomic data, beginning with funding applications submitted by 25 January 2015. It reflects NIH's commitment to responsible data stewardship and includes a number of provisions to assure the protection of human data.

2.2.3 FDA expedited review procedures for marketing applications with breakthrough therapy-designated drugs and biologics

The United States Food and Drug Administration (FDA) confirmed that it has informally institute a policy to expedite the review of certain breakthrough therapy-designated applications for the past several months. The FDA's informal policy has now found its way into a Manual of Policies and Procedures, which describes the characteristics that breakthrough therapy-designated drugs eligible for expedited review should have.[9] These include a demonstration of substantial improvement over existing therapies, designation for priority review, and a determination by the review team for a first cycle approval to be likely. Not all breakthrough therapy-designated drugs will receive expedited review as decisions will be made on a case-by-case basis.

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[7] Press release, 8 October 2014: NIH funds research consortia to study more than 200 rare diseases http://www.nih.gov/news/health/oct2014/ncats-08.htm

[8] NIH Genomic Data Sharing Policy http://gds.nih.gov/03policy2.html

[9] Office of New Drugs – Policy and Procedures, Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics that are Receiving an Expedited Review http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM437281.pdf

2.2.4 FDA new guidance regarding the use of Electronic Informed Consent in clinical investigations

The new guidance issued by the FDA could make it easier for companies to conduct clinical trials by explaining how federal regulators will permit companies to use electronic media, like interactive websites, to help facilitate the informed consent process.[10] The guidance provides recommendations for clinical investigators, sponsors, and institutional review boards (IRBs) on the use of electronic media and processes to obtain informed consent for FDA-regulated clinical investigations of medical products, including human drug and biological products, medical devices, and combinations thereof. According to the FDA, as long as the information provided is "adequate" and "understandable", the use of a variety of methods to convey informed consent should be acceptable.

2.2.5 FDA proposal of a new fast track programme to approve high-risk medical devices

The FDA proposes a new fast track programme to approve high-risk medical devices for diagnosis or treatment of serious diseases for which no technology currently exists. The Expedited Access PMA (EAP) guidance document issued in April 2015 recommends pre-market approval to provide patients with early access to safe and effective medical devices.[11] An addition to the FDA's existing four fast track programmes - Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review - for speedier development and review of new products to address unmet therapeutic needs, the EAP requires medical devices to address life-threatening conditions. Devices under investigation must represent novel and breakthrough technologies with a marked benefit for patients over existing products. The EAP emphasises the need for collaboration between the FDA and sponsors to expedite product development according to FDA safety and efficacy standards. If the product receives early approval, the FDA requires sponsors to collect post-market data for device risk/benefit assessment to strengthen patient safety.

2.2.6 Funding for precision medicine will benefit rare diseases research

The President of the United States earmarks USD215 million towards "Precision Medicine" and proposes to launch a multi-agency initiative in the 2016 fiscal year to build a cohort of one million American volunteers for genomics and other biomedical research.[12] The funding earmarked to gather medical records and genomic data will be utilised to create a databank; the resulting databank will contribute to advancing the knowledge of underlying biological causes of diseases with an aim to develop "Precision

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[10] Use of Electronic Informed Consent in Clinical Investigations – Draft Guidance for Industry
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf

[11] Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions – Guidance for Industry and FDA Staff
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf

[12] Collins F., A New Initiative on Precision Medicine; The New England Journal of Medicine 2015; 372:793-795
http://www.nejm.org/doi/full/10.1056/NEJMp1500523

Therapies" for these diseases. Such large cohort studies of both healthy and sick people that represent the general population – often referred to as biobanks – are already established in countries such as the United Kingdom and Japan. The USA cohort will be assembled by linking existing cohort studies. According to Francis Collins, the Director of NIH, this endeavour will create a repository that is superior to a biobank.

2.2.7 OPEN ACT: legislation introduced in the US Congress to encourage research in drug repurposing for rare diseases

The Orphan Product Extensions Now Accelerating Cures and Treatments Act of 2014 (OPEN ACT) has been introduced to the United States Congress to encourage pharmaceutical companies and organisations to repurpose drugs already in the market by adding a rare indication.[13] According to this bill, companies can benefit from an additional six months of market exclusivity for adding a rare disease indication to the label of a currently approved drug. The focus will be on drugs with market exclusivity. Modelled on the incentive programs in the Best Pharmaceuticals for Children Act (BPCA), the OPEN ACT would make available to drug companies an "Orphan Product Exclusivity Extension," so long as the sponsor company establishes that the therapy is designated to treat a rare disease and obtains a rare disease indication from the FDA on the drug label.

2.2.8 NIH partners with American medical universities to accelerate diagnosis of rare diseases

The US government is investing USD43 million into the NIH Undiagnosed Disease Network (UDN) fund to address diagnosis of rare and ultra-rare diseases over the next four years.[14] The NIH has partnered with six US medical institutions – each to received USD7.2 million four-year grant – to tackle these undiagnosed cases. Harvard Medical Centre will coordinate the network and the following medical institutions will participate in identifying, researching and treating rare diseases: Baylor College of Medicine; Boston Children's Hospital, Brigham and Women's Hospital, and Massachusetts General Hospital; Duke University; Stanford University; University of California; and Vanderbilt University Medical Centre. The UDN will draw on genomic, genetic, and environmental research from partner institutions to gather data on undiagnosed rare diseases. With the benefit of new tools and methods of testing and analysis, the UDN has so far linked some 4,000 diseases to one of around 23,000 genes. Launched in 2008, a pilot programme enrolled around 600 undiagnosed patients in clinical protocols, out of over 3,000 applications. Multi-disciplinary research teams have diagnosed 100 of these patients, identified fifteen new genes and discovered two unknown diseases. The NIH will continue to assess some 150 patients a year through week-long patient examination and testing protocols. By 2017, each partner institute should evaluate an additional 50 patients per year, regardless if they are medically insured or not.

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[13] HR5750 – Orphan Product Extensions Now Accelerating Cures and Treatments Act of 2014
http://www.gpo.gov/fdsys/pkg/BILLS-113hr5750ih/pdf/BILLS-113hr5750ih.pdf

[14] Press Release, 1 July 2014: NIH names new clinical sites in Undiagnosed Diseases Network
http://www.nih.gov/news/health/jul2014/nhgri-01.htm

2.2.9   FDA opens Individual Patient Expanded Access Applications for public comment

On 4 February 2015, the FDA released a draft guidance to facilitate streamlining the individual patient expanded access application process.[15] The Individual Expanded Access Applications: Form FDA 3926 proposed by the FDA is a greatly simplified process for doctors to obtain experimental drugs for patients who are suffering from serious or life threatening illnesses and have no other alternative. The FDA has released this document for a 60-day comment from the public; meanwhile the FDA says it won't turn away doctors who want to use it. Patients will be eligible only when there is no other product that can diagnose, monitor or treat the patient's disease or condition, they cannot be enrolled in a clinical study testing it, and cannot ask the manufacturer or the insurer to pay for the medication. Additionally, the doctor must determine that the probable risk from the experimental drug is not greater than the probable risk from the disease and must ensure that the manufacturer is willing to provide it. This "right to try" law, according the FDA, will give terminally ill patients the right to try experimental drugs that have passed at least the first of three phases of FDA testing (to determine safety) but have not yet obtained marketing authorisation.

2.3   Recent Joint Europe-USA Regulatory Initiatives

2.3.1   Draft joint EMA-FDA proposal to facilitate clinical research to treat Gaucher disease

The EMA and FDA released a draft joint proposal to facilitate clinical research on new medicines to treat Gaucher disease, a rare, inherited lysosomal storage disorder, in children.[16] Based on extensive consultation with various stakeholders, which began in October 2011, the proposal aims to reach an agreement on an EMA Paediatric Investigation Plan and FDA Pediatric Study Plan to conduct clinical investigation of treatments for children with Gaucher disease. While several drugs have been approved to treat patients with Gaucher disease, regulators consider treatments to be ill-adapted to paediatric patients. The treatment burden is considered to be particularly high in children with neurological symptoms. The EMA and FDA have therefore joined forces to develop a collaborative clinical research programme to demonstrate safety and efficacy of treatments, and new routes of administration for paediatric Gaucher disease Type 1 and Type 3 patients. Sponsors wishing to take part in this project are encouraged to seek advice from their regulatory authorities, as well as the EMA and FDA.

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[15] Draft guidance for Industry – Individual Patient Expanded Access Applications: Form FDA 3926
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM432717.pdf
[16] Gaucher disease: A strategic collaborative approach from EMA and FDA
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/05/WC500166587.pdf

2.4   Recent Policy Initiatives in Canada

2.4.1   Award of CAD2.3 million to the Canadian Rare Diseases: Models and Mechanisms Network

The Canadian Institutes of Health Research, in partnership with Genome Canada, has awarded CAD2.3 million to the Rare Diseases: Models and Mechanisms (RDMM) Network to investigate molecular mechanisms of rare diseases.[17] The RDMM Network aims to investigate biological mechanisms underlying rare diseases at the genetic level in model organisms (e.g. yeast, worms, flies, fish, and mice) to gain insights on rare disease mechanisms. The Network comprises of basic science researchers studying gene function in model systems and clinician scientists discovering novel disease genes in Canada thus forge collaborations across the Canadian biomedical community that will expedite the understanding of disorders, enabling the design of new therapies to the ultimate benefit of those affected by rare diseases.[18]

2.4.2   The Canadian Open Genetics Repository: a collaborative effort towards clinical genomics

An article published in the Journal of Medical Genetics describes the Canadian Open Genetics Repository (COGR) as a *"collaborative effort for the collection, storage, sharing and robust analysis of variants reported by medical diagnostics laboratories across Canada."*[19] Lerner-Ellis *et al*. reported that clinical diagnostic laboratories across Canada received instances of the GeneInsight tool to upload, transfer, access and share variant data. The survey conducted by the authors established an increased need for standardisation and data sharing among countries, which is an ongoing endeavour of the COGR. According to the authors, COGR aims to serve as a permanent resource as well as a focal point for the collaboration of Canadian laboratories to aid in diagnosing, managing and treating genetic diseases.

