



IRDiRC-EMA

Preparatory Document for Joint Workshop on Small Population Clinical Trials Challenges in the Field of Rare Diseases

Prepared by

IRDiRC Scientific Secretariat

On behalf of the

Small Population Clinical Trials Task Force

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Document notes

This document is intended to provide readers with the necessary background information on the work to date in the field of Small Population Clinical Trial (SPCT) initiatives in order to prepare discussions of an upcoming workshop, co-organised with the European Medicines Agency (EMA), in London, UK in the first trimester of 2016.

The present document includes:

- ▶ Preparatory documentation concerning small population clinical trial challenges, methodologies and regulatory efforts in the field of rare diseases, and a description of initiatives working on developing more efficient clinical trials in these populations.
- ▶ Preparatory documentation on ways to improve clinical study methods in small populations which would be acceptable for regulatory agencies.

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The IRDiRC Task Force

The International Rare Diseases Research Consortium (IRDiRC) was set up to maximise scarce resources and coordinate research efforts in the rare diseases field, with the clear goal to boost the research and development (R&D) process to help deliver effective therapies as soon as possible. IRDiRC aims to stimulate and coordinate basic and clinical research, by promoting links between existing resources, fostering the molecular and clinical characterisation of rare diseases and encouraging translational, preclinical and clinical research.

The Therapy Scientific Committee of the IRDiRC has issued recommendations on essential actions selected for their high leverage effect to unlock the potential of rare disease therapy development.

Among them, the Therapy Scientific Committee recommends:

- ▶ **Encouraging, supporting and establishing early and continuous dialogue on clinical development strategies and wide evidence generation** (e.g. natural history, registry, **clinical trial design**, clinical endpoints, surrogate endpoints, patient relevant outcomes, regulatory strategy, medical practice, public health strategy) with all relevant stakeholders such as patient representatives, medical experts, researchers, scientific societies, regulators, health technology assessors, payers and sponsors when appropriate. This could be done through dedicated workshops, safe harbours where knowledge could be shared in a non-competitive manner.
- ▶ Encouraging, supporting and developing **small population clinical trials** (e.g. exploring the application of innovative methods). This is an **essential step to gather more relevant data at the time of benefit-risk assessment**.

In order to make a decisive step to reach these objectives, the IRDiRC Executive Committee decided to set up a Task Force on Small Population Clinical Trials in the field of rare diseases, established in May 2015, composed of the following members acting as Steering Committee:

- ▶ Simon Day (Clinical Trials Consulting & Training Limited, USA)
- ▶ Ralf-Dieter Hilgers (IDeA; RWTH Aachen, Germany)
- ▶ Ilan Irony (FDA/Center for Biologics Evaluation and Research/Office of Cellular, Tissue and Gene Therapies, USA)
- ▶ Kristina Larsson (EMA/Orphan Medicines, UK)
- ▶ Nigel Stallard (InSPiRe; University of Warwick, UK)
- ▶ Kit Roes (ASTERIX; UMC Utrecht, the Netherlands)

The following IRDiRC Scientific Committee members will also participate in this Task Force:

- ▶ Jeffrey Krischer (University of South Florida, USA)
- ▶ Samantha Parker (Lysogene, France)

In addition to the Steering Committee, the following members have agreed to participate:

- ▶ Yuki Ando (Pharmaceuticals and Medical Devices Agency (PMDA), Japan)
- ▶ Paolo Baroldi (Vanda Pharmaceuticals, USA)
- ▶ Frank Bretz (Novartis, Switzerland)
- ▶ Carl-Fredrik Burman (Astra Zeneca; Chalmers University, Sweden)
- ▶ Ron Christensen (Mapigroup, USA)
- ▶ Tim Friede (University of Goettingen, Germany)
- ▶ Robert James Hemmings (Medicines and Healthcare Products Regulatory Agency, UK)
- ▶ Mats Karlsson (Uppsala University, Sweden)
- ▶ Janbernd Kirschner (Freiburg University, Germany)
- ▶ Franz König (Medical University Vienna, Austria)
- ▶ Kerry Leeson-Beevers (Alström Syndrome UK / EURORDIS volunteer, UK)
- ▶ Dirk Mentzer (Paul Ehrlich Institute, Germany)
- ▶ Geert Molenberghs (KU Leuven, Belgium)
- ▶ Gérard Nguyen (Patient Representative IDEAL, France)
- ▶ Dan O'Connor (Medicines and Healthcare Products Regulatory Agency, UK)
- ▶ May Orfali (Pfizer, USA)
- ▶ Martin Posch (Medical University Vienna, Austria)
- ▶ Franck Sasinowski (Hyman, Phelps & McNamara, P.C., USA)
- ▶ Franz Schaefer (University of Heidelberg, Germany)
- ▶ John Scott (FDA/CBER/OBE/BB, USA)
- ▶ Stephen Senn (Luxembourg Institute of Health, Luxembourg)
- ▶ Bruno Sepodes (University of Lisbon, Portugal)
- ▶ Robert Temple (FDA/CDE/ODE, USA)
- ▶ Andrew Thompson (EMA Statistics Group, UK)
- ▶ Ferran Torres (Universitat Autònoma de Barcelona, Spain)
- ▶ Sarah Zohar (INSERM, France)

This Task Force is requested to review the present document and to participate in the expert discussions at an invited workshop to discuss possible solutions to ensure methods used for clinical trials in small populations, in particular for rare diseases, are acceptable from regulatory point of view. This Task Force will also write up the conclusions of the discussions and the list of items for action which will be agreed on by the workshop participants, to be transmitted to the IRDiRC Executive Committee and to be made public for further discussion with the Community at large.

Acronyms

ASTERIX	Advances in Small Trials dEsign for Regulatory Innovation and eXcellence
BI	Boehringer Ingelheim
BLA	Biologics License Applications
CNS	Central Nervous System
CTEP	Cancer Therapy Evaluation Program
CRESim	Child-Rare-Euro-Simulation
DMCC	Data Management and Coordinating Center
EORTC	Europe an Organisation for Research and Treatment of Cancer
EMA	European Medicines Agency
ESNEE	European Study of Neonatal Exposure to Excipients
ESMO	European Society for Medical Oncology
EU	European Union
EUCERD	European Union Committee of Experts on Rare
FDA	Food and Drug Administration
FIRM-ACT	First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment
GCP	Good Clinical Practice
GRDR	Global Rare Disease Patient Registry and Data
GUID	Global Unique Identifiers
IBTA	International Brain Tumour Alliance
ICRI	International Rare Cancers Initiative
IDeAI	Integrated Design and Analysis for Small Population Group Trials
IMI	Innovative Medicines Initiative
IND	Investigational New Drug
INCa	French National Institute of Cancer
InSPiRe	Innovation in Small Populations Research
IPF	Idiopathic Pulmonary Fibrosis
IRDiRC	International Rare Disease Research Consortium
NCATS	National Center for Advancing Translational Sciences
NCRN	National Institute of Health Research Cancer Research Network
NDA	New Drug Applications
OMIM	Online Mendelian Inheritance in Man
ORDR	Office of Rare Diseases Research
PAMPERS	Paediatric Accelerator Mass Spectrometry Evaluation Research
PrioMedChild	Priority Medicines for Children
RCE	Rare Cancers Europe
R&D	Research and Development
RDCRN	Rare Disease Clinical Research Network
RD-HUB	Rare Diseases Human Biospecimens/Biorepositories
PAMPERS	Paediatric Accelerator Mass Spectrometry Evaluation Research
TDN	Therapeutics Development Network

Challenges of Conducting Clinical Trials in Rare Diseases

Introduction

Clinical research and trials in rare diseases face evident obstacles: very or exceptionally low disease prevalence, small and heterogeneous patient populations, difficulty in recruiting such patients, disease severity, lack of or limited knowledge of disease natural history and high attrition rates during research and development (R&D) processes. Rare disease trials are more likely to be early Phase I or II trials (72.5% vs. 38.5% for non-rare disease trials).¹

Incentives for industry have been implemented in the European Union (EU) and in the United States (US) to boost orphan medicinal product development:² the 1983 US Orphan Drug Act³ and the 2000 EU regulation on orphan medicinal products.⁴ These incentives have shown success since 2013, with nearly 70 orphan medicinal products reaching the market in Europe and nearly 370 in the US intended to treat around 300 diseases. These results, however, far from meet the needs of rare disease patients.

