

**INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM**

**Small Population Clinical Trials Task Force
Workshop Report and Recommendations**

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Small Population Clinical Trials: Challenges in the Field of Rare Diseases

Prepared by

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On behalf of the

Small Population Clinical Trials Task Force

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Table of Contents

The IRDiRC Task Force	6
Acronyms	7
Challenges of Conducting Clinical Trials in Rare Diseases	9
Need for efficient trial designs relevant to small populations	9
Points to Consider in Designing Trials	11
Pre-Clinical Pharmacodynamic studies	11
Micro-dose trials	11
The gold standard for trial design: randomised controlled trials	11
Challenges in identifying and recruiting patients	11
Defining the number of patients needed to demonstrate an effect	13
Recruiting methodologies for small clinical trials	14
Need for more sensitive outcome measures to quantify treatment effects	14
Methodology framework	14
Patient-centeredness in clinical trials	15
Need for natural history studies	15
Post-hoc analysis	16
Extrapolation of clinical trial data	16
Patient-Centred Outcome Measures (PCOM)	17
Methodologies for Clinical Trials	18
Regulatory Agency Guidelines	22
European Medicines Agency (EMA)	22
Food and Drug Administration (FDA)	23
Pharmaceuticals and Medical Devices Agency, Japan (PMDA)	24
Conclusions and Recommendations	26
First IRDiRC Task Force Workshop on Small Population Clinical Trials	31
Annex I: International Initiatives	33
Integrated DEsign and Analysis of small population group trial (IDEAI)	33
Innovation in Small Populations Research (InSPiRe)	33
Advances in Small Trials dEsign for Regulatory Innovation and eXcellence (ASTERIX)	34
Child-Rare-Euro-Simulation (CRESim) project	35
Rare Disease Clinical Research Network (RDCRN) Clinical Research Studies	36
The Cystic Fibrosis Foundation’s Therapeutics Development Network (TDN)	37

The International Rare Cancers Initiative (IRCI)	37
Rare Cancers Europe (RCE).....	37
European Organisation for Research and Treatment of Cancer (EORTC).....	38
TREAT-NMD Advisory Committee for Therapeutics.....	39
Annex II: Industry Initiatives	40
Genzyme	40
Sanofi	40
Boehringer Ingelheim	40
TransCelerate BioPharma.....	41
Bibliography	42

Notes

Disclaimer:

This document contains information concerning small population clinical trial design and analysis issues and a description of initiatives to discuss possible solutions to ensure methods used for clinical trials in small populations, in particular for rare diseases, are conducive to ultimately making effective therapies available to patients. The findings, conclusions and recommendations in this report are those of the individual contributors, who are responsible for the contents; the findings, conclusions and recommendations do not necessarily represent the views of the European Commission (EC), the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the International Rare Diseases Research Consortium (IRDiRC) or any employers of the Task Force members. Therefore, no statement in this report should be construed as an official position of the EC, EMA, FDA or a member of IRDiRC.

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

Among them, the Therapies 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 centred 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 Consortium Assembly established a Task Force on Small Population Clinical Trials (SPCT) in the field of rare diseases in May 2015. This Task Force was requested to review a preliminary 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 conducive to ultimately making effective therapies available to patients. This document contains the conclusions of the workshop discussions and the list of items for action agreed on by the workshop participants.

Acronyms

ASTERIX	Advances in Small Trials dEsign for Regulatory Innovation and eXcellence
BLA	Biologics License Application
CHMP	Committee for medicinal products for human use
CTEP	Cancer Therapy Evaluation Program
CRISim	Child-Rare-Euro-Simulation
DMCC	Data Management and Coordinating Centre
EC	European Commission
EORTC	European Organisation for Research and Treatment of Cancer
EMA	European Medicines Agency
ERA-NET	European Research Area Network
ESMO	European Society for Medical Oncology
EU	European Union
EUCERD	European Union Committee of Experts on Rare Diseases
FDA	Food and Drug Administration
GRDR	Global Rare Disease Patient Registry and Data
GUID	Global Unique Identifier
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
IRDiRC	International Rare Disease Research Consortium
MAPP	Medicine Adaptive Pathways to Patients
NCATS	National Center for Advancing Translational Sciences
NCRN	National Institute of Health Research Cancer Research Network
NDA	New Drug Application
OMIM	Online Mendelian Inheritance in Man
ORDR	Office of Rare Diseases Research
PCOM	Patient-Centred Outcome Measures
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PrioMedChild	Priority Medicines for Children
RCE	Rare Cancers Europe
R&D	Research and Development
RDCRN	Rare Disease Clinical Research Network
RDCRC	Rare Disease Clinical Research Consortia
RD-HUB	Rare Diseases Human Biospecimens/Biorepositories
SMART	Sequential Multiple Assessment Randomised Trial
SPCT	Small Population Clinical Trials
TACT	TREAT-NMD Advisory Committee for Therapeutics
TDN	Therapeutics Development Network

US
WP

United States
Work Package

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 of rare diseases (typically fewer than 1-2 in 10,000), heterogeneous patient populations, difficulty in recruiting such patients, lack of or limited knowledge of disease natural history and high attrition rates of experimental treatments during the research and development (R&D) processes. Additionally, approximately two thirds of rare diseases primarily affect children, adding to the complexity of trial design.

Incentives for industry have been implemented in the European Union (EU), the United States (US) and in Japan to boost orphan medicinal product development,¹ notably the 1983 US Orphan Drug Act,² the 2000 EU regulation on orphan medicinal products,³ and the 1985 Japan public policy on orphan drugs.⁴ These incentives have shown some success, with nearly 100 medicinal products that have a marketing authorization with orphan designation and reaching the market in Europe, and over 500 in the US, altogether intended to treat around 300 diseases at present.^{5,6} Some of the difference in numbers of products between the EU and US is due to slightly different criteria for “orphan” and much of it for the different length of time that legislation has been in place. Nevertheless, these results far from meet the needs of rare disease patients.

About half of the marketing authorisations are granted at a stage when evidence is not firmly established, requiring ongoing patient monitoring. The EMA pilot of adaptive licensing is based on stepwise learning under conditions of acknowledged uncertainty and including iterative phases of data gathering and regulatory evaluation.^{7,8} The FDA has proposed other tools to expedite availability of products intended for serious rare diseases with unmet needs, such as the Breakthrough Therapy Designation.⁹

Need for efficient trial designs relevant to small populations

Many rare diseases are “ultra-rare” (fewer than 1 in 100,000), life-threatening and fast progressing for which randomised, controlled trials may be very difficult to design.¹⁰ However, the EMA states in its guideline on clinical trials in rare diseases that no methods specific to small trials exist that are not also applicable to large studies.¹¹ Nonetheless, one study found that, for new products entering Phase III trials from 1 January 2000, an average 761 patients were enrolled in orphan drug trials versus 3,549 in non-orphan drug trials, with a median of 538 patients per trial versus 1,558 for non-orphan drug trials.¹² While exact numbers are unavailable, the average trial size for orphan drug trials might have been diminishing in recent years. Given the small population size and large heterogeneity in rare diseases, alternative approaches are needed.