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[17] Press release, 17 November 2014: From mice to yeast: new network to use model organisms to study rare disease http://www.uottawa.ca/media/media-release-3082.html

[18] Rare Diseases: Models and Mechanisms Network portal http://rare-diseases-catalyst-network.ca/

[19] Lerner-Ellis *et al*., Canadian Open Genetics Repository (COGR): a unified clinical genomics database as a community resource for standardising and sharing genetic interpretations; Journal of Medical Genetics 2015; 52:438-445 http://jmg.bmj.com/content/52/7/438

3.   Results of Previous Major Initiatives

3.1   Scouting for rare disease-causing genes: Results from Canada's FORGE

Launched on 1 April 2011, the outcome of Finding of Rare Disease Genes (FORGE) Canada Consortium was reported in the American Journal of Human Genetics.[20] Throughout the two-year national rare-disease gene-discovery project, 264 rare disorders were studied based on whole-exome sequencing (WES) of 783 collected DNA samples. Disease-causing mutations were identified in 67 genes not previously linked to disorders. Identified novel genes contribute towards understanding the biological mechanisms of rare diseases. Beaulieu *et al.* observed that mutations in separate genes, implicated in similar biological pathways, can either result in syndromes with common features or cause very distinct diseases. They also discovered that a number of disease-causing gene mutations are often not picked up using traditional methods, which strengthens evidence on the benefits of WES techniques.

3.2   The Deciphering Development Disorders project

The Deciphering Development Disorders (DDD) is the first nationwide study established in the UK to find if the usage of cutting edge genetic technology can lead to an increase in the rates of genetic diagnosis and, at the same time, help doctors understand why certain patients are susceptible to developmental disorders. Additionally, the project addresses whether and how genomic findings should be shared with individual research participants – a topic that is of intense international debate due to the underlying ethical implications. Jointly funded by the Health Innovation Challenge Fund and the Wellcome Trust Sanger Institute, and supported by the NHS National Institute for Health Research, this study brought together doctors throughout UK to collect high-resolution genomic and phenotypic data for children with severe undiagnosed developmental disorders and their parents. The success of this transformative venture has been shown in recent publications in Nature and The Lancet. In The Lancet, the authors described the process for finding and returning pertinent diagnoses in the first ~1000 families enrolled in the DDD project.[21] The article published in Nature showed how these researchers were able to identify 12 new genes that were strongly linked with developmental disorders in 35 patients from the project.[22] This was made possible by studying the genetic make-up of 1,133 children and their parents by using cutting-edge genomic technology such as exome sequencing and array-based detection of chromosomal rearrangements. These newly implicated genes boost diagnosis rates of the children by 10%.

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[20] Beaulieu *et al.*, FORGE Canada Consortium: Outcomes of a 2-Year National Rare-Disease Gene-Discovery Project; AJHG 2014; 94:809-817 http://www.cell.com/ajhg/pdf/S0002-9297%2814%2900223-7.pdf

[21] Wright *et al*., Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data; The Lancet 2015; 385:1305-1314
http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736%2814%2961705-0.pdf

[22] Fitzgerald *et al*., Large-scale discovery of novel genetic causes of developmental disorders; Nature 2015; 519:223-228 http://www.nature.com/nature/journal/v519/n7542/full/nature14135.html

3.3   Study of the impact of the FDA's Orphan Products Grants Program

Since the Orphan Drug Act launch in 1983, USD320 million have been awarded to clinical studies on rare disease products.[23] From an initial USD500,000 in 1983, funding has continued to rise, reaching USD12 million in 2013, a slight decrease from the USD14 to USD15 million allocated annually from 2005 to 2012. The grant programme receives on average 90 to 100 applications a year. Out of 567 awarded grants, the programme's funds have contributed to the authorisation of 34 drugs, 9 biologics and 8 devices, representing around 10% of orphan products. Incentives such as the FDA's grant programme are effective to foster research on rare diseases. Grants provide a significant source of funding for investigators with limited resources.

3.4   First candidates selected for EMA's adaptive pathways (formerly adaptive licensing) pilot project

Following the launch of the EMA's adaptive pathways/licensing pilot project, the agency has, in June 2014, selected two products from the 20 applications received from companies.[24] The EMA welcomes the rapid response and growing interest from companies to engage in the pilot project. The greater the numbers of projects, the more evidence regulators can gather to validate the adaptive licensing project. Adaptive licensing aims to improve early access to new drugs for diseases with unmet medical needs. Data for benefit/risk assessment will be collected progressively to establish safety and efficacy of medicines, with a view to treat a wider patient population. Built on multi-stakeholder cooperation, the EMA's adaptive licensing is a further effort to accelerate the design of products and treatments based on concrete evidence. In an end-of-year update, EMA announced that it has received 34 requests from companies to include their medicines in the adaptive pathways pilot project up to the beginning of December 2014, the medicines covered a broad range of therapeutic areas. Following review and discussion with companies, six medicines have so far been selected to go forward into more in-depth discussions with the company with the participation of all stakeholders, including health technology assessment (HTA) bodies and patients' representatives.[25]

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[23] Imoisili *et al.*, Fueling the development of products for rare diseases: the impact of the FDA's orphan products grants program; Expert Opinion on Orphan Drugs 2014; 2(8):807-815
http://informahealthcare.com/doi/abs/10.1517/21678707.2014.923305

[24] Press release, 6 June 2014: European Medicines Agency selects first two medicines to be included in its adaptive licensing pilot project
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002119.jsp&mid=WC0b01ac058004d5c1

[25] Press release, 22 December 2014: Status of the adaptive pathways pilot project
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/12/news_detail_002244.jsp&mid=WC0b01ac058004d5c1

3.5   NIH RDCRN contributes towards improving research and orphan medicinal products

In order to enhance the quantity and quality of research on rare diseases, the NIH's ORDR established the Rare Diseases Clinical Research Network (RDCRN) in 2003. In an article published in the Journal of General Internal Medicine, Krischer *et al*. describe the network's achievements and contribution to clinical research on rare diseases.[26] During the RDCRN's first five years, ten of its consortia initiated 40 studies. The following five years saw the launch of 88 studies by 17 consortia. A number of RDCRN projects have incorporated patient-reported outcomes and have resulted in demonstrated efficacy of new treatments and diagnostics for rare diseases. The authors suggest the RDCRN has contributed significantly to accelerate research on rare diseases and the network's use of technologies should continue evolving to maintain that momentum.

3.6   Linked2Safety project: secure medical information space for analysing clinical data

The Linked2Safety project, funded under the FP7 scheme of the European Commission, is built to "*advance clinical practice and accelerate medical research … by providing pharmaceutical companies, healthcare professionals and patients with an innovative semantic interoperability framework facilitating efficient and homogenised access to distributed Electronic Health Records (EHRs)*".[27] EHRs contain an increasing wealth of medical information and have the potential to significantly advance medical research, as well as improve health policies. However, the European healthcare information space is fragmented due to the lack of legal and technical standards, cost effective platforms, and sustainable business models. Linked2Safety is a platform for analysing EHRs from multiple institutions, while strictly adhering to the legal and ethical requirements as defined by each data provider at EU level. Benefits for this 36-month Linked2Safety project include facilitating the analyses all available data in the EHRs, which include the genetic, environmental and medical history of subjects exhibiting adverse events during clinical trial, which in turn will help in providing genotype-phenotype associations. It will also provide a platform for identification and selection of patients for clinical trials by linking EHR repositories.

3.7   ClinRegs: an online database of clinical research regulatory information

Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), ClinRegs provides is an online database of country-specific regulations on Competent Authority Oversight, Ethics Committee Oversight, Clinical Trial Lifecycle, Sponsorship, Informed Consent, Investigational Products, Specimens.[28] Currently in BETA mode, ClinRegs is intended to serve as a central resource and time-saver for individuals and organisations involved in planning and implementing international clinical research. The homepage shows a map feature, with clickable information on each country as well as a comparison

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[26] Krischer *et al*., The Rare Diseases Clinical Research Network's Organization and Approach to Observational Research and Health Outcomes Research; Journal of General Internal Medicine 2014; 29 (Suppl 3): S739-744 http://link.springer.com/content/pdf/10.1007%2Fs11606-014-2894-x.pdf

[27] Linked2Safety portal www.linked2safety-project.eu

[28] ClinRegs (BETA) portal http://clinregs.niaid.nih.gov/index.php

search tool to view abridged versions of the requirements of two countries side-by-side. The information available on this site is kept up-to-date by regular review and curation by regulatory researchers, with input from the clinical research community.

3.8   ClinGen – The clinical genome resource of the NIH in the USA

A detailed review of Clinical Genome Resource (ClinGen) is presented in New England Journal of Medicine, which was launched in 2013 and supported by the NIH, to be an *"authoritative central resource that defines the clinical relevance of genomic variants for use in precision medicine and research."*[29] The review addresses the goals of the ClinGen and discusses how the ClinVar database - the cornerstone of ClinGen - operates. The article describes ClinVar as the public portal for the deposition and retrieval of variants and the interpretation of their clinical significance. It currently contains 172,055 variant submissions across 22,864 genes out of which more than 118,000 of the unique variants in ClinVar have clinical interpretations. The authors maintain that ClinVar ensures that all variants are recorded according to standardised nomenclature and works with members of the sequence and structural variant communities to develop new standards for interpreting genetic variants. Additionally, the authors also illustrate the work of the ClinGen Gene Curation Working Group towards developing standards for assigning the level of evidence supporting a gene–disease relationship and a new database called ClinGenKB, which allows for a flexible working environment for curation. Finally, the authors highlight the activities of ClinGen Actionability Working Group and GenomeConnect.

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[29] Rehm *et al.*, ClinGen – The Clinical Genome Resource; New England Journal of Medicine 2015; 372:2235-2242
http://www.nejm.org/doi/full/10.1056/NEJMsr1406261

4.   Guidelines and Recommendations

4.1   Likely to Benefit Rare Diseases Research

4.1.1   CoBRA: Guidelines to standardised citation of bioresources in journal articles

One of the challenges involved in sharing bio-resources (e.g. biological samples, data, and databases) is the lack of structural guidance to correctly recognise and trace their use, especially in publications. An article published in BMC Medicine proposes a guideline for reporting bio-resource use in research articles, named CoBRA (Citation of BioResources in journal Articles).[30] Developed by members of the journal editors subgroup of the Bioresource Research Impact Factor (BRIF), CoBRA provides a citation system where "each individual bioresource that is used to perform a study and that is mentioned in the Methods section should be cited as an individual 'reference [BIORESOURCE]' according to a delineated format." Additionally, the European Association of Science Editors has adopted BRIF's suggestion to incorporate statements on biobanks in the Methods section of their guidelines. This will contribute to the assessment of infrastructures of relevance for researchers, a necessary step to convince funding agencies to support them appropriately.