Half the market authorisations are granted at a stage when evidence is not firmly established, requiring ongoing patient monitoring. The concept of adaptive licensing was proposed, based on stepwise learning under conditions of acknowledged uncertainty and including iterative phases of data gathering and regulatory evaluation.⁵ Additionally, two thirds of rare diseases affect children primarily and half the current trials test innovative products, adding to the complexity of trial design and acceptability by regulatory bodies. Clinical research in rare diseases faces a number of additional challenges.

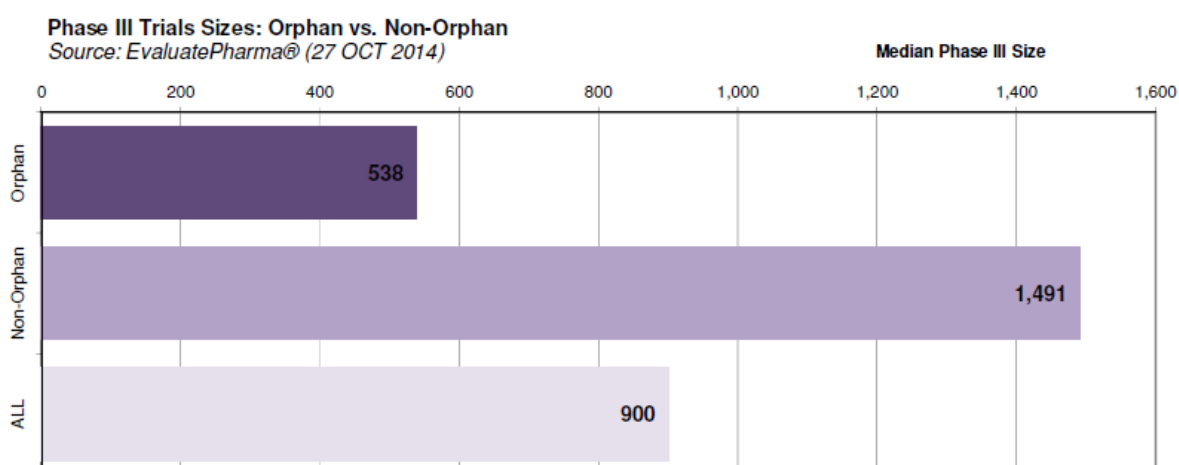
Need for trial designs adapted to small population sizes

The European Medicines Agency (EMA) states in its guideline on trials in rare disease populations that no methods specific to small trials exist that are not also applicable to large studies⁶. The reverse is also true, leading to impossible sample size requirements to conduct clinical trials in rare diseases. Studies found that, for new products entering Phase III trials from 1 January 2000, an average 731 patients were enrolled in orphan drug trials versus 3,540 in non-orphan drug trials.⁷

Average Phase III Trials Sizes (All New Drug Products Entering Phase III from 1 JAN 2000)

Product Type	Phase III Trial Size					Phase III Cost (\$m)			Potential 50% US Tax Credit	
	Median	Average	No. of Products (n=)	Total Patients	% of	Median	Average	Total	Median	Average
Orphan	538	731	421	307,620	9%	97	99	41,487	48	49
Non-Orphan	1,491	3,540	890	3,150,830	91%	143	188	167,717	143	188
ALL	900	2,638	1,311	3,458,450	100%	122	160	209,204		
Orphan / Non-Orphan = 36.1% 20.6% 47.3% 67.6% 52.3% 24.7% 33.8% 26.1%										

Source: EvaluatePharma® Success Rates (27 OCT 2014)



Traditional randomised controlled study designs are difficult to conduct in small patient groups due to population size and group heterogeneity. If feasible, controlled designs, allowing patient-patient comparisons whilst treating all patients, would enable more accurate treatment assessment.

Response-adaptive methods modify treatment allocation ratios depending on which therapy demonstrates better results. Such methods are complex and rely on real-time data, which may in fact be easier in rare disease populations due to the slow recruitment process. Sequential designs are reasonably common in industry-sponsored trials, while Bayesian methods are still relatively novel. Some trials are first-in-human clinical studies proposed for proof-of-concept assessments, they must therefore be conducted in as homogeneous populations as possible.⁸ This further reduces the available population size.

The field needs to develop cost-effective, novel, rigorous controlled study designs and relevant analyses to assess treatment efficacy in heterogeneous small populations. Besides three European Commission-funded projects selected for funding in this area (i.e. ASTERIX, IDeAl, InSPiRe) and several international initiatives to improve clinical trial methodologies, industrial actors are also seeking innovative solutions to conduct clinical trials in small populations to boost research in rare diseases.^{9,10,11} Some of these initiatives are presented in this paper, along with the regulatory landscape, to advance discussions on ways to optimise and improve commonly adopted approaches.

Review of Steps in Trial Design

Challenges in identifying and recruiting patients

Timely and adequate recruitment of eligible participants is a challenge for any rare disease study. The need to study patients at early stages for disease-modifying agents or, on the contrary, those at very advanced stages, when intervention risk is high, may not be feasible to narrow down entry criteria based on disease stage or other characteristics.

Patients' geographical dispersion requires multicentre and multinational collaboration, introducing additional regulatory and funding obstacles. For severe rare diseases, travel to research centres may be impossible. Some solutions propose monitoring patients remotely, setting up community centres to include patients in trials who would otherwise be unable to access them.¹² Effective recruitment is often supported through partnership with patient organisations, when available, and through the use of patient registries and centres of expertise.

At present, 641 rare disease registries of varying quality have been identified in Europe,¹³ of which most are national, 40 are Europe-wide and 74 are global. Disease specific registries that meet quality standards have been demonstrated to contribute to the quality of clinical trials.¹⁴ The structure and design of natural history studies are pivotal to capture clinical information efficiently and to determine safety and efficacy.

New therapies often emerge more rapidly in areas where products are already being developed or on the market. Such situations create competing interests to recruit the same small population, further reducing the number of candidate patients.

Adaptable and novel approaches must respect the need for solid evidence before offering innovative treatments to patients in need.¹⁵ Developing clinical trials for rare diseases therefore requires a concerted approach of all stakeholders. In general, the rare disease community is in favour of adaptive licensing as a means to ensure an optimal risk/benefit balance without delaying access to potentially life-saving treatments. Difficulties can only be overcome if a multi-stakeholder dialogue is conducted, as recommended by the European Union Committee of Experts on Rare Diseases (EUCERD).¹⁶

The design and specific methodological aspects of a study need to be carefully discussed with all relevant partners, in particular patients themselves. The relationship between clinicians and patients must be based on mutual trust in order for patients to agree to take part and, once in the trial, to stay in and provide outcome data. Such data must provide answers relevant to patients, clinicians and policymakers, must build on existing data and must be collected in such a way that participants wish to remain and take part in further studies.

Regulators must also be included in discussions as early on as possible in the R&D process, to ensure the most appropriate design for a specific case study is adopted. Protocol assistance and scientific advice from regulatory bodies have been demonstrated to play a key part in guiding study process to address benefit/risk analyses for market approval.

Centres of expertise, specialised in rare diseases, play an essential role in fostering clinical research networks and infrastructures and disseminating study outcomes. Investigator and patient representative training will ensure better understanding of regulatory, methodological and ethical requirements. Equally, adequate support must be given to existing infrastructures for clinical research which takes into account the intrinsic characteristics of rarity, and develops harmonised practices to submit, monitor and report multicentre and multinational rare disease clinical trials.