As an example, response-adaptive methods (see “Methodologies for Clinical Trials” section) modify treatment allocation ratios depending on which therapy seems to be demonstrating 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.

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

Points to Consider in Designing Trials

Pre-Clinical Pharmacodynamic studies

Pre-clinical pharmacodynamic studies can be useful if adequate animal models exist to inform the design of clinical trials. Such studies could help establish dose and route of administration for trials in human.

Micro-dose trials

Human Phase 0 trials, or micro-dose trials, was introduced after concern expressed about the decreasing number of drugs making it through clinical testing and reach clinical use. The first regulatory guidelines concerning these trials were issued by the EMA in 2004, followed by the FDA in 2006.^{13,14} Phase 0 trials aim to facilitate early selection of promising drug candidates prior to Phase I trials and to evaluate the pharmacokinetics and drug distribution in vivo. In these trials, micro-doses of drugs are administered to human subjects, either healthy individuals or patients, following an extended single dose toxicity study in one animal species.¹⁵ A micro-dose is defined as 1/100th of the predicted therapeutic dose. The amount of pre-clinical animal data needed before the start of a micro-dose trial is significantly reduced compared to a Phase I trial, thus potentially accelerate the development of new drugs.

The gold standard for trial design: randomised controlled trials

Randomised controlled trials are regarded as the gold standard design to provide evidence for regulatory approval, but such studies are not always conducted in rare diseases. 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).¹⁶

In the case of clinical studies, investigators discovered that uncontrolled trials to assess response rates can lead to an overestimation of drug efficacy, thus distorting risk-benefit assessments as response rates are not always representative of survival and surrogate endpoints that have not been adequately validated can be poor criteria to assess drug efficacy.^{17,18}

While challenging, large randomised trials for rare diseases have been conducted successfully thanks to broad collaborations. For instance, the first international randomised trial for treatment of locally advanced and metastatic adrenocortical carcinoma randomised over 300 patients to two cytotoxic treatments and provided reliable findings.¹⁹ Similarly, many trials in cystic fibrosis have recruited several hundred patients.^{20,21}

Challenges in identifying and recruiting patients

Timely and adequate recruitment of eligible participants is a challenge for many rare disease studies. The need to study patients at early stages for disease-modifying agents, or those at very advanced stages for disease-controlling, or even disease-reversing, will not be feasible in one study.

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.²² Effective recruitment is often supported through partnership with patient organisations, when available, and through the use of patient registries and centres of expertise.

In 2014, 641 rare disease registries of varying quality have been identified in Europe, of which most are national, 40 Europe-wide and 74 global.²³ A registry is defined as an organised system that uses observational study methods to collect uniform data (clinical and otherwise) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves a predetermined scientific, clinical or policy purpose(s).²⁴ Disease-specific registries that meet quality standards have been demonstrated to contribute to the quality of clinical trials.²⁵ In addition, the structure and design of natural history studies, studies that collect health information to understand how the disease develops, are essential to capture clinical information about the course of disease.

New therapies often emerge more rapidly in areas where products are already being developed or are on the market. Such situations create competing interests to recruit from the same pool of patients, further reducing the number of available candidate patients for any given study.

Adaptable and novel approaches must respect the need for reliable evidence before offering innovative treatments to patients in need.²⁶ 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. Adaptive licensing is a pilot of the EMA in its efforts to improve timely access for patients to new medicines, while the FDA has a similar Breakthrough Therapy Designation program.^{27,9} Parallel to the EMA's adaptive licensing pilot, the Innovative Medicines Initiative (IMI) runs ADAPT-SMART, a concept of interest for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities that aims to foster access to beneficial treatments for patients with unmet needs in a sustainable fashion.²⁸

The design and specific methodological aspects of a study need to be carefully discussed with all relevant partners, in particular patients and/or their carers. The relationship between clinicians and patients must be based on mutual trust in order for patients to agree to participate and, once in the trial, to stay in and provide outcome data. Such data must provide answers relevant to patients, clinicians and policymakers, built on existing data and be collected in a way that encourages participants 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 study is adopted. Protocol Assistance, Scientific Advice and general meetings with regulatory bodies play a key part in guiding study design and drug development 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 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 demonstrate an effect

In all clinical trials, the sample size must be planned on a rational basis. Sample size calculations require collaboration of biostatisticians and investigators with medical expertise. While sample size is subject to external factors, including duration of recruitment, disease rarity or limited financial support, it must be planned for results assessment based on sound statistical grounds. The attainable power should be calculated during planning (the lower the power, the lower the chances to demonstrate effectiveness).²⁹

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 in different clinical trial phases (vs. 62 for non-rare disease trials) and fewer trials are actively pursuing enrolment (15.9% vs. 38.5%), although this may simply indicate that the overall status of rare disease trials is more likely to be completed or active but not yet recruiting.³⁰ As previously mentioned, for new products entering Phase III trials from 1 January 2000, an average 761 and median 538 patients were enrolled in orphan drug trials (vs. average 3,549 and median 1,558 in non-orphan drug trials).¹²

In both rare and common disease clinical trials, the sample size must take into account data loss due to incomplete follow-up or patient drop-out. Investigators may consider performing a pilot study to estimate appropriate population parameters. Sample size planning based on estimates from past information must take into account the imprecision in these prior results to avoid overestimating effects as they could lead to planning inappropriately 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 (again, to achieve more events), using companion genetic testing, and possibly testing multiple treatment arms in a factorial design. In addition, several adaptive-type designs may help resolve uncertainties in sample size, such as group sequential and sample size re-estimation designs, which are discussed below.

Selecting outcome measures using a continuous outcome variable or repeated measures outcomes can, in some cases, be used to reduce sample size.³¹ Repeated measure outcomes, or longitudinal models, collect data on the outcome measure(s) from the same individual at multiple time points and provide the opportunity to gain an understanding of how outcome measures change with time in both the individuals and the population. To make a distinction between symptomatic and disease-modifying treatments, it is typically not sufficient to analyse change at one point in time but would require repeated outcome measures. Such a distinction could be of particular interest when it comes to the value of the treatment.

Recruiting 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 subsequent study designs.³² Investigators should also conduct systematic reviews of the literature before designing clinical trials.

Typically, no single design is suited to all rare disease studies, so investigators need to choose which design is the most appropriate for a given disease-treatment-outcome situation. Overall, the number of patients required for a study, the length of the trial, how disease progresses, patient variability, and the management of these, are important factors in choosing the most suitable trial design. For many disease-treatment-outcome situations, more than one trial method could be considered and each scenario should include all factors into the design to improve statistical power and optimise trial duration for patients, sponsors and investigators.

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

Need for more sensitive outcome measures to quantify treatment effects

The large variation in severity, stage, irreversibility and age of onset can lead to very large variability at baseline for many measures of efficacy, making it hard to detect clinically significant treatment effects. 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.

