MEETING REPORT

CDDF Annual Conference

Towards a Collaborative Future in Patient Access

7 - 9 February 2022

Virtual Conference

Prepared by the CDDF

PROGRAMME COMMITTEE

Chair: Jaap Verweij (CDDF, NL)
Claudia Hey (Merck Healthcare KGaA, DE)
Michael Zaiac (Novartis, CH)
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Kim H. Lyerly (AAADV, US)

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Panel discussion

Learning Objectives

- *Understanding current differences in the European regulatory approval- and HTA approaches and discussing potentials for harmonization and alignment.*
- *Forward facing discussion on de-central cancer clinical trial performance, and on use of digital tools for this purpose.*

- *Forward facing discussion on options to accelerate drug development programs*
- *Understanding the current status of global regulatory collaboration, and open discussion on options for further extension.*

SESSION 1: INTEGRATION OF REGULATORY ASSESSMENT AND THE ASSESSMENT OF REIMBURSEMENT

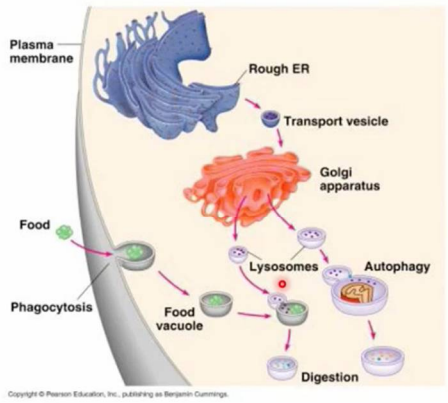
Adaptive Pathway Development: a Clinical Approach in Fabry Disease

Prof. Carla Hollak (Amsterdam University Medical Center, NL)

Treatments for lysosomal storage disorders have emerged over the last three decades.

Lysosome = a garbage bin in the cell with enzymes which can break down many substances.

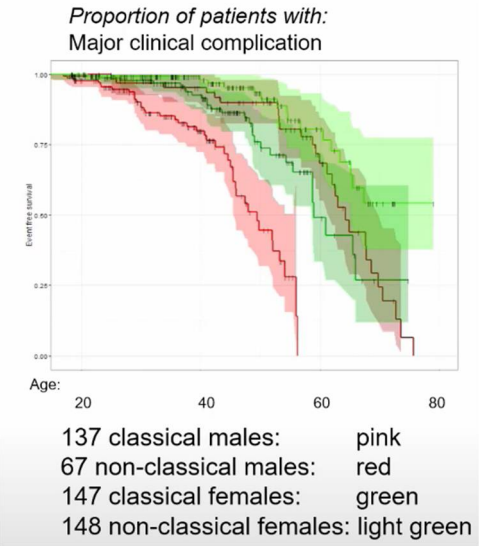
Lysosomal storage disorder (LSD) =an inherited disease characterized with a defect in a lysosomal enzyme



One of the hallmarks of lysosomal disorders is that the phenotypic diversity is enormous. This is an important limiting issue for the development of treatments. Successful treatment effects will depend on timing and disease severity. In addition, outcomes of small studies can be misleading, due to selection bias.

Gaucher disease was the first disorder for which enzyme replacement therapy (ERT) was developed: purified enzyme, administered intravenously at regular intervals, resulted in dramatic improvements in key clinical outcomes. However, the success came at a price: up to 300.000€ per patient per year. In the Netherlands, in the 1990s, a dose-finding study however showed equal effectiveness at lower, individualized doses, leading to substantial cost reduction. This exemplifies that for such rare, chronic disorders, many issues around individual effectiveness can remain after marketing authorization.

This was even clearer for Fabry disease, caused by deficiency of the enzyme alfa-galactosidase A, for which two equally expensive enzyme therapies received marketing authorization in 2001 as orphan drugs. Fabry disease is a vascular disease, X-linked, with extreme phenotypic heterogeneity. Years after authorization, we learned from post-hoc registry cohort's analyses that: diagnosis is difficult, the natural disease course differs highly, related to residual enzyme activity:

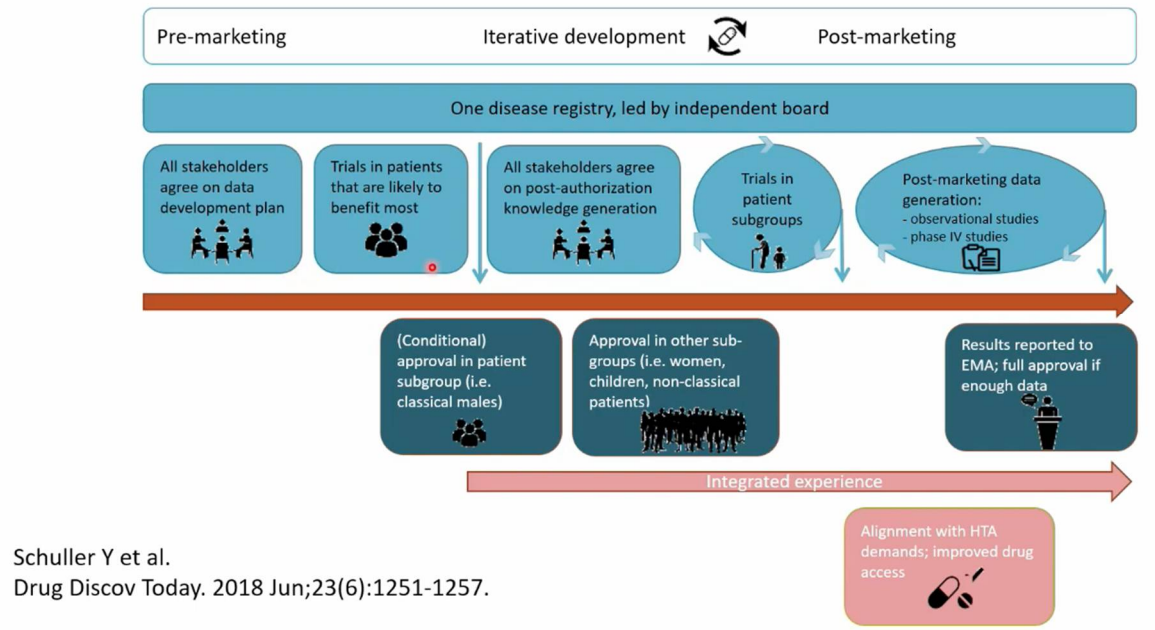


From: Arends M et al, J.Am.Soc.Nephrol, 20216, Dec 15

In addition, patients treated at a later stage have irreversible disease and progress despite therapy, and finally, antibodies may interfere with effectiveness. In addition, post-marketing evaluation failed to generate sufficient and relevant data for adequate evaluation on effectiveness and cost-effectiveness.

In view of the above-described issues, we developed a theoretical adaptive pathway, that might have benefitted Enzyme replacement therapy development. Key elements that we proposed are (i) involving healthcare professionals, patients, health technology assessment bodies, and payers in the development process; (ii) iterative development, starting with initial authorization in the severely affected, so-called classical males; (iii) a clear real-world data collection plan; (iv) an independent disease registry; and (v) a prescription control.