4.1.2   Practical guide on informed consent for paediatric participants in a biorepository

The Mayo Clinic Proceedings has published a guidance document on obtaining informed consent from paediatric population to participate in a biorepository for investigators and institutional review board (IRB) members in the United States regulatory context.[31] The evolving roles of parents and children in making decisions related to research participation as children mature and the role of the IRB are the two main issues that are addressed in this article around which the recommendations are made. The document also presents guidance on a variety of paediatric-specific consent issues that arise frequently in the development of biorepositories.

4.1.3   Proposal for international guidelines on conducting research and sharing genomic data

Knoppers published the Framework for Responsible Sharing of Genomic and Health-Related Data in The HUGO Journal.[32] Based on four founding principles regarding health, respect, research and transparency, the Framework proposes guidelines to conduct research and share genomic data internationally with respect for human privacy and non-discrimination rights. Besides ethical values and the wish to avoid

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[30] Bravo *et al*., Developing a guideline to standardize the citation of bioresources in journal articles (CoBRA); BMC Medicine 2015; 13:33 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4331335/

[31] Brothers *et al*., Practical guidance on informed consent for pediatric participants in a biorepository; Mayo Clinical Proceedings 2014; 89(11):1471-1480 http://dx.doi.org/10.1016/j.mayocp.2014.07.006

[32] BM Knoppers, Framework for responsible sharing of genomic and health-related data; The HUGO Journal 2014; 8:3 http://www.thehugojournal.com/content/8/1/3, http://genomicsandhealth.org/framework

data misuse, the guidelines are designed to adapt to evolving genomic science and data sharing practices. The Framework aims to offer political and legal dimensions to be adopted by research organisations, institutions and industry conducting work using genomic and health-related data.

4.1.4   International Charter of Principles for Sharing Bio-Specimens and Data

A paper in the European Journal of Human Genetics called "International Charter of principles for sharing bio-specimens and data" describes the best practices in providing a common overview and the foundational framework of the practice of sharing biological data; the charter is the result of careful negotiation of different stakeholders.[33] The Charter recognises that data sharing is essential for to foster biomedical research and this should be complicit with the rules of Material Transfer Agreements/Data Transfer Agreements (MTA/DTA). The five principles for the custodianship of bio-specimen repositories and data - respect for privacy and autonomy, reciprocity (feedback provided to institutions and patients), freedom of scientific enquiry (data should be exploited to the maximum extent possible), attribution, and respect for intellectual property - constitute the common premise for the Charter. The article elucidates these principles in detail and elaborates on other aspects, such as ensuring the international quality standards of data and bio-specimens usage of previously collected data samples and returning results. In addition to a framework for the acknowledgement of bio-specimens and data collections and incorporates all relevant international legal and ethical regulations, the charter has also provided a template for both MTA/DTA.

4.1.5   Recommendation for a pan-European registry for childhood cancer

A paper published in the European Journal of Cancer provides an overview of the advantages and challenges of Europe wide coverage for childhood cancer registration compared to regional registration.[34] Steliarova-Foucher *et al.* stated that since childhood cancer, although rare, contributes considerably to mortality as well as loss of years and poor quality of life in survivors, cancer registries is an essential tool for surveillance, as well as providing the basis for research and policy decisions. The authors identified over 200 cancer registries in various stages of development across Europe. They found that these registries covered 83% of the childhood population in the European Union, but could increase to around 98%, if the recently established cancer registries improved in quality. The authors recommend national registration of cancer over regional registration as they believe it is more cost-effective, can cover larger population, contain data that are less biased which are ready for national and international research.

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[33] Mascalzoni *et al.*, International Charter of principles for sharing bio-specimens and data; European Journal of Human Genetics 2015; 23:721-728 http://www.nature.com/ejhg/journal/v23/n6/full/ejhg2014197a.html

[34] Steliarova-Foucher *et al.*, Registration of childhood cancer: Moving towards pan-European coverage?; European Journal of Cancer 2015; 51(9):1064-1079
http://www.ejcancer.com/article/S0959-8049%2815%2900225-7/abstract

4.2   Likely to Benefit Rare Diseases Therapy Development

4.2.1   Rare Cancers Europe recommendations for clinical studies in rare cancers

Rare Cancers Europe, a multi-stakeholder initiative representing patient associations, medical societies and industry, has recently published a consensus paper with recommendations on conducting clinical trials for rare cancers to try to bring better medications faster into the market.[35] They have also released a press statement *"calling both the community of researchers and European authorities to address research methodologies and regulatory criteria that could limit rare cancer patient access to new therapies"*. The authors believe that the current methodologies may be discriminating against this rare disease patient population. The recommendations highlight the importance of allowing certain "high risk medications" to come to the market to avoid discriminating against small population of patients suffering from rare cancers and encouraging innovative approaches to treatment. For clinical trials RCE recommends adaptive trial designs and surrogate end points to obtain swift answers to the clinical trial process. Also highlighted in the consensus paper is the significance of *"reference networks in Europe, involving Centres of Expertise to improve the quality of care for rare cancers"*.

4.2.2   How to successfully apply for an Orphan Designation: proving medical plausibility

The Committee of Orphan Medicinal Products (COMP) has published an informative article in the Orphanet Journal of Rare Diseases with examples of medicinal products that were given orphan designation and how they were assessed for medical plausibility by the COMP.[36] Medical plausibility is judged by the ability of the sponsor to demonstrate the *"intention to diagnose, prevent or treat"* a serious and rare condition. According to the article, there are several challenges that are faced by the sponsors during the scientific assessment of the applications for orphan designation by the Committee. This is because the assessment is based on the review of non-clinical (such as in vitro and in vivo) and/or clinical data submitted. However, providing this type of data is not always straightforward at an early stage of product development. The article thus provides examples of where sponsors have successfully justified medical plausibility, to steer future sponsors of medicinal products in the right direction. The authors have provided several examples of justification based on pre-clinical data with relevant models (animals or cellular) and endpoints. They can also be based on pre-clinical data at the early stages of development, examples of which include applications defended on grounds of preliminary data. For further guidance, the authors have also provided by examples of unsuccessful efforts to justify medical plausibility which includes bridging to data from other products and to non-relevant models increases assumption and weakened medical plausibility. Finally the authors have emphasised that they judge each application on a case by case basis and even if all the appropriate models and endpoints are used, if the results obtained do not show benefit than the dossier could still be rejected.

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[35] Casali *et al.*, Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper; Annals of Oncology 2015; 26(2):300-306
http://annonc.oxfordjournals.org/content/early/2014/09/28/annonc.mdu459.full.pdf+html

[36] Tsigkos *et al.*, Establishing medical plausibility in the context of orphan medicines designation in the European Union; Orphanet Journal of Rare Diseases 2014; 9:175 http://www.ojrd.com/content/9/1/175

4.2.3 Scientific framework for using the accelerated approval pathway and for qualifying biomarkers as primary endpoints to develop orphan drugs

The accelerated approval pathway is able to serve a vital role for the development of treatments for diseases with high unmet medical needs. An article published in the Orphanet Journal of Rare Diseases describes a scientific framework for assessing biomarker endpoints with defined sets of supporting data more structured approach which will enhance the development of novel orphan drugs for rare diseases currently without adequate treatment and is based on the opinions of experts in drug development and rare disease patient groups.[37] The authors suggest the following recommendations for the development of orphan drugs using the Accelerated Approval pathway and for qualifying biomarkers as primary endpoints: (1) establishing Regulatory Rationale for Accelerated Approval Access in Rare Disease Programs, (2) implementing a Biomarker Qualification Request Process, (3) a Proposed Scientific Framework for Qualifying Biomarkers as Surrogate Primary Endpoints Although this article mainly describes the examples from the US FDA, they are relevant to sponsors applying for marketing authorisation to other world regions as well.

4.2.4 The WHO issues statement in support of all clinical trials to be reported within 12 months of their completion

The WHO issued a public statement calling for the disclosure of results from clinical trials for medical products, whatever the result, within 12 months of its completion.[38] The WHO believes that the researchers have an ethical duty to report all results of the clinical trials to ensure that decisions related to the safety and efficacy of drugs and medical devices are supported by the best available evidence. Not only does the statement asks for the public release of trial within 12 months of its completion, results from previously unpublished trials also will have to be made public. The WHO calls on organisations and governments to implement these measures. Many believe that this statement belies a new era as it may open the door for informed decision making about procedures and treatments for drugs and medical devices.

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[37] Kakkis *et al.*, Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints; Orphanet Journal of Rare Diseases 2015; 10:16 http://www.ojrd.com/content/10/1/16

[38] WHO Statement on Public Disclosure of Clinical Trial Results http://www.who.int/ictrp/results/reporting/en/

5. Trends

5.1 Trends: Patient-Centred Approaches Widely Recommended

5.1.1 The launch of Rare Diseases International – a global voice for rare disease patients

The launch of Rare Diseases International (RDI) was announced on 24 May 2015 in Madrid, Spain.[39] Over 60 patient representatives from 30 countries were present for the inauguration of RDI and to adopt a joint declaration to advocate for rare diseases as an international public health priority. RDI aims to represent rare disease patients and families from all over the world to provide a voice as well as visibility to rare diseases in the global health agenda.

5.1.2 EMA launches a pilot project to involve patients in medicines' benefit/risk assessment discussions

On 26 September 2014, the EMA announced the launch of a pilot project to include patients in discussions with the Committee for Medicinal Products for Human Use (CHMP) to assess drug benefits and risks.[40] The project aims to increase transparency and patient awareness of the medicinal product assessment process. The EMA will run the pilot project for one year in order to assess outcome and feasibility, address organisational aspects, integrate CHMP and patient feedback, and propose long term implementation of the project.

5.1.3 Methods and consequences of engaging patients in research on rare diseases

The research community has, over the years, increased efforts to involve patients with rare diseases in decisions concerning clinical investigations and treatment choices. In a systematic review of the literature, published in the Journal of General Internal Medicine, Forsythe *et al.* assess the degree of patient, caregiver and patient organisation engagement in research processes.[41] The authors conducted their review based on five considerations: the purpose of engaging patients in clinical research; the methods of identification and engagement; the effects of involving patients in research; the role of patient organisations in patient identification and recruitment; and the challenges of engaging patients in research on rare diseases. The authors' findings indicate that patients are engaged, usually, during clinical study preparation and execution phases. They are recruited through patient organisations,

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[39] Rare Diseases International portal http://www.eurordis.org/content/rare-diseases-international

[40] Press release 26 September 2014: Patients to discuss benefit-risk evaluation of medicines with the Committee for Medicinal Products for Human Use
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/09/WC500173511.pdf

[41] Forsythe *et al.*, A Systematic Review of Approaches for Engaging Patients for Research on Rare Diseases; Journal of General Internal Medicine 2014; 29 (Suppl 3):S788-800
http://link.springer.com/content/pdf/10.1007%2Fs11606-014-2895-9.pdf

clinics, agencies and online. In several cases, investigators engage patients to guide decisions on study topic, design and outcomes assessment. In addition to providing investigators with patient contacts, patient organisations often support collaborative research and patient engagement in clinical investigations. Finally, while researchers support patient involvement, engagement is time and resource intensive. The authors highlight the important role of patient organisations in facilitating contact between stakeholders, identifying research opportunities, and providing financial support and training. They suggest guidelines on methods of identifying and recruiting patients would benefit stakeholders. They believe initiatives, such as the Patient-Centered Outcomes Research Institute (PCORI), to support and evaluate the impact of patient engagement on health outcomes, which may improve collaborative research on rare diseases.