Treatment effects might not always be measurable by hard endpoints, therefore requirements to do so would diminish the likelihood that a trial could provide evidence on the drug's benefits and risks.³³ In most rare diseases, hard endpoints, such as mortality, can often not be demonstrated. While surrogate endpoints are not clinical outcomes, they can help in clinical programmes by substituting for a clinical endpoint. Nevertheless, markers for surrogate endpoints must be justified and evaluated in the context of the disease process and mode of action of the treatment.³⁴ Combining several outcomes into a single outcome measure, thereby creating composite endpoints, could increase the number of events and hence the statistical power.

Methodology framework

A systematic approach should be used to optimise the identification of the best drug/endpoint/design combinations, out of several, for a particular rare disease patient population.³⁵ This framework might entail an *in silico* modelling and trial simulation approach, including a statistical analysis of available clinical databases and integrative modelling combining mathematical disease models with pharmacokinetic-pharmacodynamic models for the selected drug candidates.

In this framework, the six steps involved for rare diseases are:

- ▶ Use available knowledge from bibliography, epidemiology and randomised clinical trial databases
- ▶ Drug-disease modelling for the N conditions identified above
- ▶ Drug-disease modelling for the N conditions above in patients whose characteristics may interact with drug efficacy
- ▶ Experimental randomised clinical trial design modelling (including alternative approaches) for N conditions above
- ▶ Simulate these options
- ▶ Identify the most relevant drugs to be evaluated in phase III randomised clinical trials and the design to be used for each of them

Based on the information of the first step, investigators can identify predictive and prognostic biomarkers for drugs and 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 trialists may not always inform participants of results after the study and if they do not, patients may lose interest and decline participation in further trials. Patient-centeredness in the design and progression of clinical trials may result in greater patient retention.³⁶ 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. Patient empowerment is key to success of clinical trials; care however must be taken to ensure patients understand and respect the confidentiality constraints regarding results of the trial they are engaged in.

In order to design trials from a patient's viewpoint, clinical protocols need to be relevant to patients by proposing broad recruitment and inclusion, meaningful patient-centred outcomes and comparison against the best available treatment, while maintaining ethical standards. Patients must be able to understand the results.

Pragmatic, patient-centred trial designs are more likely to retain already limited numbers of patients. Nevertheless, pragmatic trials are designed to reflect a 'real world' situation which is difficult to quantify and qualify. 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, including the design of clinical trials. Additionally, consideration of clinical trial costs should include costs for travel and lodging for patients recruited (and parents/family members/carers, if relevant), whilst still in accordance to criteria of economy so as not to be seen as incentives in participation. Follow-up should take place in centres of expertise close to home in order to limit drop-out rates.

Need for natural history studies

The natural history of most rare diseases is scarcely or not at all documented, yet is fundamental to inform trial design, and knowledge about disease and disease progression is one of our biggest

challenges. While the need and necessity of natural history studies is clear, these are lengthy and costly. Very few epidemiological studies are published on rare diseases due to the difficulty in identifying and documenting cases which are geographically diverse, inadequately diagnosed, and rarely or never systematically followed up by academic centres. Natural history studies should be promoted and supported according to shared protocol templates, to be adopted across different centres involved, and results should be reported according to common data standards.

Most attempts to collect good quality data are supported by short-term grants, with little or no long term perspective. The cost of conducting high quality natural history studies represents a significant barrier to their development. Both the European Union Committee of Experts on Rare Diseases (EUCERD) and IRDiRC have issued recommendations to overcome obstacles in natural history studies.^{37,38} Further guidance and training needs to be delivered on developing effective and useful natural history studies.

Additionally, natural history studies need to capture clinical information 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.^{39,40}

Post-hoc analysis

In the design and analysis of trials, post-hoc analysis consists of looking at trial data, after the trial has concluded, for patterns that were not specified *a priori*. Prospective clinical trials are constructed with high levels of internal validity. In these trials, endpoints chosen *a priori* may have failed to identify treatment effects. In these cases, post-hoc analysis of data could be of relevance to inform practitioners about possible clinical benefits or safety signals that may not be captured by primary endpoints. Post-hoc analysis has, however, many limitations. One of its major limitations: by examining the data several times, i.e. performing several statistical tests, the chance of making a false discovery increases.⁴¹ However, multiple testing can be compensated for by the application of several corrective measures although with unspecified post-hoc analyses, this is particularly challenging.

When correctly performed, post-hoc analyses should be directed at discerning patterns or trends by comparing subgroups of the sampled population, or alternative endpoints that were not resolved by the *a priori* specified endpoints. These comparisons, particularly of subgroups, can be of use if the risk of a poor outcome with or without treatment is likely to differ substantially between subgroups of patients, if heterogeneity of treatment effect is probable in relation to pathophysiology, if practical questions about when to treat apply, or if there are substantial doubts about a benefit in specific groups.^{42,43}

Extrapolation of clinical trial data

Extrapolation may be generally defined as “*extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of*

studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product."^{44,45} Extrapolation can be applied in different areas, such as from adult to paediatric population, between different (rare disease) population subsets, from animals to humans, from healthy volunteers to patients, and others.

Extrapolation could minimise the exposure of certain populations to experimental treatments, and may increase the speed and efficiency of drug development. Alternatively, in situations where the feasibility of studies is restricted, extrapolation principles may be applied to help interpretation of the limited evidence in the target population based on data from other sources. The FDA and EMA have both released draft guidance documents for drug development based on extrapolation.^{44,46} In addition, Bayesian clinical trial designs that make use of prior knowledge on efficacy for inference have been proposed.⁴⁷

Patient-Centred Outcome Measures (PCOMs)

Clinical trial outcome measures are vital for decision and policy makers to introduce appropriate recommendations. While regulatory agencies, standards organisations and international societies have issued a number of guidance documents on outcomes – i.e. what should be measured and reported in all trials in a specific area – many trials, particularly on rare diseases, do not yet include standardised assessment outcomes. PCOMs aim to place patients, their families and carers at the heart of decisions concerning the most valuable criteria in assessment of treatments, rather than leaving assessments solely to clinicians or regulators. In order to advance the development of PCOMs for rare diseases, the IRDiRC Scientific Committees have set up a PCOM Task Force to discuss actions to improve clinical research in the field of rare diseases and developed a number of recommendations and guidelines for rare diseases that are available on the IRDiRC website.⁴⁸

Methodologies for Clinical Trials

The following methods outlined are among some trial design options (conventional and alternative) that can be applied to rare disease studies. The methods are stated in alphabetical order.

- **Adaptive randomisation design**

Adaptive randomisation is a broad category that includes covariate-adaptive randomisation (e.g. minimisation), response-adaptive randomisation, and a combination of these two. Response-adaptive designs favour the treatment group with the better chance of success by increasing the probability that patients will be randomised to that group.