Adaptive pathway development for Fabry disease: Improved scenario



Schuller Y et al.
Drug Discov Today. 2018 Jun;23(6):1251-1257.

For future development of orphan drugs, the proposed early dialogue in the development phase between all stakeholders is necessary, as are strategies for early, but controlled access. An example of the latter involves the Dutch Drug Access Protocol, in this case, applied to orphan drugs.

Innovative Licensing and Access Pathway (ILAP). A streamlined approach to regulation and patient access.

Dan O'Connor (MHRA, UK)

The Innovative Licensing and Access Pathway (ILAP) has been operational in the UK since the 1st of January 2021. The ambition is to deliver safe, early, and financially sustainable patient access to innovative medicines. A key aspect is how the ILAP platform supports a novel framework for closer collaboration with ILAP partners, the Medicines and Healthcare products Regulatory Agency (MHRA), National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and more recently the All Wales Therapeutic & Toxicology Centre (AWTTC).

ILAP covers the entire development programme from before First in Human Studies through to supporting a life cycle approach to approved medicines (real world data collection and new indications).
The main components of the integrated pathway are the **Innovation Passport** designation (IP), which links to the development of a roadmap to patient access. The **Target Development Profile** (TDP) creates a unique UK roadmap, using a toolkit and providing a platform for sustained multi-stakeholder collaboration. The tools of the **TDP toolkit**, are intended to drive efficiencies in the development programme, supporting data generation and evidence requirements. Importantly and in keeping with the goal to embed the patient voice in the ILAP right from the start, patient representatives contribute to the decision making on the Innovation Passport.

The Innovation Passport includes the following principles:

- Broad and inclusive definition of innovation
- Non-clinical entry point provides ambition for long-term interactions
- Patient centred from the start
- Structured engagement between stakeholders
- Joint decision making at regulatory level

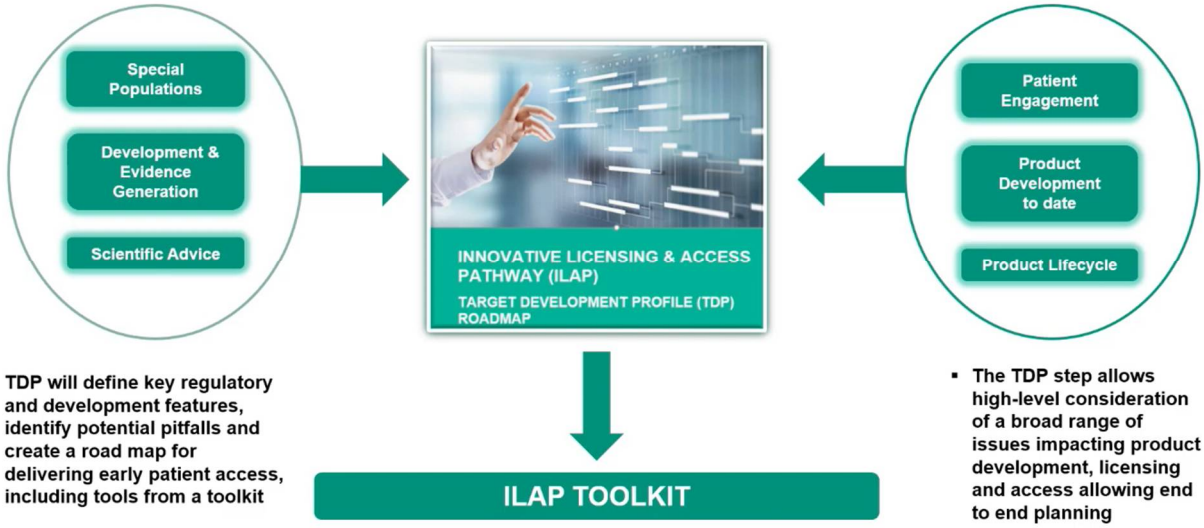
There is built-in flexibility, with multiple entry points along the pathway.

The criteria that need to be met are:

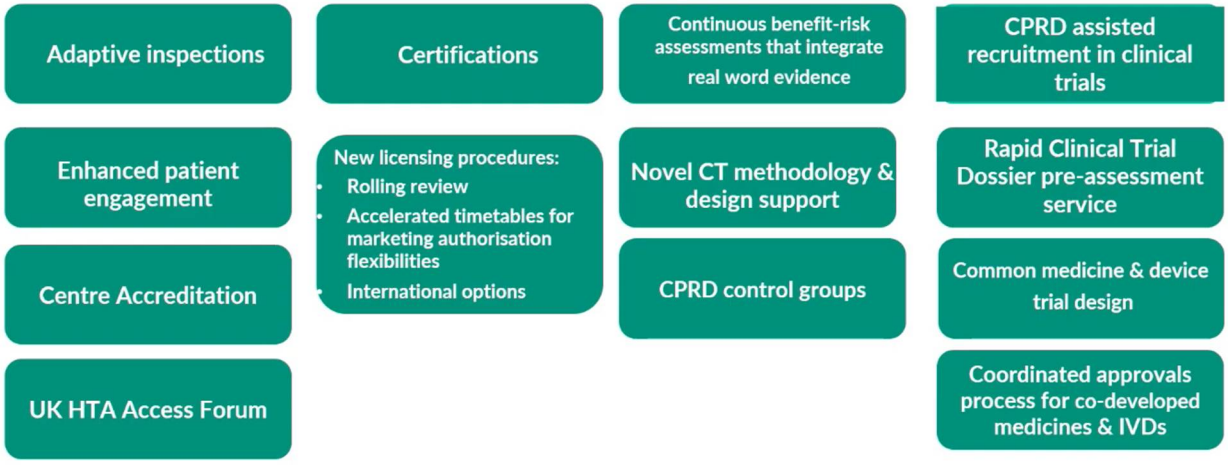
- Condition
  - A life threatening or seriously debilitating disorder
  - Significant patient- or public health need
- Type of medicine
  - Truly Innovative
  - Clinically significant new indication (for instance: repurposing)
  - Medicine for rare disease, or special populations
  - Development in line with objectives for public health priorities
- Medicine has the potential to offer benefits to patients
  - Improved efficacy or safety, or quality of life, as compared to other options.

There were 76 applications for the IP in the first year, covering both rare and common diseases, with strong interest (N=25) from the oncology pipeline. The first Innovation Passport

issued, involved development for von Hippel Lindau disease. The IP applications involved all stages of development.
The TDP will define key regulatory and development features, identify potential pitfalls, and create a road map for delivering early patient access, helping to ensure that products that are developed through ILAP are both regulatory and access ready, and with the patient in mind.



Tools that are currently being developed in the toolkit involve the following:



For the life sciences industry, ILAP has the following potential benefits:

- Early engagement with regulators and HTA on clinical trial design
- Early platform dialogue with HTA and MHRA on evidence generation requirements
- Expedited regulatory routes leading to earlier market access
- Early access planning
- Opportunity to plan at a UK level.