5.1.4   Patient-reported outcomes should be included in clinical trials for rare diseases

Identifying sets of symptoms common to all patients affected by one or several rare diseases has proven useful to clinical researchers and drug developers in order to address patient needs and substantiate drug labelling. In an article published in the Journal of General Internal Medicine, Basch and Bennett support the use of patient-reported outcomes (PROs) to measure patient reactions and progress throughout clinical trials.[42] While regulatory agencies, standards organisations and international societies have issued a number of guidance documents on PROs, many trials on rare diseases still do not include PROs in clinical data. The authors suggest that PROs be conducted by experienced investigators and tailored to patient populations and specific symptoms, such as the NIH's Patient Reported Outcomes Measurement Information System (PROMIS).

5.1.5   Not just a number: The benefits of putting patients at the heart of clinical trials

In an article published in Value for Health, Mullins *et al.* regret that classical clinical trials generally do not represent patient interests and rarely inform participants of results during the study.[43] Under such conditions, patients often lose interest and drop out of trials. Experience shows that participants' active involvement in the design and progression of clinical trials results in greater patient retention and more meaningful results. Informed patients are more willing to engage in time-consuming and effort-requiring studies as they feel valued, empowered, and capable of assessing therapeutic options. Pragmatic, Bayesian statistics and adaptive trials can improve patient safety and increase recruitment and retention. Pragmatic trials are designed to result in outcomes that are most relevant and beneficial to participants. Bayesian statistics draw on collected evidence to update knowledge on the treatment and outcome probabilities. Adaptive trials evolve on the basis of data accumulated during the trial and allow patients to be transferred to a more effective treatment if it becomes available once the trial has begun. These three trial designs are particularly relevant for rare diseases as they are more likely to retain

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[42] Basch and Bennett, Patient-Reported Outcomes in Clinical Trials of Rare Diseases; Journal of General Internal Medicine 2014; 29 (Suppl 3): S801-803 http://link.springer.com/content/pdf/10.1007%2Fs11606-014-2892-z.pdf

[43] Mullins *et al.*, Patient-Centeredness in the Design of Clinical Trials; Value in Health 2014; 17:471-475 http://www.valueinhealthjournal.com/article/S1098-3015%2814%2900047-3/pdf

already limited numbers of patients whilst potentially offering them early benefits. Nevertheless, the authors also highlight several limitations: pragmatic trials are designed to reflect a "real world" situation which is difficult to quantify and qualify; Bayesian statistics are resource-intensive; and adaptive trials might not offer the required evidence for regulatory approval. To truly qualify trial designs as patient-centred, Mullins *et al.* emphasise the primary need for sustained efforts to inform and involve patients and advocates at all stages of clinical studies.

5.1.6 Early escape crossover trials for rare diseases are better adapted to patient needs and preferences

A clinical research report, published in Contemporary Clinical Trials, illustrates the advantages of adaptive trial design for rare diseases.[44] Adaptive crossover trial designs, giving patients the option to opt out or "escape" the assigned treatment, can improve outcome efficiency and statistical significance. Increasingly designed to investigate new treatments for rare diseases, crossover trials involve two or more treatments administered in a set order to each patient and for set periods throughout the study. Crossover trials minimise patient exposure to ineffective treatments and increase efficiency since patients act as their own control and response to treatment is rapidly measured.

5.1.7 Patient-initiated guidance on clinical development of treatment for Duchenne Muscular Dystrophy

In June 2014, the Parent Project Muscular Dystrophy (PPMD) community submitted to the FDA the first patient-initiated guidance on clinical research and therapeutic development for Duchenne Muscular Dystrophy (DMD).[45] The guidance is a collaborative effort of over 80 experts and Duchenne community representatives, including parents, patients, academia, health professionals, industry and regulators. The purpose of the guidance is to assist researchers and industry in accelerating the development of medicinal products to treat DMD. Supported by peer-reviewed research, the guidance addresses six points to consider in therapeutic development. The guidance emphasises the importance of treatment preference and risk-benefit assessment from a patient representative point of view for regulatory evaluation of potential therapies, as illustrated in an article published in Clinical Therapeutics in May 2014.[46] The guidance also highlights the need for sponsors to develop clinical programmes based on

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[44] Huang *et al.*; Enhancing crossover trial design for rare diseases: limiting ineffective exposure and increasing study power by enabling patient choice to escape early; Contemporary Clinical Trials 2014; 38(2):204-212
http://www.ncbi.nlm.nih.gov/pubmed/24833067

[45] Parent Project Muscular Dystrophy submission to the FDA; Guidance for Industry: Duchenne Muscular Dystrophy Developing Drugs for Treatment over the Spectrum of Disease
http://www.parentprojectmd.org/site/DocServer/Guidance_Document_Submission_-_Duchenne_Muscular_Dystrop.pdf?docID=15283

[46] Peay *et al.*, A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy; Clinical Therapeutics 2014; 36(5):624-637
http://www.clinicaltherapeutics.com/article/S0149-2918%2814%2900209-4/pdf

patient and caregiver therapeutic preferences, as parents and patients are prepared to accept a certain level of risk for minimal benefit to slow disease progression. Five further criteria outlined in the guidance include diagnosis, natural history (based on improved disease understanding), clinical trial designs, outcome measures and considerations, and biomarkers to identify biological activity and support clinical trials. The PPMD intends the guidance to serve as a tool for discussion among stakeholders.

5.2   Trends: Clouds on the Orphan Drug Market - Call for Cheaper Drugs

5.2.1   Big Pharma more interested by products with a potential for multiple rare diseases

Following the end of the drug blockbuster age, pharmaceutical companies increasingly turned their attention to the potential gains from orphan drug development. In an article published in Expert Opinion on Orphan Drugs, Stephens and Blazynski studied the trends in orphan drug development, based on Pharmaprojects data.[47] Over the past 30 years, 657 orphan drugs were launched, representing 23% of products in development for rare diseases. The authors observe, however, that only a handful of rare diseases attract industry attention, cancer being the leader with far more drugs in development than for other rare diseases. The article reveals that companies increasingly investigate single drugs to target multiple rare diseases, thus increasing the chance for multiple indications and drug repositioning resulting in greater commercial gains. And while Big Pharma is turning its attention to rare disease markets, the authors suggest that companies follow general market trends in which even the orphan drug segment offers guaranteed returns, such as oncology. Rare diseases that are not sub-segments of well- understood diseases or for which drug repurposing is not possible attract far less industry attention. The authors fear that economic downturn and governments' reluctance to reimburse very expensive orphan drugs might further limit investment into orphan drug development for a great number of rare diseases.

5.2.2   Increasing challenges to penetrate the orphan drug market

A report from consulting firm L.E.K. proposes a business strategy view of the orphan drug industry and offers advice to pharmaceutical companies attempting to enter the marketplace.[48] Estimated to be worth over USD80 billion in 2009 and expected to reach over USD100 billion in 2014, the market for orphan drugs is rapidly outpacing other areas of the health industry. This strong growth is a result of regulatory incentives (e.g. fast track registration, user fee waivers, accepted small patient pools for clinical trials and 7-year market exclusivity), high drug prices for long term therapies and, until recently, low competition among the limited number of actors. This report suggests these trends are reversing and newcomers will face increasing challenges to penetrate the orphan drug market.

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[47] Stephens and Blazynski, Rare disease landscape: will the blockbuster model be replaced?; Expert Opinion on Orphan Drugs 2014; 2(8):797-806 http://informahealthcare.com/doi/pdf/10.1517/21678707.2014.924850

[48] Tzeng *et al.*, Raising Orphans: How Pharma Can Capture Value While Treating Rare Diseases; L.E.K. Executive Insights 2014; Vol XVI, Issue 9 http://www.lek.com/sites/default/files/LEK_1609_Orphan_Web_2.pdf

5.2.3   Combating the high prices of orphan drugs

A comment published in The Lancet by some members of the rare disease community addresses the rising cost of orphan drugs.[49] The authors state that the incentives provided by the government for the development of orphan drugs have backfired to some extent as they are now charging high prices to make up for the small patient base. To remedy the situation, the authors propose rigorous adherence to a diagnosis, and the new and expensive drugs to be validated by a designated centre. They also propose a high quality updated registry that constantly monitors the patients as well as a systematic negotiation of the drug price over a period of time.

5.2.4   The orphan drug price monopoly rages

Cystic fibrosis (CF) drug Kalydeco™ is unaffordable, according to Balfour-Lynn in an article published in Paediatric Respiratory Reviews.[50] Based on the United Kingdom (UK)'s CF Registry 2012 Annual Report, Balfour-Lynn calculated that 370 patients in the UK are eligible for treatment with Kalydeco™ (ivacaftor) for ion-channel function repair in CF patients affected by the G551D CFTR gene mutation. At GBP182,000 per patient per year, the total cost of treatment for UK patients would reach GBP67 million a year, based on the British National Formulary price list. If the treatment is extended to patients under the current six-year age limit, the number of eligible patients in the UK would rise to 470, costing GBP76 million. With the UK's CF budget of GBP130 million a year to cover some 10,000 CF patients, the drug remains unaffordable for healthcare services. In the USA, the price of Kalydeco™ started at USD294,000 per year, rising by USD17,000 each year, resulting in an additional USD17 million a year to cover all 1,000 patients receiving the drug in the USA. Such prices illustrate how unaffordable these targeted drugs are for most countries. The author fears that until personalised treatment becomes affordable to health services, high quality medical care will remain unattainable for many rare disease patients.