- **Bayesian design**

Bayesian designs cover a very broad range of possibilities. In all Bayesian *analyses*, probability statements (e.g. “the probability that the experimental treatment is effective”) are made on the basis of accumulated data.⁴⁹ In Bayesian *designs*, accumulated knowledge and expert opinion may be used as quantitative prior belief on to which subsequent trial data can be added, resulting in updated posterior belief of evidence.⁴⁹ An example of a Bayesian design is the integration of data from previous trials with data collected from an ongoing trial to create a larger evidence base.

Such designs need to be used carefully to avoid the potential that the prior evidence might be based on biased data, favouring positive outcomes. It is therefore essential that appropriate prior information be carefully selected and correctly incorporated into the analysis; all sources of prior information should be identified.^{50,51,52} Furthermore, there is a risk inherent in integrating all evidence into a single analysis rather than a series of individual studies that could be mutually supportive. Regardless of whether traditionally accepted levels of statistical significance are met, regulatory authorities generally favour evidence generated through stand-alone and mutually supportive studies.

- **Crossover design**

Participants receive two or more treatments 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 of each treatment period. As 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.⁵³ Moreover, crossover designs are limited by the wash-out, and patients may not return to the same baseline state. Prior data confirming the assumptions of adequate wash-out and lack of carry-over effects (both pharmacokinetic and pharmacodynamic effects) is essential before a crossover trial can be carried out. It is not valid to test for carryover/wash-out within the trial itself.

- **Enhanced trial design**

In enhanced trial designs, patients are used more than once and the trial itself determines which group to re-use.⁵⁴ For example, in a randomised trial with an active intervention and a placebo, after the initial treatment, apparent “responders” – but to the placebo – are re-randomised to treatment or placebo, allowing for the intervention to be given to a new group while more accurately measuring the difference between the placebo group and the active group, and ultimately giving the study more power.

- **Factorial design**

In order to test two treatments simultaneously, participants are randomised to treatment A or corresponding control, and again, randomised within each group to treatment B or its corresponding control. This multiple treatment option can provide answers to two separate questions within the same study, thus requiring fewer patients to answer both questions than running two separate trials, without reducing the number of patients answering each of the individual questions. This design also allows the possibility of exploring possible interactions between treatments A and B.

- **Group sequential design**

In this design, interim analyses are performed at pre-determined points in time (or in “information-time”). Once sufficient evidence of a treatment effect is available, the trial is stopped. In this type of design, the expected trial size will usually be less than in a fixed size design. A risk when applying group-sequential designs is that, for a fixed maximum sample size, there is a trade-off between allowing early termination of a trial for efficacy and the power of the final study analysis.⁵⁵ Furthermore, if a trial is stopped early at an interim analysis, there will be less data in important subgroups and less safety data than if the trial had continued to its maximum size.

- **High-risk allocation design**

This design can be used when investigators wish to compare high dose and standard treatments on high-risk patients. Both high- and low-risk patients are recruited, with all high-risk patients receiving high dose treatment but low-risk patients randomly receiving either high dose or standard treatment. The data from low-risk patients are used to estimate efficacy response and establish a risk prognostic model. This model is then used to predict expected benefits of high dose and standard treatments in high-risk patients. This design relies on the ability to extrapolate treatment effects from low-risk to high-risk patient groups.⁵⁶

- **Platform design**

A platform trial is a flexible trial design with several treatments in several treatment arms, each being tested for similar (although not necessarily identical) indications, sharing a common control. The different treatments and trial arms might or might not start at the same time, and treatment arms might be added or dropped as the trial progresses. An example of a platform trial using this design is I-SPY 2.^{57,58}

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

In this single case study, a patient receives one of two, or several, treatments in random order. This type of study allows investigators to determine – under controlled experimental conditions – the best treatment for a particular patient. N-of-1 trials have problems of generalisability, as the design provides no information about the magnitude of the treatment effect in other patients, or in a population.

- **Parallel group design**

In a parallel group design, patients are randomised to one of two or more different interventions. For example, a two-arm parallel design involves two treatments, or one treatment and a control. During the trial, participants in one group receive drug A "in parallel" to participants in the other group, who receive drug B (or control).

- **Patient preference trial**

Patient preference trial is an approach to deal with patient preferences in a partially randomised manner.⁵⁹ If comparing two treatments, patients with no strong preference for either treatment are randomised, while patients with a strong preference for one or other treatment are given their treatment of choice, thus resulting in four trial arms. This design allows for comparisons between patients with and without treatment preference and an exploration of patients' characteristics associated with preference. An important disadvantage of this design is that the outcome may be affected by uncontrolled confounders in the non-randomised groups, which may bias the results.

- **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. However, such designs are not ideal for the study of all rare diseases due to often long diagnostic lag time. In many rare diseases, 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 often challenging.

- **Randomised controlled trials**

Randomised controlled trials represent the "ideal" and, perhaps, simplest method to evaluate the effectiveness and safety of medicinal products, as they help protect against bias.⁶⁰ To minimise bias, possible methods such as centralised randomisation, double-blind follow-up and outcome evaluation should be applied to trial designs.⁶¹

- **Randomised withdrawal, and early escape designs**

In randomised withdrawal studies, patients receiving a test treatment for a specified time are randomly assigned to continued treatment with the test treatment or to receive placebo. Any difference that emerges between the group receiving continued treatment and the group randomised to placebo would demonstrate the effect of the active treatment. This design can be used to study long-term persistence of effects when long-term placebo treatment would not be acceptable.

Early escape designs give patients the option to opt out or “escape” their assigned treatment. These designs might improve outcome efficiency and statistical power, while limiting patient exposure to ineffective treatment.⁶²

- **Sample size re-estimation**

A sample size re-estimation design is a flexible, adaptive design with the primary purpose of allowing sample size of a study to be increased in the mid-course of the study to ensure adequate power.⁶³ This design might be acceptable if the statistical and operational concerns are adequately addressed.

- **Sequential Multiple Assessment Randomised Trial (SMART) design**

SMART allows investigators to evaluate the timing sequencing and adaptive selection of treatments by use of randomised data.⁶⁴ In a SMART, participants can move through multiple stages of treatment; each stage corresponds to a critical decision, and participants are randomised at each stage/critical decision point. Randomised treatment options at each critical decision include appropriate single- or multi-component treatment alternatives.

- **small n Sequential Multiple Assignment Randomised Trial (snSMART)**

This is a trial, based on the SMART design, to test several treatments for a disease for which no standard therapy exists.⁶⁵ It compares the efficacy of medications in which non-responders of each treatment are re-randomised to another treatment. Re-randomizing patients in the trial increases the power in the inference between the observed best treatment and the best of the other treatments.

Regulatory Agency Guidelines

European Medicines Agency (EMA)

On 16 April 2014, the 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 was applied in May 2016.⁶⁶ The Committee for medicinal products for human use's (CHMP) 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.¹¹ 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 less commonly used approaches may be used if they improve the interpretability of study results.