Defining the number of patients needed to have an effect

In all clinical trials, the sample size must be planned on a rational basis. Sample size calculation requires the collaboration of biostatisticians and investigators with expert medical. While sample size is subject to external factors, such as duration of recruitment, disease rarity or limited financial support, it must be planned to assess study results on statistical grounds. The attainable power should be calculated during planning (the lower the power, the lower the chances to demonstrate a hypothesis).¹⁷

A comparison of interventional clinical trials in rare versus non-rare diseases, based on ClinicalTrials.gov data, found that rare disease trials enrolled a median of 29 patients (vs. 62 for non-rare disease trials) and fewer trials were actively pursuing enrolment (15.9% vs. 38.5%).¹⁸ As previously mentioned, for new products entering Phase III trials from 1 January 2000, an average 731 and median 538 patients were enrolled in orphan drug trials (vs. average 3,540 and median 1,491 in non-orphan drug trials).¹⁹

In rare disease clinical trials, the sample size must take into account data loss due to follow-up or patient drop-out. Investigators might consider performing a pilot study to estimate appropriate population requirements. Sample size planning based on estimates from past information must take into account the variation in precision in these prior results to avoid overestimating effects as they could lead to planning excessively small sample sizes. Other issues, such as missing data, patient drop-out, or multiple hypotheses testing, must also be considered during sample size planning.

Some methods to reduce sample size include lengthening trial duration to achieve more events with fewer patients, focusing on high risk patients, using companion genetic testing, and testing multiple treatment arms in a factorial design. Selecting outcome measures using a continuous outcome variable, a surrogate marker, a composite endpoint or repeated measure outcomes can, in some cases, be used to reduce sample size.²⁰

The gold standard for trial design: Randomised Controlled Trials

Randomised controlled trials are regarded as being the standard design to provide evidence for regulatory approval, but such studies are not always feasible in rare disease studies. Findings suggest that rare disease trials are more likely to be single arm (63.0% vs. 29.6% for non-rare disease trials) and non-randomised (64.5% vs. 36.1% for non-rare disease trials).²¹

Requirements to meet hard endpoints in these designs, such as mortality and quality of life, would considerably reduce the number of patients able to provide evidence on the drug's benefits and risks.²²

On the other hand, designs that use historical and surrogate endpoints to support regulatory approval may not provide sufficiently strong evidence to demonstrate treatment efficacy.

In the case of clinical studies in rare cancers, investigators discovered that uncontrolled trials to assess response rates often overestimate the drug efficacy, thus distorting risk-benefit assessments in such designs. As response rates in tumours are not always representative of survival, surrogate endpoints are poor criteria to assess drug efficacy.

While challenging, large randomised trials for rare diseases have been conducted successfully thanks to broad collaborations. For instance, the First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) trial for adrenocortical cancer randomised over 300 patients to two cytotoxic treatments and provided reliable findings.

Methodologies for small clinical trials

To improve methodology in recruiting participants to small population clinical trials, investigators should evaluate recruitment strategies used in their trials. Systematic evaluation of methodologies would contribute to the literature and to subsequent study designs.²³ Investigators should also conduct systematic reviews of the literature before designing or adapting clinical trials for rare disease treatments. Additionally, they could define a statistical analysis plan when designing a trial protocol, in order to maximise statistical significance.

Where no single design is suited to all rare disease studies, investigators need to choose which design is the most appropriate for a given disease-treatment-outcome situation. (The next chapter outline some of the alternative trial designs that can be applied to rare disease studies.)

Overall, the number of patients required for the study, the length of the trial and how the variables (disease progression, patient variability) are managed will influence the choice of the most suitable trial design. For many disease-outcome situations, more than one trial method can be applied and should be able to incorporate additional factors into the design to improve statistical power, optimise trial duration for patients, sponsors and investigators.

Building clinical trial networks, while lengthy, contributes to increasing access to trials and allows investigators to conduct multicentre and multinational trials. Clinical trial networks provide broader and geographically more diversified patient groups. They also contribute to decreasing the time to complete a trial.

Need for more sensitive outcome measures to quantify disease evolution

The large variation in severity, stage, irreversibility and age of onset leads to a very large range at baseline for many measures of efficacy, making it hard to detect clinically significant efficacy changes. The frequent complexity of disease manifestations in multiple body systems requires more than one clinical endpoint for one domain to adequately assess an effective treatment.

Hard endpoints, such as mortality and quality of life, are all but impossible to demonstrate in most rare diseases. Surrogate endpoints, however, are often considered to be unreliable markers of treatment efficacy as they might indicate improved response rate without improvement in survival rate.

Outcome measures are the topic of discussion of the IRDiRC Patient-Centered Outcome Measures Task Force.

Statistics

Depending on study designs, different statistical methods should be applied to best reflect and interpret results. Based on multiple criteria decision analysis approaches, the final analysis should determine which treatment is most relevant and effective, and which experimental designs should be tested in Phase III trials. This descriptive phase should rate rare disease drug options and trial designs according to the frequency of obtaining significant results in each trial.

Methodology framework

To optimise the chances of designing the right trial for the right patient population, a methodological approach could identify the most effective treatment, out of several, for rare disease patients.²⁴ Several potential treatments are tested in Phase III clinical trials, based on optimal study design in patients selected according to specific prognostic and predictive markers. Patients are identified by analysing available clinical databases and by creating mathematical models to describe the disease, the treatment effects and clinical trial results simulated in varying patient populations and study designs.

The first step of this six-step approach is to collect all possible knowledge available in international clinical databases on a rare disease. Based on this information, investigators can retrospectively identify predictive biomarkers to help identify potential treatments of interest. Modelling and simulation aim to identify key components of the disease mechanism, characteristics of respondent patients and potential endpoints.

Patient-centeredness in clinical trials

Clinical trials generally do not represent patient interests and rarely inform participants of results during the study.²⁵ 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.

Methods to design trials from a patient's point of view rather than the investigator's include pragmatic, Bayesian statistics and adaptive trials which could improve patient safety and increase recruitment and retention. Clinical protocols need to be relevant to patients by proposing broad recruitment and inclusion, meaningful outcomes and comparison against the best current treatment. Patients must be able to understand results interpretations. Finally, protocols must be efficient, whereby patients should

be allocated to arms with the highest probability of success and be able to start, stop or continue in one arm or another based on interim results.

Pragmatic, Bayesian statistics and adaptive trial designs are more likely to retain already limited numbers of patients whilst potentially offering them early benefits. Nevertheless, 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, efforts must be put into informing and involving patients and advocates at all stages of clinical studies.

Need for natural history studies

The natural history of most rare diseases is scarcely or not at all documented, yet is necessary to inform trial design. Very few epidemiological studies are published on rare diseases due to the difficulty to identify and document cases which are widely spread geographically, inadequately diagnosed and rarely or not systematically followed up by academic centres.

Most attempts to collect good quality data are supported by short-term grants, with no long term perspective. The cost of conducting high quality natural history studies represents a significant barrier to their development. Both the EUCERD and IRDiRC have issued recommendations to identify obstacles in natural history studies which require solutions.^{26,27}

Natural history studies need to capture clinical information more cost-effectively and inform on optimal approaches to treatment development. The use of coding systems specific to rare disease, such as Orphanet and Online Mendelian Inheritance in Man (OMIM) codes would enable the emergence of real life data from healthcare information systems.^{28,29}

Methodologies for Small Clinical Trials

The following methods outline some of the alternative trial designs that can be applied to rare disease studies.

- **Randomised Controlled Trials**

Randomised controlled trials represent the ideal method to evaluate the effectiveness and safety of medicinal products, because they help protect against trial bias and statistical non-significance.³⁰ In practice however, recruitment from limited patient numbers to such trials is difficult and does not systematically meet objectives. In efforts to minimise bias, methods such as centralised randomisation, double-blind follow-up and outcome evaluation can be applied to trial designs in small populations.³¹

In silico Phase III randomised controlled trial simulation has been proposed to identify optimal trial designs based on available clinical databases and disease modelling for selected drug candidates. The EU funded ERA-Net PrioMedChild Child-Rare-Euro-Simulation (CRESim) project was set up to create a platform to perform *in silico* experiments assessing randomised controlled trial designs for drug evaluation in children with Dravet Syndrome, cystic fibrosis and lymphoblastic lymphoma.