5.3   Trends: Megafunds, Crowdfunding

5.3.1   Megafunds to finance orphan drug discovery

In the face of pharmaceutical industry productivity decline over the past several years, the authors of an article published in Drug Discovery Today propose a novel method of financing drug discovery.[51] Fagnan *et al.* introduce the concept of "megafunds" to attract investments into risky orphan drug research and development projects. A megafund would raise funds by issuing "research-backed obligations" (RBOs),

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[49] Luzzatto *et al.*, Rare diseases and effective treatments: are we delivering?; The Lancet 2015; 385(9970):750-752 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2815%2960297-5/fulltext?rss%3Dyes

[50] Balfour-Lynn, Personalised medicine in cystic fibrosis is unaffordable; Paediatric Respiratory Reviews 2014; 15 Supp 1: 2-5 http://www.ncbi.nlm.nih.gov/pubmed/24832698

[51] Fagnan *et al.*, Financing drug discovery for orphan diseases; Drug Discovery Today 2014; 19(5):533-538 http://www.sciencedirect.com/science/article/pii/S1359644613004030

i.e. bonds on potential revenues from future sales of orphan drugs and intellectual property. Instead of relying on venture capitalists and other investment funds, megafunds could attract capital into orphan drug portfolios from a much larger investor base, usually unable to invest in early-stage drug discovery. Based on their simulations and the assumption of high success rates, the authors suggest that megafund portfolios containing ten to twenty investigational compounds could deliver potentially, albeit uncertain, high returns on investment. While the authors admit their simulations are only indicative of megafund potential, they maintain that novel financing models, such as RBOs to constitute megafunds, should be developed to address growing drug discovery challenges. By pooling and diversifying resources, the authors believe that megafunds spread their risk and offer greater financial flexibility whilst ensuring more efficiency and lower drug development costs.

5.3.2   Megafund model to finance development of orphan drugs: Analysing the NCATS portfolio

A paper published in Science Translational Medicine demonstrates the potential of financing program employed by the National Center for Advancing Translational Sciences (NCATS) – the megafund model – to reduce the risk associated with investing in the development of orphan drugs.[52] A megafund is a *"financial investment fund in which investors commit capital to develop a portfolio of orphan drugs and receive the proceeds of these investigational drugs or intellectual property rights as they are sold to venture capitalists or licensed by pharmaceutical companies."* The authors apply this concept to evaluate the risks and rewards of a simulated portfolio using a real-life rare disease portfolio from NCATS. The authors calibrated the pooled data from the portfolio of research projects (to develop orphan drugs) funded by NCATS on key model parameters and sought the opinion valuation panel of experts active in the biotech industry on these. The authors estimated that after a period of 11 years, the annualised returns of this hypothetical megafund were 5% and 8% for senior and junior bondholders, respectively. They also predicted a 14.7% return for equity holders, which is equivalent to an internal rate of return of 21.6% using typical venture-capital metrics. The authors state that this study illustrates that a rare disease megafund based on the NCATS business and operation model provides a live example with which to calibrate megafund simulations for orphan drug portfolios.

5.3.3   Crowdfunding for orphan drug research and development

In an article in Drug Discovery Today, Dragojlovic and Lynd examine the impact of crowdfunding, i.e. raising small amounts of capital from a large pool of donors through web-based tools, for research on rare diseases.[53] Crowdfunding appears successful to support early-stage research of rare diseases. As pharmaceutical companies become increasingly risk-averse, fewer industry funds are allocated to early-stage investigations. The authors suggest that crowdfunding could bridge the gap between early proof-of-concept research, for which funding is difficult to obtain, and access to traditional grant competitions

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[52] Fagnan *et al.*, Financing translation: Analysis of the NCATS rare-diseases portfolio; Science Translational Medicine 2015; 7(276):276ps3 http://stm.sciencemag.org/content/7/276/276ps3.full

[53] Dragojlovic and Lynd, Crowdfunding drug development: the state of play in oncology and rare diseases; Drug Discovery Today 2014; 19(11):1775-1780 http://www.ncbi.nlm.nih.gov/pubmed/24973645

or industry funding. They suggest that, though crowdfunding appears to contribute to research on neglected rare diseases, campaigns require careful planning. To run a successful campaign, they encourage project leaders to seek support from foundations, advocacy groups or even celebrities to raise awareness. Some universities have set up fundraising programmes to sponsor university-based research. The question remains whether crowdfunding for rare disease research will continue to raise small amounts to finance early-stage research or whether not-for-profit funds might one day become a significant part of later-stage research and development.

5.4   Trends: Repurposing and Finding New Targets

5.4.1   DrugNet: A novel drug repurposing web tool

To aid drug repurposing, an article published in Artificial Intelligence in Medicine has described a novel web tool – DrugNet[54] – which they developed.[55] The authors "*built a network of interconnected drugs, proteins and diseases and applied DrugNet to different types of tests for drug repositioning*". Their work is based on the principle that biological entities are intricately networked as well as dynamic and heterogeneous. The web tool can be accessed to query for drug-disease or disease-drug prioritisations, which then returns a list of ranked drugs (active substance, not trade names) based on a given disease or provides a ranked list of diseases (possibly new indications that can be pursued) for a drug query. The authors believe that usage of DrugNet could potentially bring respite for patients with no treatment, especially rare disease patients, sooner as the identified drugs have already been shown to be safe and tolerable.

5.4.2   Uncovering disease-disease relationships through the incomplete interactome

An article published in Science presents a network-based framework to identify the location of disease modules within the interactome – a network integrating all interactions within a cell – to understand and predict disease modules relationships.[56] According to Mench *et al.*, a complete and accurate map of the interactome, which could have tremendous impact on our ability to understand human disease at a molecular level, is at least a decade away. The authors show that the current data from an "incomplete interactome" may be able to map out some disease module relationships using network science. The authors demonstrate that the "*network-based location of each disease module determines its pathobiological relationship to other diseases, where associated disease models segregate in the same neighbourhood of the human interactome,*" whilst unrelated modules form in different neighbourhoods. The authors believe that the proposed network-based distance allows us to envisage the relationships

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[54] DrugNet portal http://genome2.ugr.es/drugnet/

[55] Martínez *et al*., DrugNet: Network-based drug-disease prioritization by integrating heterogeneous data; Artificial Intelligence in Medicine 2015; 63(1):41-49 http://www.aiimjournal.com/article/S0933-3657%2814%2900144-4/pdf

[56] Menche *et al*., Uncovering disease-disease relationships through the incomplete interactome; Science 2015; 347(6224):1257601 http://www.sciencemag.org/content/347/6224/1257601

between diseases even if they do not share genes. The authors believe that the study is significant as *"the introduced network-based framework can be extended to address numerous questions at the forefront of network medicine, from interpreting genome-wide association study data to drug target identification and repurposing."*

5.4.3 Distinct rare diseases might share similar or identical biological mechanisms

In an article published in Nature Biotechnology, Brooks *et al*. suggest that groups of apparently distinct rare diseases might share similar or identical biological mechanisms.[57] Drug development challenges could therefore be overcome by grouping diseases based on their underlying cause – or aetiology –, rather than concentrating on one treatment for one rare disorder at a time; an example: recently-approved ataluren to treat Duchenne muscular dystrophy. The authors indicate that ataluren has also demonstrated efficacy in treating cystic fibrosis, suggesting that several clinically distinct disorders result from common underlying causes and might respond positively to a same drug. The authors believe that adopting this approach for drug development could have multiple benefits: greater industrial interest in rare diseases, larger patient pools to conduct clinical trials, improved understanding of the relationship between disease and drug response, and potential therapeutic benefits for a greater number of patients.

5.4.4 Novel method of creating phenotype network database

An article, published in the Journal of Biomedical Informatics, describes a novel method of creating phenotype network database which does not rely on mining textual phenotype descriptions, but on the usage of highly accurate disease-manifestation semantic relationships from Unified Medical Language System (UMLS).[58] Chen *et al*. have called this database Disease Manifestation Network (DMN).[59] According to the authors, the usage of 50,543 highly accurate disease-manifestation semantic relationships UMLS helped capture major aspects of disease phenotypes which can successfully predict disease causes. A salient feature of this phenotype network database: DMN not only contained existing knowledge but also some novel insights which the authors found by comparing DMN and mimMiner (a phenotype network database constructed through text mining). The authors also found that DMN partially correlated with the genetic network database - Human Disease Network (HDN) - based on Online Mendelian Inheritance in Man (OMIM) and GWAS. Finally, using the example of Marfan Syndrome, the authors found that DMN has the potential to provide *"new leads to discover unknown causes of Marfan Syndrome"*, thus concluding that a combinatorial approach where mimMiner and DMN disease is used would be an excellent method for gene discovery and drug.

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[57] Brooks *et al*., Expanding rare disease drug trials based on shared molecular etiology; Nature Biotechnology 2014; 32(6):515-518 http://www.nature.com/nbt/journal/v32/n6/full/nbt.2924.html

[58] Chen *et al*., Comparative analysis of a novel disease phenotype network based on clinical manifestations; Journal of Biomedical Informatics 2015; 53:113-120 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4452018/

[59] Disease Manifestation Network database nlp/case.edu/public/data/DMN

5.4.5   Chemical drugs could be an alternative to gene therapy to treat certain genetic diseases

In addition or as an alternative to gene therapy, chemical drugs could offer benefits to treat certain genetic disorders resulting from loss-of-function or gain-of-function mutations. In an article published in Drug Discovery Today, Sun *et al*. found that most chemical drug binding sites are located far from the gene mutation locus.[60] Based on this assumption, the authors suggest that chemical drugs could target certain genetic disorders without the gene mutation interfering with the drug binding site. Over a hundred drug target pairs were matched with drug indications and genetic disease traits by comparing drug targets registered in the Therapeutic Target Database and genes registered in OMIM. These drug targets were studied to assess the influence of genetic mutations on candidate chemical drugs. The authors indicate that most of the studied genetic mutations had little influence on the drug binding sites. They suggest therefore that more chemical drugs should be considered as candidates to treat genetic and rare diseases.