For instance, in 2007, the CHMP finalised a draft reflection paper “Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design”.⁶⁷ 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.^{68,69} 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.⁷⁰ 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 trials are 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. Furthermore, legislation and regulation is available to assist in the approval of therapies for life-threatening disorders such as PRiority MEdicines (PRIME), Centralised Procedure, Conditional Approval, Approval Under Exceptional Circumstances, and Accelerated Assessment.^{71,72,73,74,75}

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 are likely to be 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.¹¹

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. The EMA has launched a pilot for the collection of high-quality data on medicines through patient registries. In the pilot phase, coordinated in collaboration with the Cross-Committee Task Force on Registries, the EMA will evaluate whether the above strategy will facilitate the requirements of high quality data through real world examples.⁷⁶ The pilot phase will last two years and participation in the pilot phase will be determined on a case-by-case basis, driven by the precise objectives of the pilot phase in terms of methodological tools and approach to be tested.

Food and Drug Administration (FDA)

The Center for Drug Evaluation and Research (CDER) at the FDA highlights the challenges of clinical development and regulation for small populations.⁷⁷ 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, in adequate and well-controlled clinical studies. FDA has discretion in interpreting what constitutes a valid comparison with a control. Blinding and randomisation is strongly recommended in all trial designs, but due to patient profiles, trials designs for orphan drugs have sometimes been open-label studies with no control groups.

Current legislation and regulation available for serious disorders includes Fast Track Designation, Accelerated Approval based on surrogate endpoints, Priority Review Designation and Breakthrough Therapy Designation.⁷⁸ 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.⁷⁹

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.⁸⁰ Study design modifications that can be planned in a prospectively written protocol may 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.⁸¹ 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 disease-related endpoint event or 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.⁸²

In most cases, besides some exceptions in adaptive designs, these strategies shape patient selection prior to randomisation. They generally do not reduce 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, investigators are recommended to 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.

Pharmaceuticals and Medical Devices Agency, Japan (PMDA)

On 17 April 2008, the PMDA issued “Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug”.⁸³ The document summarises the points that need to be considered by the PMDA review teams during the evaluation process of new drugs. The points covered are limited to basic points generally considered and there may be many other points that need to be judged on a case-by-case basis. For drugs in the field of orphan diseases or serious diseases for which existing therapies have not yet been established, final decisions should not be based exclusively on the points covered in but to also take into consideration other points such as clinical significance of the drug. Even for such drugs, however, the scientific evaluation using appropriate data should be based on a full understanding of the purpose and principle of the document.

The following five points that should be considered by PMDA reviewers when conducting evaluation of a new drug under the regulation of the Pharmaceutical and Medical Device Act:

- ▶ Has the reliability of the conducted studies and submitted documents been ensured?
- ▶ Is the efficacy in the study population considered to be more effective than placebo according to the results of properly designed clinical studies?
- ▶ Do obtained results have clinical significance?
- ▶ Are there any unacceptable risks as compared to the benefits?
- ▶ Can the drug be supplied continuously with stable efficacy and safety from a quality assurance standpoint?

The comparison of the efficacy of the drug to placebo is one of the major points to be considered. However, there is possibility that sufficient efficacy could be confirmed even by an unblinded study

without a concurrent control under particular conditions, i.e. there is a rational reason a controlled study cannot to be done, and a clear pharmacological mechanism exists. In particular, for the development of drugs for orphan diseases with small population clinical trials, the PMDA review teams provide consultations to advise on alternatives to traditional approach at the face-to-face meeting during the development stage of new drugs.

The PMDA offers consultations to give guidance and advice on clinical trials of drugs, medical devices, and cellular and tissue-based products, as well as data for regulatory submissions. In clinical trial consultations for new drugs, the PMDA checks whether a proposed clinical trial complies with the requirements for regulatory submission, taking into consideration the ethical and scientific aspects and reliability of the clinical trial as well as the safety of trial subjects, and also gives advice to facilitate the improvement of the clinical trial. In addition to general consultations, the PMDA launched the Pharmaceutical Affairs Consultation on R&D Strategy in July 2011, mainly for academia, research institutions, and venture companies that possess promising “seed-stage” research or technologies. The targets of these consultations, as a general rule, are products that correspond to priority areas, including regenerative medicine (cell- and tissue-based products), difficult-to-treat diseases and rare diseases, and paediatrics. The consultations of such areas, in most cases, involve the issues of small population. Guidance and advice are provided in these consultations regarding the tests needed in the early development stage and the necessary clinical trials toward commercialisation.

Since 2014, the Japanese Ministry of Health, Labour and Welfare (MHLW) has been providing support for the PMDA for establishing its system to collect and analyse clinical study data for efficient development of orphan drugs, etc. as a part of the Initiative to Facilitate Development of Orphan Drugs.⁸⁴ The PMDA established internally the Advanced Review with Electronic Data Promotion Group on 1 April 2014 to discuss specific operations of reviews and consultations further using the application data. In 2015, MHLW announced that study data on which new drug application is made should be submitted electronically after 1 October 2016 with a transitional period until 31 March 2020.⁸⁵

Standardised methods of collecting data from various products’ studies will allow cross-product evaluations. Promotion of research using the collected electronic study data is expected to contribute to increased efficiency of the developments of orphan drugs and paediatric drugs, otherwise they may have higher chances to face obstacles due to the difficulty in collecting data for the small number of patients and to their yet established evaluation methods. It is also expected that guidance documents on methodological issues related to the small population clinical trials would be developed based on the research of electronic study data stored in the PMDA.

Conclusions and Recommendations

Introduction

The IRDiRC Task Force on Small Population Clinical Trials organised a workshop, which was held on 3 March 2016 at the EMA premises, to discuss technical solutions to make the best use of scarce clinical data in the context of small studies, typically in rare diseases, and to identify points of agreement between the different stakeholders regarding various design options. The workshop was also aimed at identifying further areas where research is needed.

Six topics were explored during breakout sessions:

- ▶ Different study methods/designs vs. types of conditions
- ▶ Adequate safety data
- ▶ Multi-arm designs and platform trial designs
- ▶ Decision analytic approaches and rational approaches to adjusting levels of evidence
- ▶ Extrapolation problems and opportunities
- ▶ Patients' engagement in study design

The following recommendations resulted from the workshop; these are intended to be of guidance to clinicians, researchers and regulators.