Industry experience with ILAP

Daniel Martin (Merck Healthcare KGaA, DE)

The first experience with ILAP involved a very early engagement with MRHA. MRHA was flexible and available to guide the applicants through the scheme.

There was ample opportunity for additional interactions and discussions, identification of pitfalls and weak spots, provision of clarification, and for the assessors to obtain familiarity with the new product via preliminary data, ahead of filing application.

The earlier interactions enabled a more robust application. The rolling review can accelerate the assessment. ILAP also offers the opportunity for international collaborative assessment within project ORBIS.

The benefits in the HTA process are less significant up to now.

Moving the statistical analysis of randomized trials from a single endpoint to a patient-centric benefit-risk assessment

Marc Buyse (IDDI, BE)

The common analyses that statisticians perform on randomized clinical trials have two essential problems:

1. The focus is on a single primary endpoint, while other endpoints are looked at with a descriptive intent only.
2. The statistics are hard to understand for non-statisticians.

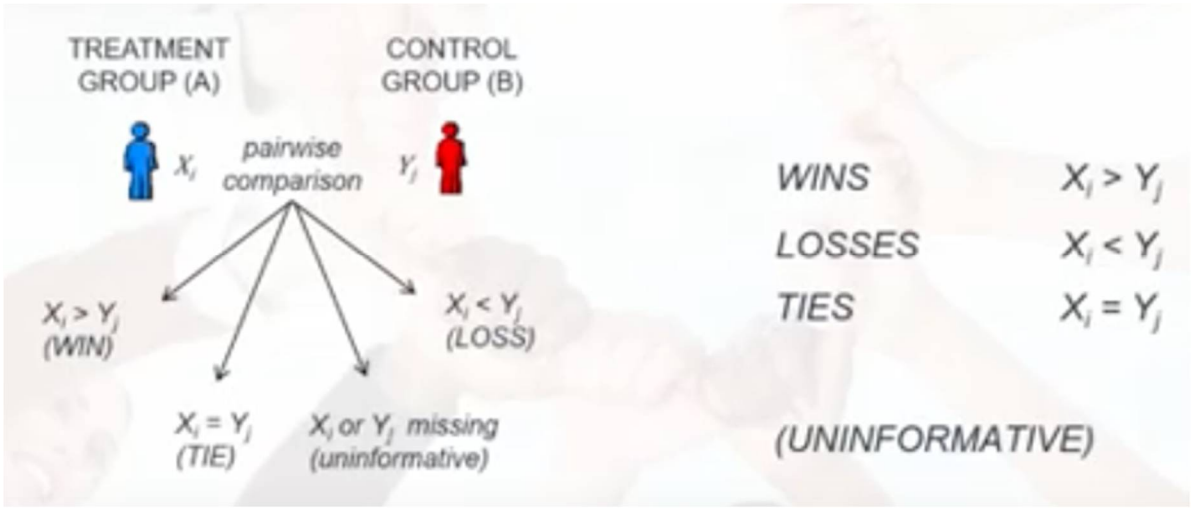
What matters to patients may differ from what matters to statisticians, and even to clinicians. Patients, in general, want to know about their estimated life expectancy, and the relief of their disease symptoms, which is a individual benefit/risk assessment. So, better positioning a patient-centric view in the analysis of clinical trials seems essential. The method of ***Generalized Pairwise Comparisons (GPC)*** allows this. It facilitates analysis of all outcomes of interest at the same time, and in a desired order of preference.

A GPC analysis starts with listing and ordering the treatment outcomes that matter most to patients. Then in one patient in arm 1 and one patient in arm 2 of the trial, the results of these two patients are compared for each outcome considered. The method assesses if this outcome was achieved favorably by one treatment or the other. Should the results be equal, then a second outcome is analyzed in the same way. This way one gets a ***Net Treatment Benefit***.

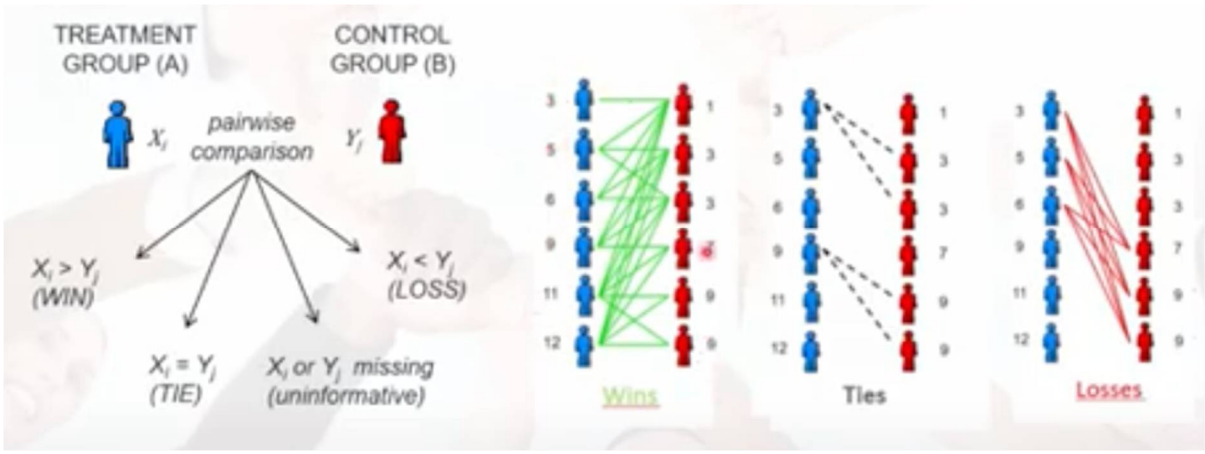
Without GPC, treatment decisions are based on general expert consensus, which may not necessarily reflect patient preference. GPC empowers patients to participate in making treatment choices.

Not only does the analysis list the preferred outcomes, but it can also use a prespecified threshold of clinical relevance for each of the outcomes.

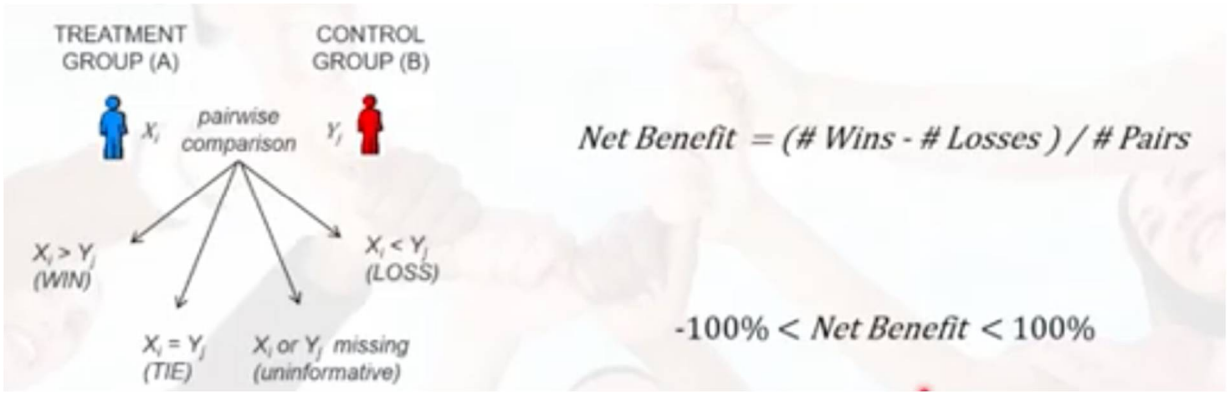
Subsequent to listing, and assessing, a formal statistical analysis is performed, using pairwise comparisons.