- **Parallel group design**

Individuals are randomised to receive the tested treatment or the control. This design requires large sample sizes.

- **Factorial design**

In order to test two hypotheses simultaneously, participants are randomised to treatment A or corresponding placebo, and again, randomised within each group to treatment B or corresponding placebo. This design requires that no interaction occurs between treatment A and B. This multiple treatment option can provide answers to several questions within a same study population, thus requiring fewer patients to answer all the questions without reducing the number of patients answering individual questions.

- **Crossover design**

Participants receive two treatments each in random order and act as their own control. This type of trial supposes, however, that the disease is stable and the patient's health status is identical at the beginning and at the end of each treatment period. Because each treatment period must be followed by a wash-out period, the patient follow-up duration is therefore long and the risk that patients drop out of the study is greater.³²

- **High-risk allocation design**

This design can be used when investigators wish to compare high dose and standard treatments on high risk patients without putting patients at risk. Both high- and low-risk patients are recruited, with high-risk patients receiving only high dose treatment and low-risk patients receiving either high dose or standard treatments randomly. The data extrapolated from low-risk patient responses are used to estimate efficacy response and establish a risk prognostic model. This model can then be used to predict expected benefits of high dose and standard treatments on high-risk patients. This design relies on the ability to extrapolate treatment effects from low-risk patient groups.³³

- **Statistical prediction design**

This design stems from hypothesis testing. It aims to establish the distribution of control measurements for an observed condition in order to establish an expected range of future measurements. If future measurements fall within the prediction ranges, the treatment is considered to have no impact on the observed condition. If future measurements exceed prediction ranges, the intervention is considered to have an effect. This type of design is particularly interesting if the protocol aims to test several outcomes and if few patients are available.

- **Latin square design**

This design is used when several treatments are tested and compared. For instance, when testing three treatments, participants receive all treatments sequentially and following a wash-out period between each treatment.

- **Ranking and selection design**

This approach aims to identify the best treatment among several, by ruling out ineffective treatments. While investigators might not be able to identify immediately the best treatment, this method allows them to identify a group of effective treatments among several. Investigators can then narrow down the treatment options until they identify the single best option. Similar to hypothesis tests, selection trials generally require smaller patient numbers.

- **N-of-1 or single-subject design**

In this single case study, one participant receives one of two, or several, treatments sequentially. This type of study allows investigators to achieve experimental progress without having to design a group comparison study. N-of-1 trials can be effective in confirming causality. Nevertheless, the long term effects of certain treatments in crossover and N-of-1 trials could hamper the analysis of study results.³⁴ These trials might not produce significant results if the disease is fast evolving or in which relapse and remission periods are erratic.

- **Case-control design**

This design might be applied to situations in which outcomes are rare and require methods to collect primary data. Case-control designs aim to establish a link between exposure to risk factors and disease. Risk factor information is collected retrospectively and constitutes cases. This design is used in the study of rare diseases to provide preliminary study material when little is known about the disease and its risk factors. As these study designs can, however, be prone to bias, controls should be selected from the same population as the at-risk population, but must not have the disease. This design was applied to conduct a case-control study using the International Collaborative Gaucher Group Registry.³⁵

- **Delayed start design**

All patients receive the active treatment following an initial placebo controlled phase. This trial design, however, requires treatment periods to be sufficiently long to obtain some therapeutic effect. Another limitation of this design is the absence of double-blinding once the placebo phase is over. Furthermore, symptom evolution during the follow-up phase might enable patient identification, resulting in evaluation bias. This design should, therefore, be used essentially to evaluate the effect of a treatment on symptoms and the evolution of the disease.

- **Prospective inception cohorts**

Also referred to as “new user” designs, these studies allow investigators to establish temporality between baseline confounders, exposures and outcomes, and enable them to observe outcome events occurring after entry to the study. Such designs are not ideal, however, for the study of rare diseases due to often long diagnostic lag time. Patients are likely to have had the disease and be undergoing some form of treatment for some time. Identifying “new users” in the rare disease population is therefore challenging.

- **Randomised withdrawal, early escape, randomised placebo phase, stepped wedge designs**

In randomised withdrawal studies, patients receive open-label treatment for a set period in order to identify a subgroup of patients who are more likely to respond to treatment. Patients in the subgroup are then randomised to receive the treatment or placebo in a double-blinded study. The design aims to assess the optimal treatment duration in respondents.

Early escape designs give patients the option to opt out or escape the assigned treatment. These designs can improve outcome efficiency and statistical significance, while limiting patient exposure to ineffective treatment³⁶. Increasingly designed to investigate new treatments for rare diseases, early escape crossover trials involve two or more treatments administered in a set order to each patient and for set periods throughout the study.³⁷ Patient 1 will receive treatment A followed by treatment B, whilst patient 2 will receive treatment B followed by treatment A for the same period. Crossover trials therefore minimise patient exposure to ineffective treatments and increase efficiency since patients act as their own control and response to treatment is rapidly measured.

Randomised placebo phase and stepped wedge designs minimise the time patients spend on placebo and all patients end up receiving the active treatment.

- **Adaptive randomisation design**

This design aims to favour the participant group with the better chance of success by increasing the probability that patients will be randomised to that group. In this ‘play the winner’ strategy, the successful treatment is added to the treatment options, thus increasing the chance that a patient receives that treatment. In the ‘drop the loser’ approach, the ineffective treatment is removed, thus reducing the probability of unsuccessful outcomes. This design, however, lacks clear methodology concerning delayed test responses and is limited to trials with binary responses.

- **Response-adaptive design**

Adaptive trials may increase statistical significance and be more efficient in small patient groups, by increasing flexibility.³⁸ Participants act as their own control since their reaction to the different treatments may be assessed in short timeframes.³⁹ Patients suffering from often life-threatening rare conditions are not exposed to long periods without treatment.

- **Group sequential (adaptive) design**

In this design, patient recruitment is staggered and the total sample size is not determined at the start of the trial. A fixed number of patients are recruited at several stages. An interim analysis is performed following each recruitment round. Once sufficient information is collected, the trial is stopped. In this type of design, the smaller-than-required trial size can usually be calculated based on assumptions of the treatment effects and random variation, established prior to data collection. The risk when applying this design, however, is over- or under-estimating treatment efficacy which could lead to weak statistical analyses of results and inaccurate estimation of assumptions for subsequent trial recruitment rounds.⁴⁰

- **Bayesian design**

In these study designs, probability statements are made on the basis of accumulated data.⁴¹ Accumulated knowledge may be used as quantitative prior belief upon which subsequent trial data can be added, resulting in updated posterior belief to support evidence. Data from separate trials are therefore integrated to create a larger set of evidence.

Two concerns, however, limit the use of Bayesian methods: the potential that the prior evidence might be based on biased data, favouring positive outcomes; and the risk of integrating all evidence into a single analysis rather than a series of individual studies that could be mutually supportive. While traditionally accepted levels of significance might not be met, regulatory authorities generally favour evidence generated through stand-alone and mutually supportive studies.

■ Surrogate endpoint design

While surrogate endpoints might not truly predict clinical outcome, they can help develop clinical programmes in rare disease studies by substituting for a clinical endpoint. Nevertheless, markers for surrogate endpoints must be justified and evaluated in the context of the disease process⁴². Selecting an outcome measure using a continuous outcome variable could help enhance statistical efficiency. Furthermore, combining several outcomes into a single outcome measure could also increase the number of events and hence increase the statistical power.