Different study methods/designs and different types of conditions

The gold standard for clinical trials – randomised clinical trials, with strong, clinically-relevant endpoints, and long follow up – is well known and should be used whenever feasible. However, adequately powered studies in rare diseases are not always possible. To assist choosing a suitable trial design, the following points were considered:

- ▶ For stable diseases with relatively short treatment duration, and where there are sufficient data to determine an appropriate washout period, consider cross-over designs (which can sometimes achieve up to 60-80% reduction of sample size)
- ▶ Consider group-sequential designs (can achieve about 30% reduction of sample size, but may also increase study size in some circumstances)
- ▶ Use inferentially seamless adaptive designs
- ▶ When relevant, make full use of longitudinal data (can achieve about 30% reduction of sample size vs. change score analysis; not as useful for very stable diseases)
- ▶ Do not dichotomise continuous endpoints in the primary analysis (although possibly do so for sensitivity analyses)
- ▶ In survival trials, let patients stay in it for as long as possible to minimise censoring and in all studies collecting longitudinal data, let patients stay in trials for as long as possible to maximise information
- ▶ Use ANCOVA instead of simple “change from baseline” analyses
- ▶ Historic data may be helpful, but need to be properly weighted
- ▶ Consider using multiple endpoints (where it might be sufficient to “win” on any one)

- ▶ Consider using composites endpoints
- ▶ Consider using different formulations, doses, endpoints in different subpopulations and consider the possibility to combine analyses of these different groups
- ▶ Consider trial designs that allow subjects to be used more than once (e.g., n-of-1 trials; randomised withdrawals)
- ▶ Always consider different design options; discuss applicability of different designs with respect to efficiency and risk of bias, discuss risks and opportunities for alternative trial designs. Within this context, in particular in small population group trials, a discussion of appropriateness of the randomisation procedure as a design option is important.

It is recommended that trialists should consider all different design options, and quantify what could be gained from each particular trial design and carry out a solid risk assessment before choosing a particular trial design. In order to gain more trial data, it is recommended that patients should remain in the trial as long as possible, that missing data should be minimised to the extent possible, and that long-term patient data should also be collected after the trial.

Adequate safety data

Safety is an essential component of the benefit-risk profile. However, it is not possible to state with absolute certainty a definition of what constitute adequate safety data; it depends on the nature of the disease. In addition to the size of the disease population and the nature of the disease, the adequacy of the safety database will depend on multiple factors, including the nature and severity of adverse events associated with the product during clinical development, the magnitude of the benefit associated with the product in the studies that provide the primary evidence of effectiveness, and the patients' tolerance for risk.

In order to obtain adequate safety data and a full safety picture of a drug, it is advisable to capture different sources of data that have a safety element in them and not only be restricted to clinical trials data, such as:

- ▶ Registry data
- ▶ Electronic health records (especially for drugs that are already used)
- ▶ Non-clinical data (e.g. animal models)
- ▶ Post-marketing/ post-approval safety data (more health-care professional reporting of adverse events)
- ▶ Extrapolation of data from the clinical experience with similar compounds (questions should be considered about what would be the regulatory acceptability of this data; might be of particular interest for drug repurposing, in particular populations)
- ▶ Risk management plan data
- ▶ Social media data (although ownership issues needs to be addressed prior to usage)
- ▶ Use of product outside the clinical trial in e.g. compassionate use setting

In small studies, clinical trial data alone typically do not give sufficient safety data. Therefore, it is important that several data sources are combined to give a fuller picture of the safety profile. Some of the above-mentioned sources are currently underused, and it is recommended that researchers are better informed about the value of these data and how they might be used so that the contributions of

these different sources of data will be improved. In order to make better use of the different sources, it is recommended that a prospective quality control system be put in place.

Regulatory approval should be the starting point to collect additional safety data; uncertainty will get smaller with more data collected. There is however a balance needed between more data, potentially of lesser quality, and better controlled randomised control data; attention should be given to improving the quality of the post-approval data.

Multi-arm designs and platform designs

A platform trial is a flexible trial solution that can be defined as a design with several treatments in several treatment arms, each being tested for similar (although not necessarily identical) indications, sharing a common control. The different treatments and trial arms may or may not start at the same time, and treatment arms may be added or dropped as the trial progresses. This trial design may be used in a proof-of-concept Phase II or definitive Phase III trial. An example of platform trials is the series of I-SPY trials.

Advantages of this trial design are:

- ▶ Efficiency of sharing a control group
- ▶ Diminished chance for patients of receiving a placebo, thereby encouraging participation
- ▶ Comparison of active substances
- ▶ Pooling data from active treatments, when feasible
- ▶ Sharing of resources, diminished trial costs

Disadvantages of this trial design are:

- ▶ The need for companies to cooperate and agree to a common protocol
- ▶ Need for additional time to design such a complex study
- ▶ Challenges of operating the clinical trial
- ▶ Challenges of trial leadership
- ▶ Differences of interest between competitive companies, charities, investigators
- ▶ Legislative challenges
- ▶ Potential of heterogeneity and thus loss in efficiency due heterogeneous settings

Multi-arm trials should be considered as an opportunity by trial funders and patient organisations for studies in rare diseases. Expertise centres, such as the European Reference Network for rare diseases, should try to channel the patient flow towards this trial design if possible. Funders should be encouraged to fund platform trials via international networks to trial multiple treatments more efficiently.

Decision analytic approaches and rational approaches to adjusting levels of evidence

If sufficient knowledge is available about a treatment, how are the best decisions made and which standards of evidence are required for decision making? In the topic of decision analytic approaches and rational approaches to adjusting the level of evidence, three main questions were discussed.

The first question of interest is: “If we know enough about a treatment, how do we make a decision if it is valuable?” Several aspects should be taken into account, such as:

- ▶ Benefit-risk assessment
- ▶ The patient horizon
- ▶ Ethical judgment
- ▶ The stakeholder perspectives
- ▶ The rate of innovation

The second question is “What standards of evidence do we require?” For this question, it is important to realise that the same standard of evidence may not be valid in every disease especially when the number of patients who may benefit from the treatment is small and, whilst some think a standard of statistical significance less stringent than 5% should be allowed, others believe that more stringent levels should be applied. This may indicate the need to make decisions on weaker levels of evidence, as compared to more common diseases. Although not relevant to regulatory approval, required standards of evidence of reimbursement bodies should also be taken into account.

The final question concerned “What technical issues are there regarding decision analytic approaches?” A particular issue is being that of methods for elicitation of informative Bayesian prior distributions.

No solid conclusions or recommendations have been reached on this topic. However, various Work Packages from IDeAI, ASTERIX and InSPiRe are currently working on solutions to these problems. They have not yet fully come to a conclusion regarding the best strategy to address the gap between design theory and practice. Follow-up discussions on this topic are needed once informed by the results reporting, out in 2017.

Extrapolation problems and opportunities

Extrapolation is defined, according to the EMA as “*extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.*” The EMA has released a draft guidance document on extrapolation on 1 April 2016.

As indicated in the EMA draft Reflection Paper, the data to support extrapolation of efficacy can come from many sources, including Pharmacokinetic/Pharmacodynamic (PK / PD) models but also registries, off-label data or electronic health records. The quantity and quality of data to be used for extrapolation, as well as the time for extrapolation (early phase trials, late phase trials) is still decided on a case-by-case basis.

Limited experience is currently available for the extrapolation from one rare disease study to another or from one population to another, for example on how to incorporate data in the context of paediatric investigation plans (PIPs).

It is recommended that examples, preferably with clear illustration of their advantages, pitfalls and proper use, should be outlined or developed, including their methods of validation. There is also a gap in education which should be addressed; a common language between clinicians, biostatisticians and modelling and simulation experts is needed.