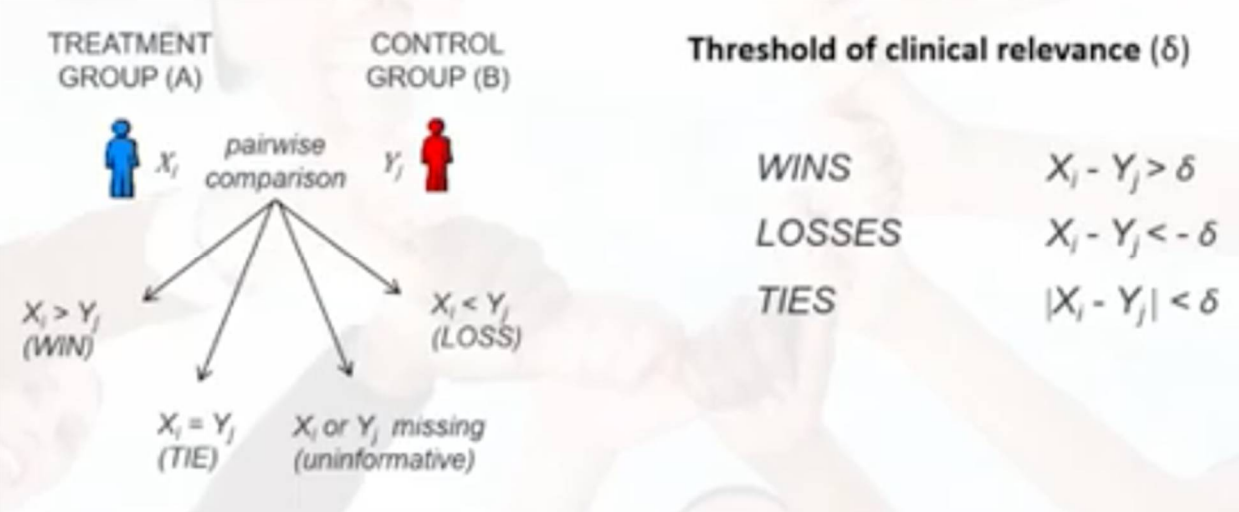
This process is repeated on all pairwise comparisons.



So, for each pair one decides on a win, a loss or a tie. This ultimately leads to the Net Treatment Benefit:



The analysis can include thresholds of clinical relevance:



GPC has several advantages:

- It is a non-parametric approach to account for multiple outcomes of any type
- It permits a mathematically rigorous benefit/risk assessment, when outcomes are correlated
- The net benefit is a universal measure of treatment effect that has a straightforward probabilistic interpretation
- Prioritizing outcomes is natural and patient centric.

It has several potential applications:

- Thresholds of clinical relevance
- Non-standard situations
- Time to most relevant event, rather than time to first outcome
- Mixed outcomes
- Multidimensional scales
- Highly multidimensional data

Panel discussion

The panel is joined by Mrs. Anne Willemsen (EUnetHTA, NL)

Q: How can high-quality follow-up information in a registry be obtained?
A: It may work best by using a prespecified structured list of data to be collected, which can be monitored prospectively.

Q: Do regulators pay enough attention to the use of Real-World Data?
A: This seems to be the case, but one needs a very robust structuring, as well as monitoring of such data, for them to be useful. It also requires an early discussion with the regulators, should one decide to make use of RWD in an application dossier.

Q: How can an early ILAP application be used in a global dossier? Is there alignment?
A: ILAP can support discussions around challenging areas. The first experiences of industries with ILAP confirm that there is appropriate alignment.

Q: Are patients indeed actively involved in the ILAP process?
A: This is confirmed. From the early beginning, ILAP aimed to be patient centric. There is a dedicated patient's group within the ILAP process, that helps to evolve the structures. Patients

actively participate in meetings. At the HTA level, there is increasing involvement of patient advocacy groups as well.

Q: Can GPC be applied in comparing more than 2 treatments?
A: What matters is to have comparable groups, and preferably to make use of a true standard of care that is beyond debate. There should be more post-registrational trials, to assess the true value of drugs.

Q: Could a system like ILAP work for orphan drugs?
A: In principle, it could. What is sometimes missing, however, is the early involvement of true clinical experts in the particular domain. Much of the discussion is industry- centric and not infrequently the endpoints employed are of questionable relevance. So, a better alignment of stakeholders remains crucial. And the ILAP team is keen to continuously keep an eye on this aspect.

Q: GPC was presented more than 10 years ago. How has it picked up? And can it completely replace current statistical methods?
A: The answer to the latter is clearly No. As to the first part of the question, with the desire of better alignment between marketing approval and patient access (the topic of this session), GPC becomes more relevant than it may have been perceived at the time of its launch. Regulators are also very interested in innovative methodologies for new drug approval.

Session 2: REFLECTION ON CDDF WORKSHOPS 2021

Endpoints in cancer drug development

Chitkala Kalidas (Bayer, US)

The workshop aimed to address current challenges with the definition and contextualization of endpoints in cancer drug development and commercialization. With a focus on problem-solving aspects.
There were 3 key sessions:

When Overall Survival (OS)cannot be the primary endpoint

OS is still the most important endpoint in cancer drug development. But it is increasingly challenged by the successes in drug development in the recent past.
Therefor there is an urgent need of novel endpoint. These cannot be assessed in isolation and will need to be carefully validated with evidence across different trials. They do not always correlate with survival. Such alternative endpoint can be *Progression free survival* (PFS, which should not have a detrimental effect on OS), *overall response rate* (ORR, which is not necessarily related to clinical benefit), and *Patient Reported Outcomes* (PRO, that often lack quality and are hampered by missing data).
Two case studies discussed alternatives that were used successfully:
Best Overall Response (BOR, Response rate with defined follow-up) was used for marketing approval based on a single-arm trial with historical control, in a rare disease (Merkel Cell Carcinoma) with a high unmet need, where a randomized controlled trial (RCT) was considered not feasible.
Metastasis Free Survival (MFS) was considered a reasonable endpoint for clinical benefit in non-metastatic castrate resistant prostatic cancer, if it was of acceptable magnitude in absence of detrimental toxicity and with a positive trend in OS.

Endpoints in expedited regulatory pathways

Expedited pathways could serve patient needs. Earlier endpoint, however, need to be seen in the context of novel treatments, and disease over time.
For regulators OS is still the gold standard endpoint. Earlier endpoint can be used for accelerated approvals, particularly in molecularly well-defined subpopulations. However, one needs to realize that there is still a major regulator-HTA gap, so early approval does not lead to early access, since the relationship between the "surrogate endpoint" with OS and Health Related Quality of Life is frequently not clear, and data sets are small. So, an early dialogue with the HTA's is considered key.