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Regulatory Agency Guidelines

European Medicines Agency (EMA)

On 16 April 2014, the new Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, entered into force and will be applied in May 2016.⁴³ The EMA's guideline on clinical trials in small populations recognises that no single methodology exists to conduct small population clinical trials which are not also applicable to large clinical studies.⁴⁴ Most orphan drugs and paediatric indications submitted for regulatory approval should undergo randomised controlled trials based on accepted rules and guidance. However, the EMA accepts that certain unconventional approaches may be used if they improve the interpretability of study results.

For instance, in 2007, the EMA finalised a draft reflection paper 'Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design'.⁴⁵ According to this guidance, a study design is adaptive '*if statistical methodology allows the modification of a design element (e.g., sample-size, randomisation ratio and number of treatment arms) at an interim analysis with full control of the type I error rate.*' This document provides the first regulatory guidance on adaptive designs. It acknowledged potential benefits of adaptive trials whilst emphasising caution, and alternative methods are considered only when completely unavoidable and must be fully justified.

In October 2014, the EMA released a policy on publication of clinical data for medicinal products for human use, in efforts to increase clinical trial transparency and protect patient interests.^{46,47} On 3 October 2014, the EMA hosted a meeting with Rare Cancers Europe (RCE) representatives, to discuss RCE's publication of a consensus paper on clinical trial methodology in rare cancers.⁴⁸ The same month, the EMA and European Society for Medical Oncology (ESMO) Rare Cancers Europe initiative conducted a joint workshop on chordoma, a model for very rare cancers, to discuss how to facilitate the development of therapies for this and other rare cancers.

In situations where randomised controlled trial is not possible, regulators are open to discuss the adoption of complementary methodologies and evidence sources to enhance the overall evidence base. Approval mechanisms exist to recognise uncertainties that are inherent to trials with small sample sizes in the EMA's decision making.

As the use of alternative approaches to conduct clinical trials in small patient populations implies increased uncertainty concerning the reliability of results and product effectiveness, safety and risk-benefit, follow-up data is essential. The EMA highlights that the trade-off between small quantities of high quality evidence (from small randomised trials) and large quantities of lower quality evidence (from larger uncontrolled case series) must be considered and judged on a case-by-case basis.

Marketing authorisation applications for orphan products tested in small populations are assessed according to the same standards as those for other products, but take into account limitations due to low patient recruitment. In rare diseases, the combined evaluation of single case studies might be the only way to provide evidence. In such cases, treatment conditions and data collection must therefore be

standardised and data must comply with good clinical practice (GCP) standards. Such studies must be prospectively planned and described in study protocols. Systematic reviews of all data and combined analysis of individual case reports and observational studies should be considered to contribute to the evidence.

Pre-clinical pharmacodynamics studies can be useful if adequate animal models exist to inform the design of clinical trials. Such studies would help establish dose and route of administration for trials in man. To address variability, within-patient comparisons in progressive disorders could provide useful data to support benefit-risk assessments. Nevertheless, comparative trials might still be required and expected. Efficient design and analysis still require a clear understanding of potential sources of variability. It is essential that rare disease patients participating in clinical trials contribute as much information as possible to make a benefit-risk assessment possible. Well-planned use of available techniques to obtain and analyse data is essential. Pharmacology studies and patients registers should be used to support evidence and help design studies. Surrogate endpoints can be used, but must be justified, and control groups, even in small populations, are essential to support the reliability of trials.

Food and Drug Administration (FDA)

The Center for Drug Evaluation and Research at the FDA highlights the challenges of clinical development and regulation for small populations.⁴⁹ Among them are the nature of rare disorders (chronic, progressive, life-threatening and life-limiting), heterogeneity among patients and within disorders, lack of natural history studies, undefined endpoints and treatment targets (many treatments do not enter the central nervous system).

While the Orphan Drug Act provides financial incentives, it does not offer markedly different assessment standards from non-orphan drugs. Orphan drugs must demonstrate substantial evidence of effectiveness and clinical benefit, and adequate and well-controlled clinical studies. The lack of drug characterisation and pre- or non-clinical data (animal toxicity) during early- or pre- Investigational New Drug (IND) phases does therefore represent a barrier to entering orphan drugs into Phase I or first-in-human clinical trials. On the other hand, the Code of Federal Regulations which requires a *“design that permits a valid comparison with a control”* may be relaxed at the FDA’s discretion. Orphan drugs thus end up being approved, based on lower assessment standards, resulting in inadequate safety and efficacy drug profiles, such as the case of gemtuzumab ozogamicin, approved in 2000 for acute myeloid leukemia,⁵⁰ or nilotinib and dasatinib which both received negative reviews by the UK’s National Institute for Clinical Excellence. Blinding and randomisation is strongly recommended in all trial designs, but due to patient profiles, trials designs for orphan drugs have often been open-label studies with no control groups or surrogate endpoints.

Current legislation and regulation available for serious disorders includes Fast Track Designation, Accelerated Approval based on surrogate endpoints and Priority Review Designation.⁵¹ The FDA also encourages early and frequent communication to *“aid in the evaluation of the drug and in the solution of scientific problems...”* and enable *“free, full, and open communication about any scientific or medical question that may arise during the clinical investigation”*. Better communication at clinical stages and around Special Protocol Assessments with the review division increases the chances of successful clinical outcomes.⁵²

The FDA published a draft Guidance for Industry - Adaptive Design Clinical Trials for Drugs and Biologics in 2010, in order to advise sponsors on methods to best develop adaptive clinical trials.⁵³ Study design modifications that can be planned in the prospectively written protocol might include study eligibility criteria, randomisation procedure, treatment regimens of the different study groups, total sample size of the study, selection and/or order of secondary endpoints, etc. While the FDA outlines these various methods to overcome the challenges of designing trials in small populations, the agency warns against risks associated with adaptive trials. Bias can result from adaptive trial design and could affect the validity of the statistical conclusions reached for a study.

In December 2012, the FDA introduced its Guidance for Industry Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products.⁵⁴ The document proposes strategies to use in the context of randomised controlled trials to support safety and efficacy claims in early stage drug development, new drug applications (NDAs) and biologics license applications (BLAs).

These enrichment strategies aim to:

- ▶ **Decrease heterogeneity** by decreasing inter- and intra-patient variability to increase study power.
- ▶ **Improve disease prognosis** by choosing patients with a higher likelihood of having a disease-related endpoint event or a condition deterioration to increase the difference in effect between groups.
- ▶ **Improve disease prediction** by choosing patients more likely to respond to the treatment, leading to a larger effect size and therefore allowing for a smaller study population.⁵⁵

In most cases, besides some exceptions in adaptive designs, these strategies shape patient selection prior to randomisation. They generally do not include trial statistical validity or the meaningfulness of conclusions reached regarding the studied population.

The main concerns about using enrichment strategies are ‘generalisability’ and ‘applicability’ of study results. When considering using an enrichment design, it is recommended that investigators consider whether an enrichment strategy can be used in practice to identify patients to whom the drug should be given and whether the drug might also be used in a broader population than the studied one. Investigators must therefore integrate measurement accuracy and enrichment criteria sensitivity and specificity to identify the enrichment population and distinguish responders and non-responders.

Purpose of the Workshop and Questions to be Debated

The **purpose** of this workshop is to:

- ▶ Contribute to advancing technical solutions to make the best use of scarce clinical data collected in the context of trials
- ▶ Identify points of agreement between stakeholders regarding non-classical trial designs
- ▶ Identify further areas where research is needed
- ▶ Issue recommendations useful to clinicians and researchers when planning trials and acceptable to Regulatory Agencies

Suggested **topics** for discussion are:

- ▶ Rational approach to potentially adjusting the level of evidence needed for trials in rare diseases
- ▶ Patient-relevant outcomes that allow efficient trial design
- ▶ Potential extrapolation between adult and paediatric studies; this is an aspect that many are beginning to look into
- ▶ Risk optimization procedure vs. fixed sample size trials
- ▶ Control group in invasive treatments, e.g. cell and gene therapy, and overarching/basic principle of sharing natural history data in pre-competitive space (this may be topic for a specific Task Force and workshop on its own?)