Patients' engagement in study design

The patients' voice is essential in the set-up of clinical trials but at present there is no clear process, nor a conclusion, on optimal contribution for its incorporation. Consultation with patients experienced in clinical trials is advised to take place, the earlier the better. The pharmaceutical industry is still relatively new on how to incorporate patients' opinions into the trial process, therefore guidance from the regulators and patient organisations should be provided, on the topic of when patient engagement is essential, how patient engagement should be sought, and from which particular group of patients. Patient involvement could concern trial design, safety aspects, benefit-risk assessment or endpoints.

Whenever patient preference for more than one available treatment is important in regulatory decision-making, carefully designed and powered patient preference studies may be considered, as part of the clinical development.

It is recommended that commercial sponsors, regulators and patient organisations should set up a best practice guidance document for the interactions between companies and patient representatives. This best practice document should provide knowledge about patient representation in trial design and should focus on the potential benefit of consultation of patient representatives and how to manage potential conflicts of interest. Patient engagement is the topic of one of the next IRDiRC Task Forces.

Concluding remarks

Besides the traditional randomised controlled trial, a systematic look at alternative design options when setting up a clinical trial for a rare disease is advised. Not every rare disease trial is as challenging as others, but if a randomised control design is not feasible, other trial options should be considered. Better use of scientific advice from regulators regarding small population clinical trials should be promoted. Regulators are often very accepting and supportive for new clinical trial designs, provided they are well thought through and justified, and welcome discussions and questions on this topic. Parallel advice for multiregional development programs should be considered.

First IRDiRC Task Force Workshop on Small Population Clinical Trials

The first workshop on SPCT initiatives in the field of rare diseases was held on March 3, 2016 in London, UK at the EMA premises.

This workshop was attended by the following members of the Steering Committee:

- ▶ Simon Day (Clinical Trials Consulting & Training Limited, UK)
- ▶ Ralf-Dieter Hilgers (IDeAl; 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)
- ▶ Kit Roes (ASTERIX; UMC Utrecht, the Netherlands)
- ▶ Nigel Stallard (InSPIRe; University of Warwick, UK)

The following IRDiRC Scientific Committee members attended the workshop:

- ▶ Virginie Hivert (EURORDIS, France)
- ▶ Yann Le Cam (EURORDIS, France)

In addition to the Steering Committee, the following members also participated to the workshop:

- ▶ 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 (Mapi Group, USA)
- ▶ Olivier Collignon (EMA, UK)
- ▶ Tim Friede (University of Gottingen, Germany)
- ▶ Mohamed Hamdani (Shire, USA)
- ▶ Janbernd Kirschner (University Medical Center Freiburg, Germany)
- ▶ Franz König (Medical University Vienna, Austria)
- ▶ Catherine Lewis (Alström Syndrome UK)
- ▶ Dirk Mentzer (Paul Ehrlich Institute, Germany)
- ▶ Geert Molenberghs (KU Leuven, Belgium)
- ▶ Gérard Nguyen (Rett Syndrome Europe, France)
- ▶ Dan O'Connor (Medicines and Healthcare Products Regulatory Agency, UK)
- ▶ May Orfali (Pfizer, USA)
- ▶ Martin Posch (Medical University Vienna, Austria)
- ▶ Franz Schaefer (University of Heidelberg, Germany)
- ▶ John Scott (FDA/CBER/OBE/BB, USA)
- ▶ Stephen Senn (Luxembourg Institute of Health, Luxembourg)
- ▶ Andrew Thompson (EMA, UK)
- ▶ Ferran Torres (Universitat Autònoma de Barcelona, Spain)
- ▶ Sarah Zohar (INSERM, France)

In addition to the workshop attendees, the following are members of the IRDiRC's SPCT Task Force:

- ▶ Robert James Hemmings (Medicines and Healthcare Products Regulatory Agency, UK)
- ▶ Mats Karlsson (Uppsala University, Sweden)
- ▶ Petra Kaufmann (NIH/NCATS/ORDR, USA)
- ▶ Jeffrey Krischer (University of South Florida, USA)
- ▶ Kerry Leeson-Beevers (Alström Syndrome UK / EURORDIS volunteer, UK)
- ▶ Samantha Parker (Lysogene, France)
- ▶ Franck Sasinowski (Hyman, Phelps & McNamara, P.C., USA)
- ▶ Bruno Sepodes (University of Lisbon, Portugal)
- ▶ Robert Temple (FDA/CDE/ODE, USA)

The workshop was organised by:

- ▶ Anneliene Jonker (IRDiRC Scientific Secretariat, France)
- ▶ Lilian Lau (IRDiRC Scientific Secretariat, France)
- ▶ Isabel Perez (European Medicine Agency, United Kingdom)

Annex I: International Initiatives

Several international initiatives have been launched to improve small population clinical trial methodologies, and clinical trials in rare diseases. Some of these initiatives are described in this Annex.

Integrated DEsign 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) are 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 EU-funded InSPIRE project (<http://www2.warwick.ac.uk/fac/med/research/hscience/stats/currentprojects/inspire/>), which brings together international experts in innovative clinical trial design methodology from across the globe.

The focus is 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.

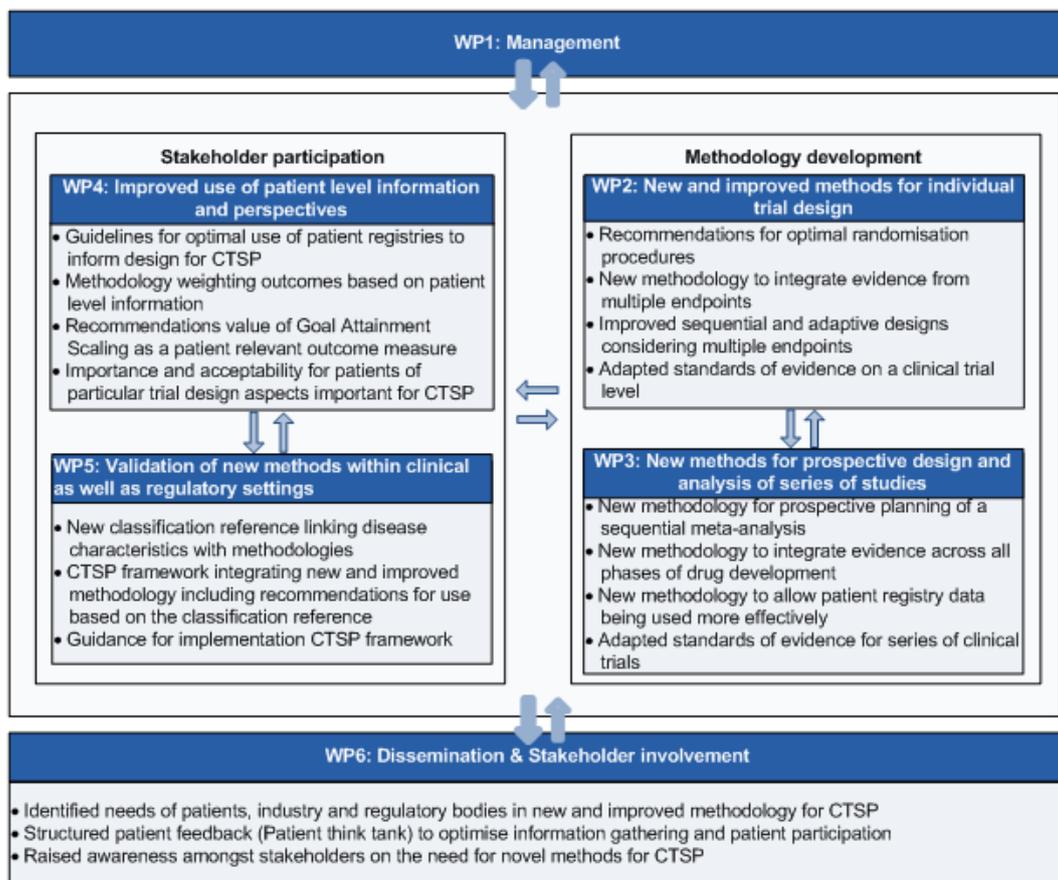
This project will develop methods that will enable more reliable results to be obtained from clinical trials more quickly, ultimately leading to improved healthcare for these small population groups.