5.4.6   Rethinking drug development for rare diseases: a combinatorial approach to treat Charcot-Marie Tooth disease

A preclinical[61] and a clinical[62] study published in the Orphanet Journal of Rare Diseases have introduced a crucial development in the field of drug development for rare diseases. Here, the researchers tested a combination of three already approved compounds – baclofen, naltrexone and sorbitol – for its potential to treat Charcot-Marie-Tooth Type 1A disease (CMT1A). The objective of the proposed treatment is that instead of just one drug, multiple drugs can tackle the symptoms of this disease by down-regulating PMP22. This blend was first tested in a rat-model of CMT1A, which showed that the combination of these three drugs synergistically down-regulated PMP22, confirming its efficacy. Due to the success of the preclinical study, the three drugs combination was tested in CMT1A patients. The clinical trial confirmed its safety and tolerance, and demonstrated that patients receiving the highest dose showed the least deterioration. Not only did this treatment stop the further deterioration of clinical symptoms in these patients, they also displayed some improvements, which is a desirable feature of any treatment approach. While the results published in the clinical study are exploratory in nature, the researchers are geared for the next phases of clinical trials due to the promising outcome. This kind of combinatorial approach to treat diseases is often used in clinical practice by doctors but this is the first time, instead of finding that one drug that will affect a molecular mechanism in a major way, individual drugs selected for their potential to act on specific elements of a biological pathway are used together for a pleiotropic

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[60] Sun *et al*., Finding chemical drugs for genetic diseases; Drug Discovery Today 2014; 19(12):1836-1840 http://www.sciencedirect.com/science/article/pii/S1359644614003791

[61] Chumakov *et al*., Polytherapy with a combination of three repurposed drugs (PXT3003) down-regulates *Pmp22* over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy; Orphanet Journal of Rare Diseases 2014; 9:201 http://www.ojrd.com/content/9/1/201

[62] Attarian *et al*., An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot-Marie-Tooth disease type 1A; Orphanet Journal of Rare Diseases 2014; 9:199 http://www.ojrd.com/content/9/1/199

method of action. The encouraging result of this treatment route has piqued the interest of many in the rare disease community.

5.4.7   The Children's Pharmacy Collaborative™: a tool to support paediatric drug repurposing

Developing orphan drugs for children is typically challenging due to the limited number of patients, age-dependent dosage and tight regulation to conduct clinical trials on minors. To date, around 500 drugs only are FDA approved for paediatric use. Drug repositioning represents a relatively quicker option to develop drugs for children as clinical testing for new indications does not require initial toxicity studies. On the other hand, testing existing drugs in children will require dose finding and pharmacokinetic studies. In an article published in Drug Discovery Today, Blatt *et al.* introduce the Children's Pharmacy Collaborative™, a non-exhaustive database of drugs reported to have been used previously in children.[63] Based on existing databases, such as the Johns Hopkins Clinical Compound Library, the authors identified around 1,250 drugs reported to have been used in minors. This figure suggests that many drugs are therefore used off-label in children. The authors believe this first paediatric-focused database will help identify candidate drugs for repurposing in paediatrics.

5.4.8   Drug repurposing based on a new concept: Homopharma

Drug repurposing is increasingly being recognised as an important pathway to bring treatments for rare diseases quicker to the patients. New tools are being designed to discover new targets for medications that already have marketing authorisation, one of which is described in the BMC Genomics called "Homopharma".[64] This concept is based on the fact that a set of proteins which have the conserved binding environment can be matched with a set of compounds are often able to inhibit these proteins. According to the authors this method can identify potential targets of compounds and reveal key binding environment and thus be instrumental in for discovering new usages for existing drugs. The experimental work of the authors showed that the four flavonoid derivatives, which can be used as anticancer compounds, selected by the authors, was able to inhibit multiple protein-kinases with similar physiochemical properties efficiently. The authors believe that "the Homopharma concept can have the potential for understanding molecular binding mechanisms and providing new clues for drug development".

5.4.9   Drug repositioning can accelerate discovery of pharmacological chaperones

A short article published in the Orphanet Journal of Rare Diseases describes pharmacological chaperone therapy as a "*promising strategy for the treatment of genetic diseases as it exploits small molecules*

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[63] Blatt *et al.*, Expanding the scope of drug repurposing in pediatrics: the Children's Pharmacy Collaborative; Drug Discovery Today 2014; 19(11):1696-1698 http://www.sciencedirect.com/science/article/pii/S1359644614003304

[64] Chiu *et al.*, Homopharma: A new concept for exploring the molecular binding mechanisms and drug repurposing; BMC Genomics 2014; 15(Suppl 9):S8 http://www.biomedcentral.com/1471-2164/15/S9/S8

which can be administered orally, reach difficult tissues such as the brain and have low cost."[65] The authors postulate that drug repositioning should be run systematically for the discovery of pharmacological chaperones. To this end, the authors gathered *"proteins that are associated to rare diseases, by the entries that have a link to Orphanet in Uniprot and linked them to DrugBank, a database including FDA-approved small molecules, experimental and nutraceuticals drugs and found that several Orphan proteins interact with one or more approved small molecules."*

5.5   Trends: Revisiting Health Technology Assessment Approach for Orphan Drugs

5.5.1   Health Technology Assessment for rare diseases should incorporate multiple criteria

In an editorial published in Expert Review of Pharmacoeconomics & Outcomes Research, Simoens defends the validity of Health Technology Assessment (HTA) using multi-criteria decision analysis to evaluate medicines and technologies for rare diseases.[66] As he points out, HTA does in theory appear suitable to assess health products for rare diseases based on the European Network for Health Technology Assessment's (EUnetHTA) definition of HTA as "*a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient focused and seek to achieve best value*." In practice, however, HTA is often and almost exclusively based on the cost-effectiveness of orphan products.

5.5.2   Divergence between policies to stimulate orphan drug development and policies to reimburse these medicines

In an article published in the European Journal of Health Economics, Drummond and Towse state that unless orphan drugs acquire "special" status, policies to stimulate orphan drug development and policies to reimburse these medicines will continue to diverge.[67] They suggest that increased collaboration between governments internationally, reflecting the global reach of pharmaceutical companies, might be part of the solution to reconcile these opposing policies. At the European level, the EMA and EUnetHTA have in fact examined HTA policies in efforts to coordinate regulatory approval and reimbursement decisions. The outcome report of their joint initiative was published in Value in Health. The EMA and EUnetHTA continue to investigate ways of addressing regulatory obstacles early on in

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[65] Hay Mele *et al.*, Drug repositioning can accelerate discovery of pharmacological chaperones; Orphanet Journal of Rare Diseases 2015; 10:55 http://www.ojrd.com/content/10/1/55

[66] Simoens S, Health technologies for rare diseases: does conventional HTA still apply?; Expert Review of Pharmacoeconomics & Outcomes Research 2014; 14(3):315-317
http://informahealthcare.com/doi/pdf/10.1586/14737167.2014.906903

[67] Drummond and Towse, Orphan drugs policies: a suitable case for treatment; European Journal of Health Economics 2014; 15:335-340 http://link.springer.com/article/10.1007%2Fs10198-014-0560-1

efforts to improve medicines and orphan product evaluation, based on multi-stakeholder and multi-disciplinary criteria.

5.5.3 Sustainability of the orphan medicinal drug model in Europe: an industry perspective

A paper published in the Orphanet Journal of Rare Diseases provides the perspective of a biopharmaceutical company on the debate of the orphan medicinal product (OMP) model by "proposing a set of principles to improve the consistency, effectiveness and sustainability of OMP value assessment mechanisms in Europe, while maintaining flexibility and innovation in decision making between countries".[68] The authors propose ten principles to be considered when undertaking reforms to improve access of OMPs, from the perspective of an OMP manufacturer. They put forward several practical recommendations that among others include continued prioritisation of rare diseases by policymakers and greater collaboration among stakeholders. The authors consider OMP Regulation to be an example of successful health policy as it has contributed to boosting research, development and marketing of orphan medicinal products in Europe after decades in which no new treatments were approved.

5.5.4 Methods for generating evidence on health outcomes in patients with rare diseases

The authors of an article published in the British Medical Journal assessed information related to the proposed methods for generating evidence on health outcomes in patients with rare diseases.[69] Gagne *et al*. found that most articles focused on innovations in methods for clinical trials intended to minimise the number of participants needed to meet the study goals or to maximise the proportion of participants who receive active treatment to encourage enrolment. Several promising strategies were uncovered, which aimed to minimise trial sample size, including making adjustments to traditional randomised trials by choosing a longer trial duration and capturing more events, focusing on high risk patients, using genetic testing to reduce variability or by using factorial designs, in which two (or more) treatment comparisons are carried out simultaneously. A second approach identified by the authors through literature was to select an outcome measure using a continuous outcome variable, a surrogate marker, a composite endpoint, or repeated measure outcome. Another method is to build networks to allow broader access to trials as they can facilitate the recruitment of larger and more geographically diverse patient populations. The strategies to maximise treatment participants include reducing recruitment requirements by utilising methods such as crossover trial design which involve randomising patients from treatment to no treatment, or an N-of-1 trial which involves offering a patient multiple active or placebo treatment in a double-blind, randomised manner, while regularly measuring key endpoints. Studies using observational data to assess patient health outcomes in rare diseases, such as the use of propensity scores, which *"summarises all potential confounders into a single scalar score"* and self-

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[68] Gutierrez *et al*., Principles of consistent value assessment and sustainable funding of orphan drugs in Europe; Orphanet Journal of Rare Diseases 2015; 10:53 http://www.ojrd.com/content/10/1/53

[69] Gagne *et al*., Innovative research methods for studying treatments for rare diseases: methodological review; British Medical Journal 2014; 349:g6802 http://www.bmj.com/content/349/bmj.g6802.long

controlled observational designs in which patients act as their own controls, were also identified in the literature.

5.5.5   Methods for rare diseases to generate evidence for robust HTA decisions

An article in the International Journal of Technology Assessment in Health Care summarises research methods for rare diseases so that evidence can be generated to inform robust HTA decisions.[70] Facey *et al*. pay particular attention to adaptive trials such as Bayesian adaptive trials. They also believe that it is important to take into account the experiences of patients when evaluating medicines for rare disease patients. They support the use of structured instruments for patient reported outcomes to measure functioning and well-being by means of quality or life/patient-reported outcome measures. These instruments allow a patient to evaluate their health in terms of the impact a given health state has on the ability to function and enjoy life. The views of patients, their families and carers/carer-givers, who have unique knowledge about living with a condition, can be elicited by means of qualitative research. The authors believe that obtaining an international consensus is imperative to improve evidence collection and assessment of technologies for rare diseases.

5.6   Trends: Data Registration and Codification

5.6.1   A framework to integrate heterogeneous clinical data into a central registry

An article published in e-Health – For Continuity of Care describes a framework to integrate heterogeneous clinical data into a central repository which has been noted as necessary for clinical research.[71] The authors state that it is especially crucial for rare disease research as it is often necessary to "*aggregate study data from several sites in order to achieve a statistically significant cohort size*." The authors describe a best practice framework that consists of three sequential steps which involves "*(1) creating a harmonisation table, (2) setting up an ETL process and finally (3) putting the resulting data structure into a central repository that enables custom queries*." To decrease the work load and improve the understanding of the complexity behind data integration, they provide spreadsheets and extract-transform-load (ETL) templates to support an individual implementation. Integrating heterogeneous clinical data into a central data repository is considered a necessary step for clinical research.