These objectives are aligned with IRDiRC goals to maximise resources and coordinate research efforts in the rare diseases field in order to boost the R&D process to help deliver effective therapies as soon as possible. IRDiRC aims to stimulate and coordinate basic and clinical research, by promoting links between existing resources, fostering the molecular and clinical characterisation of rare diseases and encouraging translational, preclinical and clinical research.

Annex I: International Initiatives

Integrated DDesign and Analysis of small population group trial (IDeAI)

This EU-funded IDeAI (<http://www.ideal.rwth-aachen.de/>) project investigates new methods of design and analysis for clinical trials in small participant pools. The project aims to generate clinical trial methodologies better adapted to rare diseases. The objective of this research is to produce methods of general applicability irrespective of indication through a multidisciplinary, closely collaborating consortium of researchers from European universities, research institutes and industry.

The consortium works in 11 Working Packages (WPs), coordinated by Professor Ralf-Dieter Hilgers of the RWTH Aachen, focused on assessment of randomisation procedures, extrapolating dose-response information, investigation of adaptive designs, optimal designs in mixed models, pharmacogenetic designs, simulation of clinical trials, genetic factors influencing the response, decision analysis and biomarker surrogate endpoints, as well as project management and dissemination of results.

Relevant stakeholder concerns (e.g. patient needs, regulatory issues, reimbursement, clinical feasibility) will be monitored by a Clinical Scientific Advisory Board. Because of its integrative structure, this research programme extends previous approaches, which focus on a certain methodology only. The WPs constitute a logically coherent set of methodologies to tackle these multidisciplinary challenges. By combining, enhancing and developing different statistical methodologies and assessment methods, this research programme aims to impact the scientific discussion in promoting efficient statistical methodology for clinical trials in small patient groups, in view of existing regulatory guidance in the EU.

Innovation in Small Populations Research (InSPiRe)

Based at Warwick Medical School, Professor Nigel Stallard leads the €2.3m EU-funded InSPiRe project (<http://www2.warwick.ac.uk/fac/med/research/hscience/stats/currentprojects/inspire/>), who together with Project Manager Nadine Flowers, to bring together international experts in innovative clinical trial design methodology from across the globe. The

The focus will be on the development of novel methods to design and analyse clinical trials in rare diseases or small populations defined, for example, by a rare genetic marker. New approaches to the design of such studies, or improved methods of data analysis and subsequent decision-making, are needed.

According to Professor Stallard, *“the conduct of clinical trials in small populations is exceedingly challenging and this acts as a brake on the development of new treatments. This project will develop methods that will enable more reliable results to be obtained from clinical trials more quickly, ultimately leading to improved healthcare for these small population groups.”*

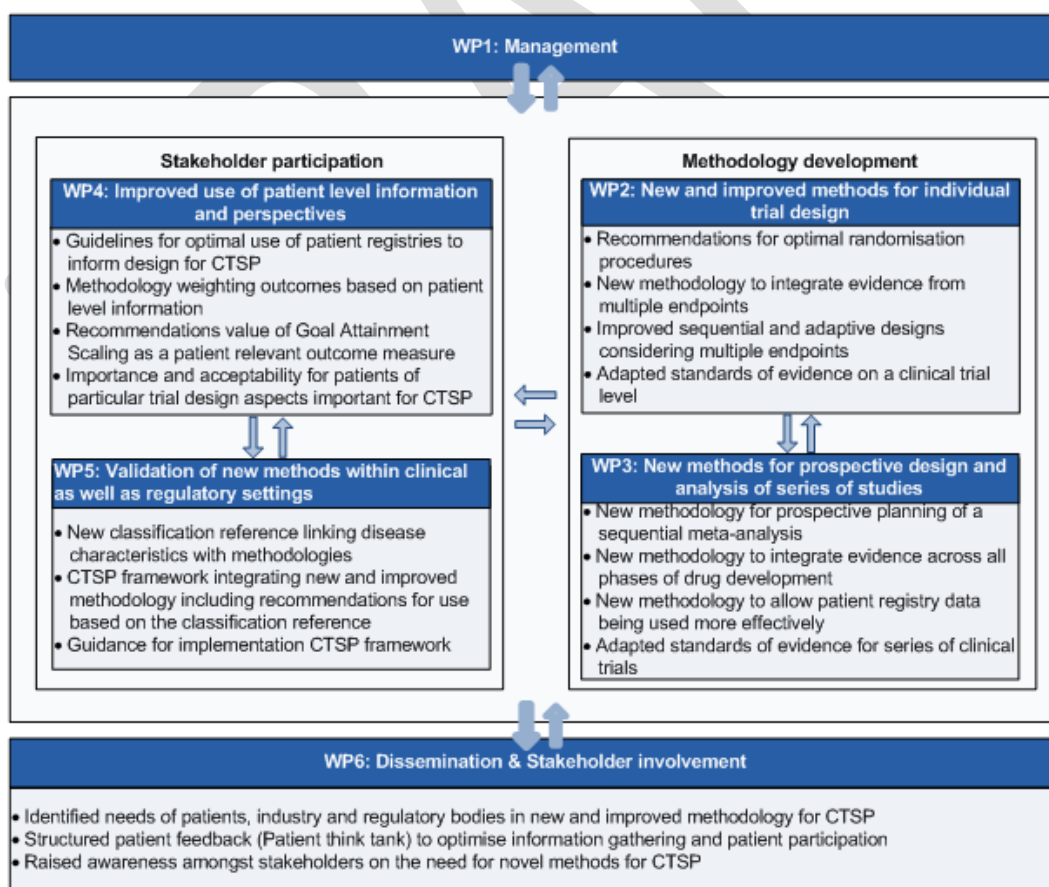
“It’s important that these new, improved methods enable rapid evaluation of treatments whilst maintaining scientific and statistical rigour. New methods will include the combination of trial data with

information from other studies, adaptive trial designs that allow most efficient use of the data and optimal decision-making processes that allow a conclusion to be made as quickly as possible.”

Advances in Small Trials dEsign for Regulatory Innovation and eXcellence (ASTERIX)

Kit Roes and Armin Koch are the project’s principal investigators. ASTERIX (<http://www.asterix-fp7.eu/>) is a collaboration between statisticians with regulatory and clinical development experience, epidemiology and patient representatives. This novel EU-funded research project focuses on the development of more efficient and effective research designs to study new drugs and treatments for rare diseases. The consortium brings together expertise in innovative statistical methodology, clinical science for rare diseases, drug development, patient involvement, regulatory science and research ethics expertise. This will ensure both synergy as well as critical mass in the execution of the ASTERIX project.

ASTERIX is specifically designed to optimise methodology for clinical trials in small populations to achieve more reliable and cost efficient clinical development of treatments for rare diseases. The group aims to develop design and analysis methods for single trials and series of trials in small populations. This includes patient level information and perspectives in design and decision making throughout the clinical trial process. The project will validate new methods and propose improvements for regulatory purposes. ASTERIX works through six interactive and interdependent Work Packages, ranging from development of methodology, stakeholder participation to dissemination of the results.



Patients are directly involved in the research process and their input is taken into account in design and analysis of studies. The combination of patient involvement in trial design and increasing their knowledge on these aspects of trial designs allow for a better motivation for patients to (or not to) participate in these trials, and hence improve patient recruitment, adherence to protocol and reduce drop outs, to perform these trials in the most cost-effective way. The ASTERIX project will explore what type of information should be included in registries to make them most useful for novel trial designs.

A Patient Think Tank will be set up in which patient representatives collaborate with the researchers across the project to optimise the methods of information gathering and ensure a process of constant feedback. This Patient Think Tank will be active during the entire project, and will also be consulted regarding knowledge translation and dissemination of the methodology developed in WP2 and 3. This think tank will function as an innovative and creative platform to develop new methodology.

A patient survey will be conducted as part of WP4 and translation of ASTERIX results in proper layman language will ensure adequate dissemination of scientific results to patients, patient organisations and other non-academic target groups.