It is 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. The ASTERIX project (<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. This ensures 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 is being 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.

Child-Rare-Euro-Simulation (CRESim) project

Funded by the European Commission PrioMedChild European Research Area Network (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 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.

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
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 United Kingdom
- ▶ European Study of Neonatal Exposure to Excipients
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

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 NCR 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.⁸⁶

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.⁸⁷

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 ICRI 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.⁸⁸ 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.

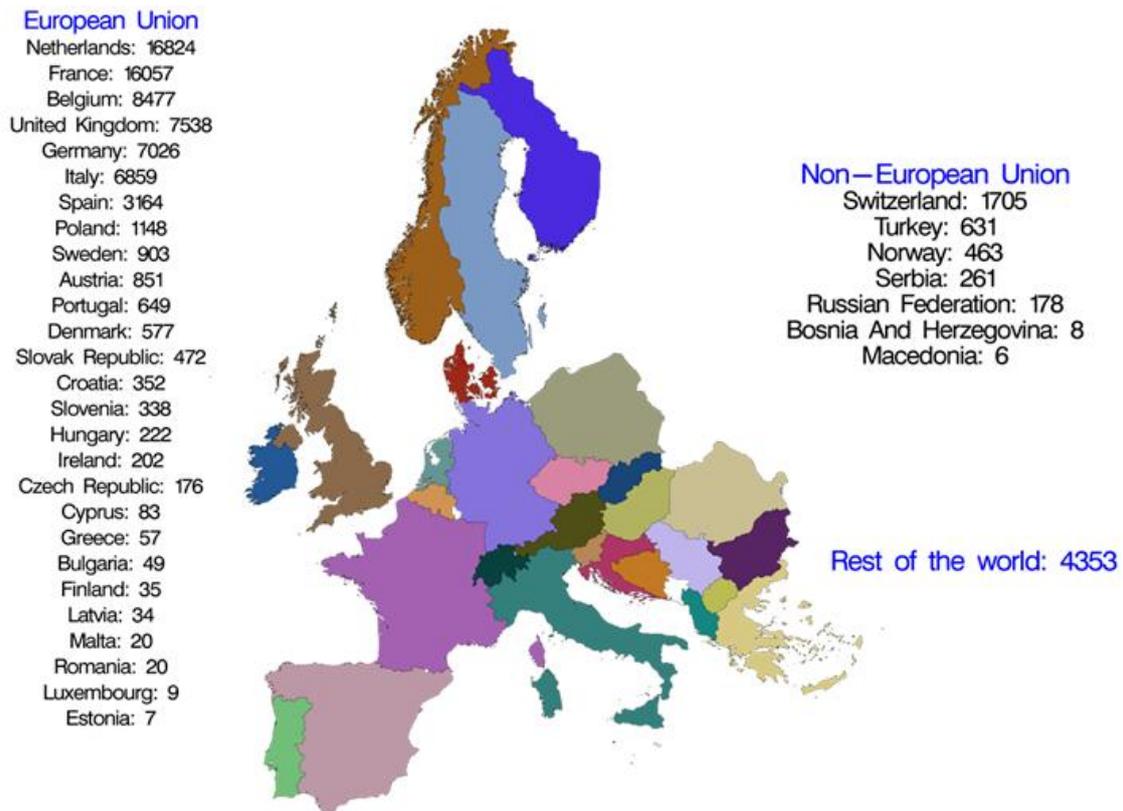
The RCE urges multidisciplinary, national, international and global collaboration to overcome regulatory obstacles and increase database sharing in order to assess the value of new treatment strategies. In October 2014, the International Brain Tumour Alliance (IBTA) joined the RCE initiative to help 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, the Belgian Federal Science Policy Office, 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 from the countries shown in the following figure.



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

TREAT-NMD Advisory Committee for Therapeutics

TREAT-NMD was established in 2009. As an international network for translational research in neuromuscular diseases, TREAT-NMD has contributed significantly to clinical research and multicentre trials in these diseases. One of its resources is the TREAT-NMD Advisory Committee for Therapeutics (TACT). It is a unique multi-disciplinary international group of well recognised academic and industry drug development experts as well as representatives of patient foundations and institutional governmental scientific research centres, who meet twice a year to review and provide guidance on the translation and development path of therapeutics programs in rare neuromuscular diseases with large unmet need, such as muscular dystrophies and amyotrophic lateral sclerosis. The confidential and comprehensive review provides recommendations including go-no-go milestones, is independent of any funding stream.

The goal of each TACT review is to help the sponsor to position the candidate compound along a realistic and well-informed plan to clinical trials, and eventual registration. The reviews and subsequent recommendations are focused on generating meaningful and rigorous data that can enable clear go/no-go decisions and facilitate longer term funding or partnering opportunities. The review process thereby acts to comment on viability and de-risking the process of proceeding on a development programme.

Since its establishment TACT has amassed a body of experience that can be extrapolated to other groups of rare diseases to improve the community's chances of successfully bringing new rare disease drugs to registration and ultimately to market. The focus on de-risking the process of proceeding to trial and or ultimate registration is distinct from the role of individual scientific funding boards.

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.⁸⁹ Several big pharmaceutical companies have developed methods to optimise clinical research in rare diseases, in efforts to boost their pipelines. Some examples are given below:

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 has addressed challenges prior to implementing clinical studies and throughout trials by seeking expert support through an idiopathic pulmonary fibrosis 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.⁹⁰ 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, in accordance with clinical experts and regulatory requirements is, however, challenging. In order overcome such challenges and to achieve high quality and homogenous data, Boehringer Ingelheim 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.⁹¹ 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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