5.6.2   Do-it-yourself patient registries: Proposed user-friendly design software from Australia

In an article published in Source Code for Biology and Medicine, Bellgard *et al*. propose new features for rare disease registry frameworks (RDRF) that allow non-professional software developers to generate

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[70] Facey *et al*., Generating health technology assessment evidence for rare diseases; International Journal of Technology Assessment in Health Care 2014; 30(4):416-422 http://dx.doi.org/10.1017/S0266462314000464

[71] Karmen *et al*., A Framework for Integrating Heterogeneous Clinical Data for a Disease Area into a Central Data Warehouse; e-Health – For Continuity of Care 2014; 205:1060-1064 http://ebooks.iospress.nl/publication/37653

and manage patient registries.[72] As the number of identified rare diseases grows, the need for dynamic registries has become increasingly important to manage the quantity of information and data. The ability to exchange information between registries is also essential to develop and optimise patient databases. Most registries, however, are still constructed on static programmes and data elements requiring assistance from software developers. Exchanging information between registries therefore becomes complex and inefficient. In efforts to standardise data elements to optimise registry use, update and aggregation, Bellgard *et al.* encourage the use of software that can be applied across different registries by all administrators. They propose constructing registries using several web framework programmes and open source database systems. The aim is to design dynamic and user-friendly patient registries that do not require additional software development or professional assistance. Python programming and MongoDB open-source document repository allow non-professional administrators to build efficient, dynamic and interrelated registries. Data coding programmes such as YAML also allow designers to import and export documents whenever necessary to complete information – such as patient consent – or share data with other research communities. Bellgard *et al.* believe these programmes and features to enhance RDRF design will improve data mining, sharing and re-use across registries, essential to conduct research and clinical trials on rare diseases.

5.6.3   Do-it-yourself patient registries: The proposed approach in Germany

The first version of the OSSE registry framework created on behalf of the German Federal Ministry of Health was released on 1 January 2015. The OSSE registry framework allows building of individual rare disease registry without additional programming effort and includes a set of basic data forms and longitudinal data forms, workflow support and role-based access control. Data entry forms rely on metadata stored in a central repository, which will in the long-term lead to a new level of interoperability between registries of rare diseases. For example, a registry can participate in a cross-registry decentral search infrastructure connecting it with potential research partners while preserving data sovereignty. The built-in pseudonymisation provides not only "out of the box" support of the open source product "Mainzelliste" (or compatible pseudonymisation software) including duplicate detection, but also allows authorised persons to display medical and identifying data on the same webpage while preserving the informational separation of powers. Current installation packages, guides and further information can be downloaded.[73]

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[72] Bellgard *et al.*, Second generation registry framework; Source Code for Biology and Medicine 2014; 9:14
http://www.scfbm.org/content/pdf/1751-0473-9-14.pdf
[73] OSSE portal http://osse-register.de

5.6.4 The need to build minimum and common data sets to research, diagnose and treat rare diseases more efficiently

In an article published in the Journal of the American Medical Informatics Association, Choquet *et al*. propose a methodology to establish standards for rare disease data collection.[74] Based on systematic review of the literature and the identification of data elements, the authors aim to establish homogeneous data elements common to all rare diseases, collect electronic health records at the bedside, and promote the development of standardised European rare disease registries. The authors highlight the need for appropriate methodology and stakeholder consensus to establish common data elements (CDEs) in order to render data collected in clinical settings reusable for patient care, epidemiology and research. Since European countries have begun launching their national plans to advance rare disease research and treatment, the necessity and the difficulty to collect consistent and harmonised data sets on rare disorders has become all the more apparent. France's first National Plan on Rare Diseases (2005-2009) focused on groups of diseases and aimed to develop a network of rare disease centres and research units. France's second National Plan on Rare Diseases (2011-2014) funded information technology tools for these disease centres to develop a French minimum data set for rare diseases, building on 42 CDEs and 16 national data elements.

5.6.5 Clinic-developed software to support NIH/NCATS global rare diseases registry

A computer software developed at the Marshfield Clinic Research Foundation (MCRF) will support the NIH/NCATS' Global Rare Diseases Patient Registry Data Repository® (GRDR) program, designed to advance research for rare diseases.[75] Developed as a collaborative effort of MCRF's Biomedical Informatics Research Center and its Clinical Research Center, the software is available free of charge to institutions and patient advocacy organisations developing rare disease registries to be included in the GRDR. The main goal of the GRDR program is to create a central web-based global data repository that will aggregate coded patient information and clinical data to be available to investigators to conduct various biomedical studies, including clinical trials. This will be done by collecting and aggregating data from rare disease registries in a standardised manner and linking the registry data to CDEs using nationally accepted standards and standard terminologies. Organisations that choose to use the registry software will be able to build and customise their registry and questionnaires using the dynamic form and other developed features in the framework. A two-year proof-of-concept pilot by NIH/NCATS concluded in September 2013 and the rare disease community has accepted the importance of using CDEs and standard vocabularies & terminologies. NIH/NCATS is moving forward with the next steps to develop the NIH/NCATS GRDR Program. The GRDR program will collaborate and link to other major national and international rare disease databases to maximise the efforts in rare disease research.

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[74] Choquet *et al.*, A methodology for a minimum data set for rare diseases to support national centers of excellence for healthcare and research; Journal of the American Medical Informatics Association 2015; 22(1): 76-85 http://jamia.oxfordjournals.org/content/22/1/76.long

[75] NIH/NCATS GRDR® Program portal https://grdr.ncats.nih.gov/

5.6.6 NIH/NCATS/GRDR® Common Data Elements

An article published in the Contemporary Clinical Trials presents the manner in which NIH/NCATS GRDR programme serves as a central web-based global data repository and the development of a set of CDEs, which are controlled terminologies that represent collected data the use of which facilitates the integration of patient information.[76] The article reviews the programme which integrates de-identified patient clinical data from rare disease registries, EHR, clinical data and other data sources, in a standardised manner, to be available to researchers for conducting various biomedical studies, including clinical trials and to support analyses within and across diseases. According to Rubinstein and McInnes, the establishment of the GRDR program has elevated the issue of data standardisation and interoperability for rare disease patient registries, to international attention, resulting in a global dialogue and significant change in the mindset of registry developers, patient advocacy groups, and other national and international organisations. The authors also delineate the additional tools and other resources developed through the GRDR program, to accelerate the rate of establishing high quality patient registries in a standardized manner, will be shared and disseminated.

5.6.7 Automated search tools to retrieve published rare disease cases would improve patient identification and diagnosis

As the number of published clinical case reports and literature on rare diseases increases, so does the need to develop automated tools to identify and analyse the literature. This is particularly relevant in the field of rare diseases, where practitioners rely frequently on manually retrieved case reports to support their diagnosis of patients with rare conditions. In an article published in Database, Taboada *et al.* propose their methods of identifying and annotating relevant case reports in efforts to improve phenotypic descriptions for rare disease diagnosis.[77] Currently available tools, including Medical Subject Headings (MeSH), Gene Ontology (GO), GoPubMed, and SEGOPubmed, offer various methods of retrieving abstracts using key term searches. While MeSH and GO are the most frequently used tools, others such as the Open Biological and Biomedical Ontologies (OBO), the National Center of Biomedical Ontology (NCBO) bioportal, and the Human Phenotype Ontology (HPO) are more suitably adapted to certain diseases. The authors suggest developing methods, using the various available tools, to facilitate automated and exhaustive extraction of reports on patients with phenotypic similarities. They propose techniques to generate semantic patient data indexing using linguistic patterns which can be further analysed, and believe their approach would contribute towards data curation for rare disease indexing and analysis.

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[76] Rubinstein and McInnes, NIH/NCATS GRDR® Common Data Elements: A leading force for standardized data collection; Contemporary Clinical Trials 2015; 42:78-80 http://www.contemporaryclinicaltrials.com/article/S1551-7144%2815%2900047-6/abstract

[77] Taboada *et al.*, Automated semantic annotation of rare disease cases: A case study; Database 2014:1-13 http://database.oxfordjournals.org/content/2014/bau045.full.pdf

5.6.8   Rare Diseases in ICD-11: Progress and pitfalls

Because of their individual rarity, genetic diseases and other types of rare diseases are under-represented in healthcare coding systems. This contributes to a lack of ascertainment and recognition of their importance for healthcare planning and resource allocation, and prevents clinical research from being performed. This is why the EC supported, from 2007 on, the development by Orphanet of an inventory of rare diseases and a classification system which could serve as a template to update international terminologies. When the WHO launched the revision process of the ICD, a Topic Advisory Group for rare diseases was established in 2009, managed by Orphanet and funded by the EC. Five years on, 5,400 rare diseases listed in the Orphanet database have an endorsed representation in the foundation layer of ICD-11 and are thus provided with a unique identifier in the beta version of ICD-11, which is ten times more than in ICD-10.The current beta version is open for public consultation and comments, and to be used for field testing. ICD-11 adoption by the World Health Assembly is planned for 2018. The authors of an article published in the Orphanet Journal of Rare Diseases describe the work carried out during the past years with very limited means considering the scope, ambition and strategic significance of the revision of ICD.[78] They report significant hurdles and setbacks, including the lack of funding which impacted the level of professionalism that could be attained. The contrast between the initially declared goals and the currently foreseen final product is disappointing even if it is a satisfaction to see that most rare diseases will have a specific code. The authors also reported that, due to uncertainty around the outcome of the field testing and the potential willingness of countries to adopt this new version, the EUCERD adopted, in November 2014, a recommendation for healthcare coding systems to consider using Orphacodes in addition to ICD-10 codes for rare diseases having no specific ICD-10 codes.

5.7   Trends: Genomics and Phenomics Data Sharing

5.7.1   An automatically populated database of exome variant-calling and annotation in Mendelian disorders

A recent publication in BMC Genomics describes the development of a database of variations collected from patients with Mendelian disorders freely available online.[79] This unique database to automatically populate due to an associated exome-sequencing pipeline that identifies, annotates and stores insertions, deletions and mutations in the database. The exome-sequencing pipeline has been designed using state-of-the-art software tools to run on a computing cluster to simultaneously analyse several samples. The detected variants are annotated with the standard variant annotations as well as with

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[78] Aymé *et al.*, Rare diseases in ICD11: making rare diseases visible in health information systems through appropriate coding; Orphanet Journal of Rare Diseases 2015; 10:35 http://www.ojrd.com/content/10/1/35

[79] Mutarelli *et al.*, A community-based resource for automatic exome variant-calling and annotation in Mendelian disorders; BMC Genomics 2014; 15 (suppl 3):S5 http://www.biomedcentral.com/content/pdf/1471-2164-15-S3-S5.pdf; TIGEM Exome Mendelian Disorder portal http://exome.tigem.it

"allele frequencies across samples progressively collected in the database itself, stratified by Mendelian disorder."