CRESim project

Funded by the European Commission PrioMedChild ERA-NET Programme, the CRESim project aimed to develop a web-based platform to perform *in silico* experiments to assess different designs for drug evaluation in children with rare diseases.

The ERA-NET PrioMedChild (Priority Medicines for Children, <http://www.priomedchild.eu/>) is a network of eleven research funding organisations from different EU-member states working on the development of research around medicines for children. Under the umbrella of ERA-NET PrioMedChild, the national funding organisations of the Netherlands, Estonia, Finland, France, Great Britain, Italy, Latvia and Poland jointly provided funds in the order of €8 million to support the European call. The research projects were funded for three years in consortia with a minimum of three participants from at least three countries and a maximum number of 8 research groups.

The ERA-NET PrioMedChild received €1.7 million from the European Commission's DG Research to set up the network and collaboration, but no funds for research. The Joint Call was funded out of national research budgets. Six projects submitted in the ERA-NET PRIOMEDCHILD Joint Call of 2010 received a grant:

- ▶ New drugs for rare diseases: cost-effectiveness modelling in cryopyrin associated periodic syndromes (CAPS)
Coordinator: Prof. AM Martini, partnership between Italy, France and The Netherlands
- ▶ Rare disease: use of clinical trial simulation for the choice and optimization of study design
Coordinator: Dr PN Nony, partnership between France, Italy, The Netherlands and the UK
- ▶ European Study of Neonatal Exposure to Excipients (ESNEE)
Coordinator: Dr MA Turner, partnership between the UK, Estonia and France
- ▶ Validating non invasive imaging of the serotonergic- and dopaminergic system and adult neurogenesis with MRI; towards a better insight in the neurobiological mechanisms underlying psychiatric disorders in the paediatric population

Coordinator: Dr L Reneman, partnership between The Netherlands, France and Italy

- ▶ Assessment of treatment effectiveness in childhood acute lymphoblastic leukaemia by monitoring minimal residual disease with 8-color flow cytometry

Coordinator: Dr TS Szczepanski, partnership between Poland, The Netherlands and Czech Republic

- ▶ Paediatric Accelerator Mass Spectrometry Evaluation Research Study (PAMPERS)

Coordinator: Prof BK Park, partnership between the UK, Estonia, Poland and The Netherlands

Rare Disease Clinical Research Network (RDCRN) Clinical Research Studies

The Rare Diseases Clinical Research Network (RDCRN, <https://www.rarediseasesnetwork.org/studies/>), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), is made up of 22 distinctive consortia and a Data Management and Coordinating Center, working in concert to improve availability of rare disease information, treatment, clinical studies and general awareness for both patients and the medical community.

RDCRN's goal is to contribute to the research and treatment of rare diseases by identifying biomarkers for disease risk, disease severity and activity, and clinical outcome, while encouraging development of new approaches to diagnosis, prevention, and treatment.

The Data Management and Coordinating Center (DMCC) houses all data for the RDCRN centrally via in-house scalable and customisable electronic data capture systems. The DMCC, funded by ORDR, NCATS, provides a secure, customisable, scalable coordinated clinical data management system for the collection, storage and analysis of diverse data types from clinical researchers working on many different types of rare diseases.

In the first RDCRN cooperative agreement award cycle (2003-2009), the DMCC was funded by NCRR to provide statistical and project manager support for each of the 10 funded Rare Diseases Clinical Research Consortia (RDCRCs). In the second award cycle (2009-2014), each consortium was responsible for identifying an administrative core (project manager support) and statistical support. All five of the re-funded consortia from the first award cycle entered into a sub-contract with the DMCC for the DMCC to provide the administrative core and statistical support. There were 19 consortia funded initially in 2009.

ORDR has conducted a large meeting and workshop to bring together all the stakeholders in the rare disease community to discuss these issues and develop recommendations and future plans. ORDR is working to bring the community together and accept a common set of standards. ORDR launched the Global Rare Disease Patient Registry and Data Repository (GRDR) in February 2012, to collect and aggregate de-identified patient information in a standardised way to facilitate different types of studies, including clinical trials, translational research.

In addition, GRDR will work to link patient clinical information to biospecimens data using unique coded identifiers. ORDR has developed a searchable database/website for rare diseases biorepositories/biospecimens around the globe, the Rare Diseases Human Biospecimens/Biorepositories database (RD-HUB) with the ability to link the two sets of data (patient clinical information and biospecimens data)

using a coded global unique identifiers (GUID). Once the de-identified data is aggregated, investigators can access the data to develop hypothesis, clinical trials or any other studies.

Dr Yaffa Rubinstein is Director of Patient Resources for Clinical and Translational Research, in charge of the GRDR and the Biorepositories/Biospecimens database and website, RD-HUB.

The Cystic Fibrosis Foundation's Therapeutics Development Network (TDN)

The collaborative TDN (<http://www.cff.org/research/TDN/>) was set up in 1998 and includes 77 centres that draw on experts throughout the United States to evaluate the safety and effectiveness of new cystic fibrosis therapies and works to improve clinical study methods. Through efficient study design, clinical trial methodology and quality data, the TDN aims to accelerate the delivery of improved treatments for patients with cystic fibrosis. The network also tests the utility of new outcome measures and collects data on cystic fibrosis natural history through observational studies.

Identified factors of success in this type of network include shared leadership between principal investigators and research coordinators, and the importance of communication between clinical care and research teams when designing and conducting clinical studies.⁵⁶

The International Rare Cancers Initiative (IRCI)

The IRCI (<http://www.irci.info/>) was formed in 2011 as a partnership between the National Institute of Health Research Cancer Research Network (NCRN) in the UK, Cancer Research UK, the European Organisation for Research and Treatment of Cancer (EORTC) and the US National Cancer Institute Cancer Therapy Evaluation Program (CTEP). The French National Institute of Cancer (INCa) joined in 2013. IRCI aims to boost and facilitate the development of international clinical trials for rare cancer patients, representing 20% of cancer cases. It focuses on interventional – usually randomised – clinical trials to improve outcomes for patients.⁵⁷

IRCI aims to bring together researchers from many countries, in efforts to achieve consensus and overcome regulatory and financial barriers, and design innovative methodologies to conduct clinical research effectively. IRCI investigators have discussed essential parameters necessary to design clinical trials and main concerns to execute such trials in rare cancer populations.

A multi-disciplinary workshop to review methods used in IRCI portfolio trials was held in Amsterdam in September 2013. Alternative methods were also discussed. The aim was to share findings with other researchers for future trials based on a clear understanding of each study design.

Rare Cancers Europe (RCE)

RCE, <http://www.rarecancerseurope.org/>, a multi-stakeholder initiative, aims to put rare cancers on the European policy agenda and implement 39 political and stakeholder recommendations. In October 2014, RCE published a consensus paper stating that new approaches to summarise evidence are required for

rare cancer studies.⁵⁸ They include factoring in pre-clinical evidence, uncontrolled studies, observational evidence and analysis of retrospective (or anecdotal) cases, and large or small randomised clinical trials. RCE argue that a higher degree of uncertainty should be accepted for regulatory and clinically informed decision-making in rare cancers, to overcome the limitations of small population trials.

The RCE consensus paper addresses four major issues:

- ▶ Clinical decision-making in rare cancers should take into consideration patients' attitude towards risk, allow a degree of uncertainty higher than usual and make use of all available knowledge and innovative approaches to collect the best possible evidence.
- ▶ Study design in rare cancers should consider adaptive trials, research biomarkers and factor in all available evidence to best measure treatment effectiveness.
- ▶ Surrogate endpoints in rare cancers could replace clinical endpoints to compensate for study limitations.
- ▶ Reference Networks and more patient registries should be more widely developed in Europe, involving Centres of Expertise, to improve study recruitment and participation, patient access to information and quality of care.