PRO-endpoints. Review of strategies

For patients, outcomes reported by their peers are very relevant. Patient organizations can help in solving the issues related to multiregional studies.
For regulators, it is important that PRO's focus on areas directly related to the disease and its management and are meaningful for patients. The regulators are open to considering the various modern alternative methods of PRO data (e.g., wearables, sensors, etc.), but stress that the quality of these data remains key.
So, it is important to involve patients in the various stages of the drug life cycle. Which requires early planning and standardization. PRO is a challenge in expedited pathways.
For HTA, survival and QoL remain key, and PROs are a great challenge.

Digital tools and artificial intelligence

Nafsika Kronidou Horst (Roche, CH)

Digital Health (DH) tools offer multiple opportunities to support the patient journey and collect objective longitudinal data which we are sometimes not able to collect in a traditional CT. In addition, the use of software and algorithms can now help us generate insights from a large volume of data. Several open questions on how to use DH tools and AI in clinical studies remain and examples include those related to ethical aspects of AI (e.g., in maintaining human logic and intelligence), on data (e.g., standards, quality, privacy, and interoperability) and evidence requirements related to the technology (e.g. validation of the technology). Therefore, building a global regulatory environment which can keep up with the fast pace of innovation while protecting the privacy and safety of patients remains a key consideration.
Clearly all these elements need to operate in an ecosystem and our ability to execute on the promise of DH to improve global healthcare relies to a large extent on building a coordinated environment which enables collaboration and convergence between key stakeholders.
With the above in mind, Nafsika invited the audience to explore and discuss how we could generate a more coordinated health ecosystem, for example through:

Build flexible "learning" environments

- Which allow continuous learning, innovation and unlock opportunities to support patients
- Expertise based set-up and culture of mutual trust in scientific work

Build trust with society and patients

- Earlier dialogue with patients; understand their needs and concerns
- Design studies which address patient needs and enable more inclusive participation in CTs through the use of DHT with equitable access to innovation

Reduce fragmentation through strategic partnership

- Enhance awareness of ongoing activities
    - e.g., an across discipline oversight body consolidating global efforts

- More frequent publications of important advancements in technology and methods
- Aim for consolidation of opinions when it makes sense
    - e.g., co-authoring or commenting (vs preparing new papers or publications)

Early engagement and communication by regulators

- More open and early dialogue and flexible interactions with regulators with dynamic regulatory processes to inform the development of regulatory practice/ guidelines. For example:
    - Regulators to sponsor pilots and collaborate in identifying solutions
    - More open dialogue with scientific committees and expert groups
    - Less burdensome procedures e.g., qualification procedure

Modernize regulatory frameworks to 'fit-for-future''

- Regulatory systems that enable global regulatory convergence while supporting the timely delivery of safe, effective, and innovative solutions

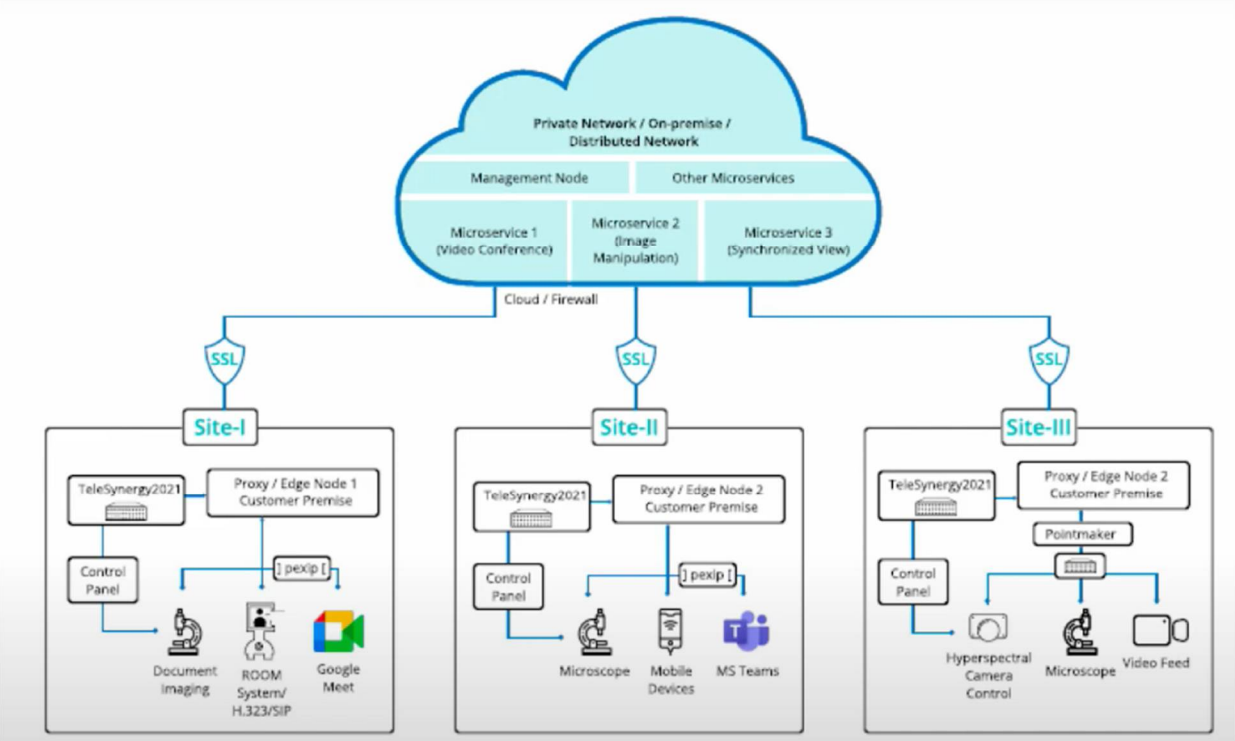
CDDF-AAADV satellite session on global pediatric neuro-oncology network

Kim Lyerly (AAADV, US)

Globally, more than 400.000 children develop cancer every year. And brain tumors constitute the most common solid tumor and are the leading cause of cancer-related death in children aged 0-14 years. There is a great variety of subtypes, which renders each into a very rare disease. Global collaboration in drug development is clearly key in the performance of clinical trials. Clinical consortia play a major role, and it is crucial that they have a global reach. The outcome of their work has tremendously improved the prognosis of pediatric brain tumors, but there is still a major space for improvement. Importantly, there is a considerable disconnect in outcome, in high-income countries vs low-income countries. There are now major efforts to make drugs (as well as radiotherapy) available also in low-income countries. The WHO's Global Initiative for Childhood Cancer (GICC) targets to double the current global cure rate for all children with cancer.

In the workshop there was a major part of the discussion focused on how the various stakeholders can help to create a Global Pediatric Neuro-Oncology Network. The pharmaceutical industry is looking for ways to build a sustainable corporate model to address drug development and regulatory requirements in pediatric Neuro-Oncology, with a global footprint.