5.7.2 The opportunities and technical challenges of sharing genomic data for research and diagnosis of genetic and rare disorders

Rapid advances in sequencing technologies are constantly contributing towards improving clinical diagnostic powers to identify and treat genetic disorders and rare diseases appropriately. In an article published in Genome Medicine, Robinson describes the potential benefits but also the challenges of sharing and exploiting data generated by genomics technologies.[80] The author highlights the technical barriers to store and share vast datasets using currently available bioinformatics tools. Databases such as ClinVar, DECIPHER and PhenomeCentral allow researchers to search, share and store genetic data for research on rare diseases, while other recent projects, such as Human Genome Variation Society (HGVS) and Human Variome Project (HVP), were initiated to standardise data collection and facilitate data sharing. While data repositories are useful to access individual datasets, users are invariably unable to access multiple datasets from different sources. The author describes next-generation sequencing (NGS)-Logistics software as a potential solution for researchers to retrieve and share large datasets from multiple data centres. If installed in each data centre, NGS-Logistics software can locate data in different centres according to searched genes or variants. Robinson suggests that NGS-Logistics could help researchers engage in collaborative efforts to share data and accelerate therapeutic development.

5.7.3 Challenges and bottlenecks for genomic data sharing

An article published in Applied & Translational Genomics addressed the issues hindering efficient and ethical genomic data sharing in the human genomics research community.[81] The interviews identified four bottlenecks for data sharing which includes finding relevant and usable data (data discovery), getting authorisation to access data, formatting data as well as storing and moving data. Depending on the field, researchers cited either lack of time or potential loss of future publications as some of the reasons for not making more of their own data available to others even when they have the authority and consent to do so. A lack of sufficient resources to make their data available was also an oft-expressed concern by these researchers. The results of the online survey, containing questions that addressed the issues identified through the interviews, showed very good agreement with the findings described above. According to the authors, *"it is important to continuously assess available solutions which facilitate data sharing/access and promote the mechanisms and practices that make the greatest impact"*.

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[80] Robinson P., Genomic data sharing for translational research and diagnostics; Genome Medicine 2014; 6:78-80 http://www.genomemedicine.com/content/pdf/s13073-014-0078-2.pdf

[81] van Schaik *et al.*, The need to redefine genomic data sharing: A focus on data accessibility; Applied and Translational Genomics 2014; 3(4):100-104 http://www.sciencedirect.com/science/article/pii/S2212066114000386

5.7.4 Anonymising and sharing individual patient data

A review published in the BMJ tackles the issue of anonymisation of patient data to share it for secondary purposes, particularly for research.[82] El Emam *et al.* emphasise the current need for anonymisation standards that can provide operational guidance to data custodians and promote consistency in the applications of anonymisation. This article describes the key concepts and principles for anonymising health data while ensuring it remain suitable for meaningful analysis. The authors believe that methods for measuring the risk of re-identification can be used to decide how much to anonymise health data for different types of data release. They note that although these methods cannot ensure that the risk of re-identification is zero, it is not the threshold that is expected by privacy laws and regulations in any jurisdiction for which there are strong precedents to choose suitable probability thresholds for anonymising data. Finally the authors state that organisations such as the EMA could help address such gaps by *"providing or recommending robust and scalable methods that can provide quantitative anonymity assurances while producing high quality data."*

5.8 Trends: Adaptive Trials

5.8.1 Methods of overcoming the challenges of small patient populations in clinical trials on rare diseases

Clinical trials on rare diseases are typically difficult to conduct due to limited patient numbers. In an article published in Expert Opinion on Orphan Drugs, O'Connor and Hemmings identify several challenges associated with small patient pools.[83] To optimise clinical trials on small patient numbers, investigators must consider the choice of trial design and methodology to gain significant results, depending on rare diseases and patient profiles. The authors suggest investigators increase patient participation through collaboration with international patient associations and expert centres. Researchers should provide education to engage participants actively and increase their interest in trial design and process; predicting patient drop-out and subsequent loss of data would allow investigators to design trials adequately and maximise patient input. Various study designs have been developed to address small patient numbers. Adaptive trials allow investigators to modify aspects of the study as it progresses, obtain intermediate results and integrate results into subsequent trial phases. Bayesian methods enable investigators to make assumptions and define endpoints based on accumulated data. Regulators recognise the challenges of designing clinical trials for small patient numbers and have consequently developed flexible evaluation frameworks. Conditional marketing authorisation and adaptive licensing offer sponsors the possibility to market orphan drugs, provided they continue collecting ongoing clinical and post-marketing evidence on drug safety and efficacy. O'Connor and Hemmings highlight recent efforts to promote clinical research on rare diseases in small populations: EU-

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[82] El Emam *et al*., Anonymising and sharing individual patient data; BMJ 2015; 350:h1139
http://www.bmj.com/content/350/bmj.h1139.long

[83] O'Connor and Hemmings, Coping with small populations of patients in clinical trials; Expert Opinion on Orphan Drugs 2014; 2(8):765-768 http://informahealthcare.com/doi/abs/10.1517/21678707.2014.931221

funded projects IDEAL, InSPiRe, ASTERIX and CAVOD aim to develop innovative approaches to adapt and assess clinical trials on small populations and rare diseases.

5.8.2   Bayesian model: an adaptive method of analysing clinical trials

Different statistical methods are used to evaluate clinical trials for rare diseases. Clinical trials for rare diseases need novel approaches to combat the small populations. Along with other things, many are now considering the use of different statistical models to interpret the results of the trial. Many researchers are considering the Bayesian model for analysing trials for orphan drugs. An article published in Statistics in Medicine describes how the Bayesian approach to conduct of rare disease trials, which compares an experimental treatment with a control where patient responses are classified as a success or failure, could be applied.[84] According to Hampson *et al.*, Bayesian model does not rely on the hypothesis testing/confidence intervals paradigm, but allows determination of the posterior probability of whether an effect is beneficial. The authors assert that this approach is suited to adapting to information that accrues during a trial, potentially allowing for smaller more informative trials and for patients to receive better treatment. Additionally, accumulating results can be assessed at any time, including continually, with the possibility of modifying the design of the trial, for example, by slowing (or stopping) or expanding accrual, imbalancing randomisation to favour better-performing therapies, dropping or adding treatment arms, and changing the trial population to focus on patient subsets that are responding better to the experimental therapies. The authors also note that Bayesian analyses use available patient-outcome information, including biomarkers that accumulating data indicate might be related to clinical outcome and allow for the use of historical information and for synthesizing results of relevant trials.

5.8.3   Clinical trial designs for rare diseases: International Rare Cancers Initiative portfolio

The International Rare Cancers Initiative (IRCI) is a partnership which aims to stimulate and facilitate the development of international clinical trials for patients with rare cancers. European Journal of Cancer has published the methods used in ICRI portfolio which was presented in the multi-disciplinary workshop held in Amsterdam in September 2013 as well as other methods that have not yet been realised.[85] The article explains that clinical trials can be designed using a wide array of possibilities as there is no 'one size fits all' solution, due to the challenges faced while studying rare cancers. Notable approaches to conducting clinical trials for rare cancers within the constraints of sample size and insufficient background information, common to rare cancers, are exemplified in this article. Other unrealised trial designs are also discussed, providing the readers and overview of the different types of clinical trials that are possible to combat the challenges of bringing treatments for rare cancers to the fore. The article

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[84] Hampson *et al.*, Bayesian methods for the design and interpretation of clinical trials in very rare diseases; Statistics in Medicine 2014; 33(24):4186-4201 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260127/

[85] Bogaerts *et al.*, Clinical trial designs for rare diseases: Studies developed and discussed by the International Rare Cancers Initiative; European Journal of Cancer 2015; 51(3):271-281
http://www.ejcancer.com/article/S0959-8049%2814%2901063-6/pdf

notes that *"progress in the rare diseases, decisions to change practice will have to be based on less direct evidence from clinical trials than in more common diseases"*, therefore warranting the use of non-traditional methods for conducting trials.

6. Breakthroughs in Therapy

6.1 Progress and challenges of targeted delivery of siRNA therapeutics

"*Therapeutic gene silencing promises significant progress in pharmacotherapy, including considerable expansion of the druggable target space and the possibility for treating orphan diseases*", according to Lorenzer *et al.* in a recent publication in the Journal of Controlled Release.[86] The authors review the current clinical status of silencing RNA (siRNA) therapeutics, along with hurdles faced in achieving knockdown in non-liver tissues and tumours, including insufficient pharmacokinetic properties and poor biodistribution. Innovative and promising pre-clinical strategies are summarised and their targets and ligands identified. An increase of understanding in siRNA design and delivery brings anticipation of progress to be made in the near future, encouraging further development in therapeutic translation.

6.2 First stem-cell therapy recommended for conditional marketing approval in EU

Holoclar is the first stem cell therapy to be recommended by the EMA for approval in the EU.[87] This advanced therapy medicinal product (ATMP) containing stem cells is the first medicine developed to treat moderate to severe limbal stem cell deficiency (LSCD) due to physical or chemical burns to the eye(s) in adults, a rare eye condition that can result in blindness. Holoclar is based on autologous cultures of limbal stem cells, where a small sample of remaining stem cells in patients with LSCD are taken and grown into larger numbers in the laboratory and placed back on to the surface of the eye. Based on a robust assessment carried out by the Committee for Advanced Therapies (CAT) and the Agency's expert committee for ATMPs, the CHMP recommended a conditional marketing authorisation of Holoclar in the EU. According to the EMA, *"although the data supplied by the applicant show that the medicine's benefits outweigh its risks, the data are based on retrospective studies and are not yet comprehensive (and) therefore, an additional study on the use of Holoclar should be conducted"*.

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[86] Lorenzer *et al*., Going beyond the liver: progress and challenges of targeted delivery of siRNA therapeutics; Journal of Controlled Release 2015; 203:1-15
http://www.sciencedirect.com/science/article/pii/S0168365915000930

[87] Press release, 19 December 2014: First stem-cell therapy recommended for approval in EU
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/12/news_detail_002239.jsp&mid=WC0b01ac058004d5c1