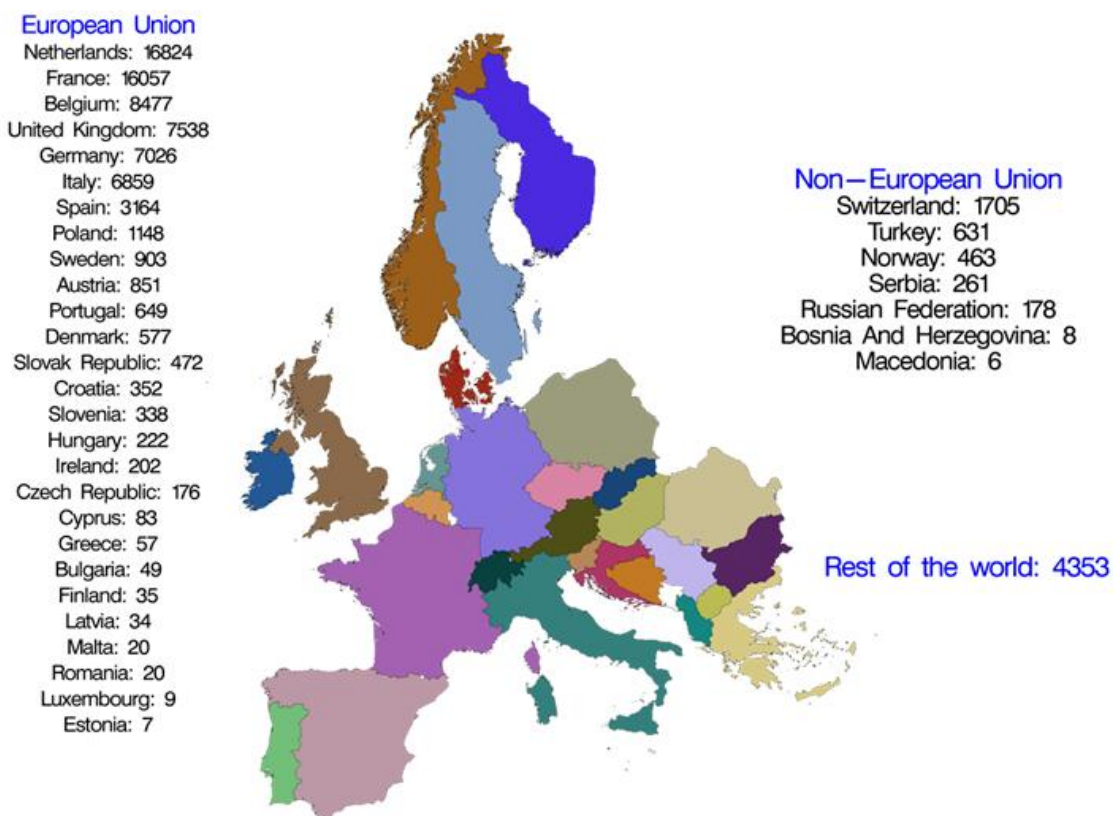
The RCE urges multidisciplinary, national, international and global collaboration to overcome regulatory obstacles and increase database sharing in order to assess the value of new treatment strategies. In October 2014, the International Brain Tumour Alliance (IBTA) joined the RCE initiative to help improve trial methodology in rare cancers and met with the EMA to discuss new initiatives.

European Organisation for Research and Treatment of Cancer (EORTC)

EORTC (<http://www.eortc.org/>) is funded and supported, through the EORTC Charitable Trust, by the US National Cancer Institute, Fonds Cancer (FOCA, Belgium), the Belgian Federal Science Policy Office (BELSPO), the Belgian National Lottery, the Vlaamse Liga tegen Kanker, the Dutch Koningin Wilhelmina Fonds Kankerbestrijding, the Schroeder Foundation, the Melvin Seiden Foundation and the Pfizer Foundation. EORTC research projects receive grants from the European Commission under the 6th and the 7th Framework Programme and the Innovative Medicines Initiative (IMI).

Since one in every five new cancer patients is diagnosed with a rare cancer, the EORTC aims to improve the standard of cancer treatment through testing effective therapeutic strategies based on drugs, surgery and/or radiotherapy already in use. EORTC contributes to developing new drugs and innovative approaches in partnership with the pharmaceutical industry, through conducting large, multicenter, prospective, randomised, Phase III clinical trials.

A number of EORTC trials are conducted in collaboration with other clinical cancer research groups in Europe and on other continents. These groups provide a complementary portfolio of cancer clinical trials to the EORTC network and contribute to the recruitment within EORTC intergroup trials. Between 2000 and 2014, EORTC clinical trials screened 79 754 patients.



Source: EORTC website (<http://www.eortc.org/clinical-trials/clinical-studies-patient-accrual/>)

Annex II: Industry Initiatives

When designing a clinical trial for an orphan drug, pharmaceutical companies must analyse how rare disease prevalence affects their patient recruitment strategies.⁵⁹ Several big pharmaceutical companies have developed methods to optimise clinical research in rare diseases, in efforts to boost their pipelines.

Genzyme

Genzyme design studies that build support, capacity and infrastructure around the patient long before the trial begins. This reverses the traditional model and takes the trial to the patient wherever possible. Instead of telling a patient to travel to a trial site, a nurse visits the person's home to do the infusion. When travel is unavoidable, the sponsor helps with logistics. The process starts upstream in the study designs, where the input and engagement of patients and advocacy groups is essential. Technology can facilitate novel approach. Telemetry (wireless data transmission and reception) innovations can enable remote data capture, severing the link between a patient's location and their ability to join a study. While the potential to collect widespread data is large, this technology is not widely accepted in clinical trials. The scale of Big Pharma companies necessitates reliable, industrialised development processes.

Sanofi

Sanofi works with key research institutions from around the world. The strategy has reduced the overall number of sites needed in a given study. Sanofi and the sites try to understand how and where patients access clinical trials, and ways to reduce the burden of their protocol designs. Through these partnerships, investigators and study nurses are able to provide Sanofi with real-life clinical perspectives as part of programme and protocol development. This site-focused method should cut down on turnover of investigators which is often a problem for efficiency and quality. This method should also reduce the proportion of locations that never recruit.

Boehringer Ingelheim

To develop drugs for respiratory disease treatment, Boehringer Ingelheim (BI) has addressed challenges prior to implementing clinical studies and throughout trials by seeking expert support through an idiopathic pulmonary fibrosis (IPF) advisory board. The company conducts discussions with clinicians involved in the (rare) disease management in various countries to gain better insight into the diagnostic and therapeutic situation.⁶⁰ Eligibility criteria and endpoints are therefore defined based on strong scientific evidence and advice. While dialogue between research, sponsors and regulators is essential, conducting trials based on scientific development and guidelines, and in accordance with clinical experts and regulatory requirements is, however, challenging. In order overcome such challenges and to achieve high quality and homogenous data, BI develops uniform global standard protocols, includes training courses for trial staff and a centralised control system, and an independent data monitoring committee to ensure patient rights and safety.

New technologies go through long maturation periods before being accepted as standards. Gradual, phased introductions allow Big Pharma to test innovative technologies without disrupting the running of standard clinical machinery. The introduction of post-authorisation safety studies, for instance, can provide grounds for new tools. One example, iPad technology for informed consent, replaces paper-based, 20-page documents with interactive electronic forms. By allowing patients to give consent at home, in a less stressful, time-pressured environment than in the clinic, and using video tutorials, pharmaceutical companies can make the process more informative and less daunting. In the future, sites will also benefit when new versions of consent forms are administered and tracked through electronic updates, eliminating the risk of using outdated documents.

TransCelerate BioPharma

Ten Big Pharma companies founded TransCelerate BioPharma in 2012, as a non-profit organisation, to collaborate on overcoming their shared problems, such as sourcing comparator drugs and communicating with trial sites.⁶¹ With a focus on trials, TransCelerate creates a space in which ideas from different firms can be shared to help pharmaceutical firms overcome obstacles associated with adopting new tools. Collective adoption of innovative methods will help pharmaceutical companies communicate with regulatory bodies in a united way. A further eight members joined TransCelerate, since its creation, in its first year.

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