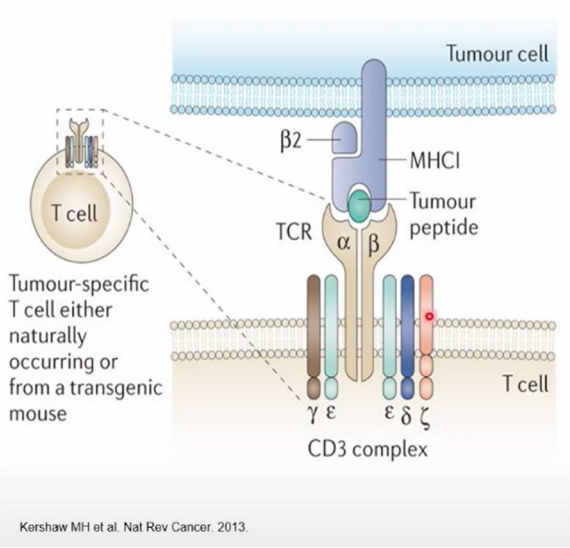
In performing the research, the use of telehealth solutions could help to facilitate. The first generation of Telesynergy platform were outlined. Next generation platforms are now under study and can help to further improve global collaboration in networks and can serve as a further springboard.



Gene and cell therapies

Jaap Verweij (CDDF, NL)

T cells are part of the immune system. Their cell killing function triggered by signaling through the heterodimeric protein T-cell surface receptor (TCR). The TCR is able to recognize and bind to a combination of peptides found in the groove of a molecule MHC, one of the tissue type proteins which is expressed on the surface of all nucleated body cells, including tumor cells



Binding to the receptor leads to a signal to the T-cell and activates it. This induces a clonal expansion of T-cells that all express the same receptor. They can differentiate, and secrete cytokines and enzymes, that lead to death of the target-cell.
Importantly, T cell memory persists in the body for the rest of the hosts live.

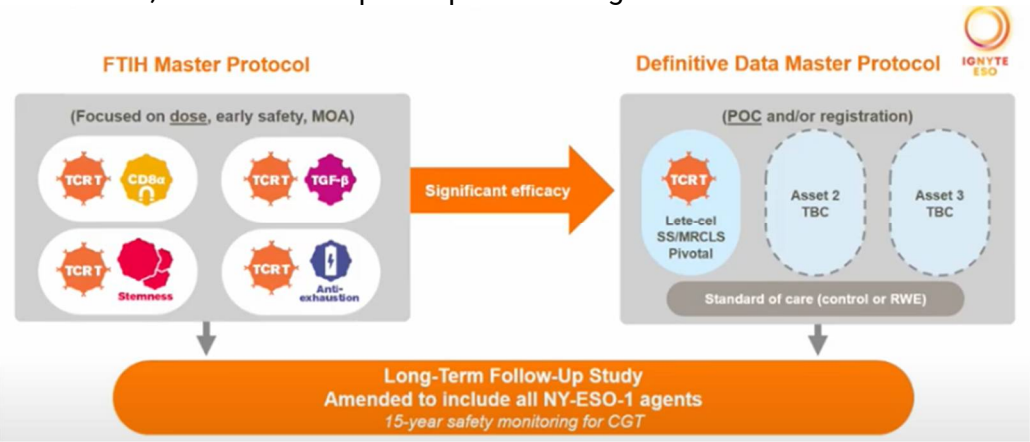
So, if T cells can be manipulated to recognize cancer cells, they can become an army against the cancer involved. An army that will persist long-term.
This manipulation is performed extra-corporal, after collecting T-cells from the blood of a patient. in a laboratory, after the engineering in of the cancer cell proteins, the cells can be cultured and expanded, and then reinfused into the patient. Once in the body, the cells travel to the tumor site, recognize the tumor cells, and kill them.

There are various laboratory procedures applied in T cell engineering:

- The most commonly genetically engineered T-cells in clinical use are the chimeric Antigen Receptor (CAR) T-cells.
- There are different kinds of receptors that can be introduced into the T-cell. These receptors are based on the fragments of an antibody. This has the advantage that antibodies recognize antigens on the surface of cells that have not been processed and presented by MHC. This means that T-cells expressing a chimeric antigen receptor, can be used in any patient regardless of their tissue type.
- The majority of clinical trials on T-cell therapies in hematological malignancies are involving application of CAR-T cells, but also Natural Killer cells are used.

An advantage of using natural killer cells is that they can be derived from a high variety of sources, including healthy donor's peripheral blood mononuclear cells, core blood, placental blood, induced pluripotent stem cells), embryonic stem cells and even NK-cell derived cell lines.

In the regulatory environment, both EMA and FDA have specialized teams for the assessment of dossiers on advanced cell and gene- therapies. At EMA this involves the Committee for Advanced Therapies, at FDA it involves the Office of Tissues and Advanced Therapies (OTAT) within the Center for Biologics Evaluation and Research (CBER). Both have issued specific guidance, that helps applicants of dossiers in finding their way.y.
Importantly. The recently activated EMA Clinical Trial Application Regulation involves a harmonized procedure for the EU with a single application towards a portal located at the EMA. There will be a coordinated multinational assessment, with a rapporteur. EU member states do retain authorization and oversight. In the last 9 years 19 ATMPs have been approved by EMA, including 4 CART products, focusing on (relapsed or refractory) hematological malignancies. This is quite similar to FDA.
Past focus has been on single arm studies, in areas of unmet medical needs, and in rare populations. The rareness of the population could cause attrition issues and screening exhaustion, but also create operational challenges in manufacturing and therapy delivery.
Interesting developments such as the so-called "Parent-Child" protocol development strategy shown here, allow to develop multiple technologies in a faster and more cost-efficient way.



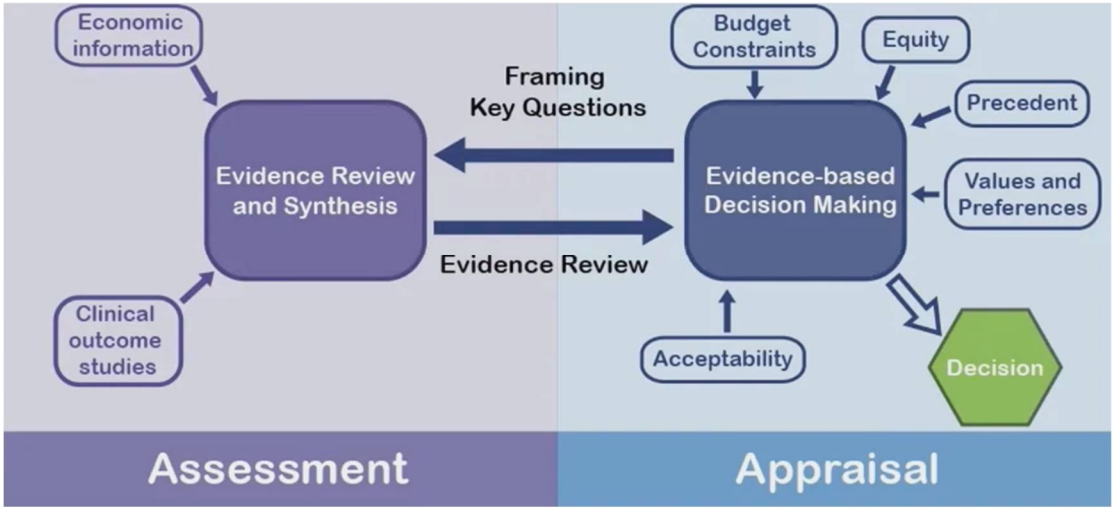
The first in human master protocol on the left is a platform protocol, consisting of a core and multiple independent sub-studies focused on dose, early safety and multiple mechanisms of action. On the right is the definitive Data Master Protocol, that has the same structure, but is focused on proof of concept and/or registration. The 3rd, on the bottom, is a single long-term follow-up study, to which all patients from all sub-studies, and all agents, transfer following end of the treatment study for the patient. This approach provides an ideal framework for cell therapy development.
In practical terms this allows parallel examinations of multiple assets in a single master protocol with cross-referenced IND's.

After marketing approval, there is a social responsibility to have a broad geographic worldwide patient access to CAR-T cell therapy. This is facing us with specific new challenges:

1. T-cell therapy is different from more usual drug therapy. It is not a daily or weekly repetitive treatment, but it involves a one-time procedure. This requires different approaches to ensure patient access.
2. Most studies on T cell therapy up to now are small single arm studies, with major limitation in translation of outcome into the real world. The absence of such definitive evidence for clinical value, is a serious drawback for HTA appraisal.

Even for existing, much less expensive and much simpler standard of care treatments there is major inequity in patient access at the pan-European level.
Many EU countries are many years behind ESMO standards and do simply not have the experience nor the hospital capacity to provide a simple standard of care, let be complex CAR-T therapies.

The ultimate aim in the HTA process is to ensure affordable and equitable access for (all) patients to effective therapies in a sustainable manner. With emphasis on Affordable and on Effective.



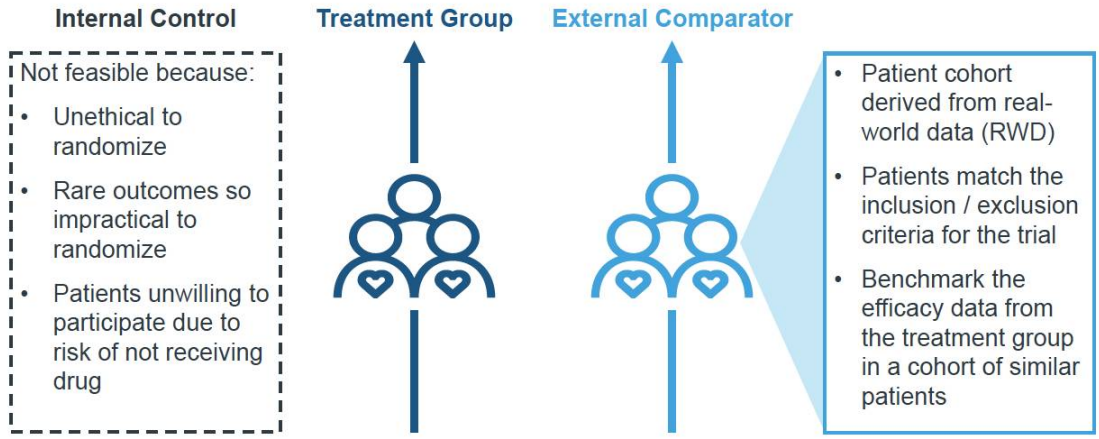
The HTA process involves the assessment based on available evidence, as shown on the left of this graph, and subsequently, the appraisal takes several other aspects into account for balancing. Each EU country decides for itself in the HTA pathway. There is no central EU procedure. All those countries struggle with the problem that the current medical systems are financially not sustainable. In this landscape and taking into account that what is spent on one patient cannot be spend on another (so-called "opportunity costs"), the per-patient costs for CAR-T cell therapies that amount € 300.000-400.000, create a challenge. They can likely not be covered within the allowed maximum yearly budget growth of 1.2% for medicines.

A leading question countries face, is how to reduce spending, rather than to add to it.
To address this, value based pricing has been introduced. This includes factors such as:

- Cost per QALY (with major differences between countries)
- Pay for performance (P4P), and
- Volume-price arrangements, and more recently
- Coverage with evidence development (CED)

The latter is particularly applied for drugs for which adequate large data sets are yet lacking, such as for the Gene- and Cell therapies
Clearly, in actual practice, patient access has by far been guaranteed within the EU.

The requirement of evidence-providing large studies for patient access was also discussed. Speakers discussed the potential of using registries, or other sources of Real world data as an external comparator that, in theory, could establish context for single-arm trials .



In assessing external comparators, one should differentiate External controls (that include adjustment of data at patient-level) from Benchmark controls (that exclude such adjustments).
The good message is that there is increasing use of RWD with External controls, for regulatory purposes, now also involving the use of Artificial intelligence and development of so-called Federated Learning systems, that leave the data within the hospital firewall. Only the algorithm travels, to be trained at different clinical sites. Which also has the advantage of safeguarding patient privacy.

Session 3: ENHANCING THE FUTURE OF CLINICAL TRIALS

CTFG's perspective on enhancing the future of clinical trials

Elke Stahl (BfArM, DE)

The Clinical Trials Facilitation and Coordination Group (CTFG), is a Working Group of the Heads of Medicines Agencies (HMA) , the European Regulatory Network of national competent authorities in charge of clinical trials (CT).
Within the EU goals on harmonization and facilitation of clinical trials the CTFG is involved in regulatory-, scientific- and operational issues. It produces:

- common oprocesses andbest practices
- (e.g., assessment of clinical trial applications, and – (safety) surveillance in clinical trials)

- common opinions, positions, and recommendations (e.g. on contraception in clinical trials; initiation and conduct of complex CT's, IVD in CTs, QnA on safety reporting in CT)
- suport to joint guidances (e.g., on CT during pandemics, CT on First in human or early clinical trials)

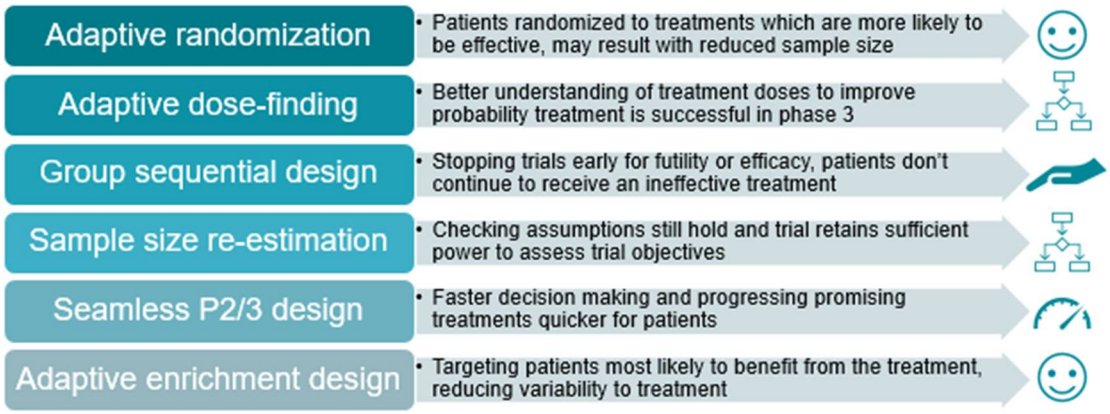
With the kickoff of the EU Clinical Trial Regulation CTR536/2014 and the Accelerate Clinical Trials in Europe initiative (ACT-EU, which aims to foster innovation in clinical research in the EU), CTFG will transition to the Clinical Trials Coordination Group (CTGG) with a new mandate and workplan (currently in work) on 31 January 2022. There will be new nominations of members, and selection of a new chair and vice-chair.
CTCG aims to increase cooperation with relevant working groups in the European Medicines Regulatory Network (EMRN: HMA, COM, EMA) (e.g., update on complex clinical trials QnA with EMA/COM, decentralized CT recommendations with COM's CT Expert Groupand the GCP-Inspectors Working Group) and will further harmonize and facilitate CT in EU/EEA, support implementation of the CTR and further improvements. CTCG will be part to develop a one stop job for questions related to CT in EU/EEA. CTCG will support further evolution and innovation in CTs, and work on harmonization and coordination to guarantee full implementation of the CTR, including pharmacovigilance in CTs.

Delivering on innovative trials: an industry's perspective

Mireille Muller (Novartis, CH)

Clinical research has undergone a fundamental shift in the last years. Many traditional processes have taken on new formats to increase clinical development efficiencies: increased patient-centricity, innovative trial designs, broader evidence generating toolkit, and last but not least digitalization.
Diagnostics have become more refined, leading to more precisely defined disease descriptions and hence smaller patient populations for targeted therapies.
The classic parallel-group randomized clinical trials have thus become one of the rate-limiting factors in drug development, and more innovative trial designs are needed.
Biomarkers are increasingly used to define small subsets of patients with specific diseases. This granularity challenges current trial designs. Complex innovative clinical trials (such as basket, umbrella, platform and historical controlled trials) could remedy the problem because such trial designs allow for the evaluation of investigational treatments in multiple subgroups of a study population within the same overall clinical trial structure compared with traditional randomized controlled trials.

Master protocols and complex innovative designs contribute to increased efficiency and other enhancements of medical research to ultimately accelerate patient access to innovative therapies. While uptake of master protocols was smooth, the uptake of complex adaptive designs using Bayesian techniques, was slower.
Adaptive designs have several benefits:



The benefits of complex clinical trials can be summarized as follows:

- Increased and earlier patient access to targeted therapies
- Earlier identification of promising or ineffective medicines, reduction of Phase 3 failures, reduction of exposure of patients to ineffective drugs
- Enable to study multiple compounds/targets in one operational set-up
- Flexible design to adapt to collected data and a change in treatment landscape
- Operational- and resource efficiency
- Centralized molecular screening: faster accrual and increased likelihood of patient eligibility
- Accelerated drug development

There is an obvious need for the European regulatory network to ensure

- sufficient technical capability/capacity for the review and assessment of these trials,
- increased collaboration between regulators and stakeholders such as ethics committees, health technology assessment bodies, patient associations
- Timely, iterative scientific advice
- facilitation of a global convergence of regulatory requirements

As the global clinical research space is highly competitive and as the EU landscape is complex, it is important for Europe to ensure a healthy and enabling clinical research ecosystem.

Patient centric, decentralized clinical trials – a national project

Gunilla Andrew-Nielsen (Swedish MPA, SE)

During 2020-2021, the Swedish Medical Products Agency (MPA) has carried out a feasibility study and a subsequent project about patient centric, decentralized clinical trials. The project aim was to establish conditions for how interventional clinical trials can be carried out decentralized in Sweden. The work was partly financed by the Swedish Innovation Authority.
A decentralized interventional clinical trial can be described as a method for, remotely and/or with the help of digital tools, collecting data within the framework of the trial. Trials that contain both decentralized and traditional elements are often referred to as hybrid trials. The decentral part can be consent data, randomization, and inclusion but also safety and efficacy data for the investigational medicinal product in the trial.
Five interventional clinical trials with decentralized elements were followed in the project. The decentral elements included:

- Remote electronic consent
- Home sampling self-administered by the patient
- Remove visits
- Medical device solutions to capture possible side effects

- Distribution of the investigational medicinal products
- Medical device solutions to record treatment compliance.

During the feasibility study regulations, guidelines and established practice were analysed.
It was concluded that there are no formal obstacles to conducting clinical drug trials with decentralized elements linked to the regulations included in our assignment.

- Planning of such trials requires a careful and study-specific risk-benefit assessment.
- It is important that the reasons for performing decentral elements must be scientifically based. Cost-efficiency is not an acceptable reason to include decentral elements.
- The same requirements regarding ICH, GCP, GMP, the scientific value of the study and the safety of the patients, apply for decentral trials as for traditional trials.

The Swedish MPA and other key national stakeholders have gathered to highlight existing difficulties and what actors need to work on to further improve the conditions for the implementation of these clinical trials. The experiences from the project and the conditions in Sweden have been shared both nationally and internationally.
For further information, and for suggestions, visit the website of the Swedish MPA.

Panel Discussion

Q: Will the role of CTCG be much different of the role of CTFG?
A: Difficult to say at the point of shift, but the aim is to have a change. Particularly there was a desire to change the position in the Network.

Q: What are the biggest barriers for the implementation of adaptive designs?
A: The possibility to have an early dialogue with the regulators, is a major gain. Lack of familiarity with these designs in industry as well as in ethics committees, is currently still a barrier. There is a need for alignment with the global regulatory agencies, since many of these trials are now performed globally. There are now initiatives to provide best practices, templates etc., that will be helpful.

Q: FDA has proposed to use a common control arm, for cross-companies development of agents with the same biological target. How is this perceived within companies?
A: I-Spy was an example, that was executed successfully. There is willingness for cooperation among companies.

Q: With the new IVDR, how do we bring novel devices to the level of acceptance by health authorities globally?
A: There is a window of opportunity with this introduction, also to meet the issues related to true personalized treatments. IVDR offers the opportunity to align the complex machinery involved in diagnoses, and the option to involve Artificial Intelligence. The aspects of IVDR will also be new to the regulators. CTFG is working on a Q&A document to support the introduction of IVDR. This will be released shortly.

Q: Is there a plan in the EU regulatory field, to provide further broad education to stakeholders on the IVDR?
A: There is the EU funded project STARS, that aims to provide this.

Q: How can we address the unmet educational need of healthcare professionals on complex clinical trials?

A: It will be important to find a platform that is commonly trusted. EFPIA is working on different scenarios to help move this forward.

Q: Will there be more development of master protocols, involving all aspects of therapy development (dose-finding, safety, efficacy), using the adaptive designs?

A: Particularly for cell- and gene products this is expected to happen. Also, the inclusion of RWD will be important and is a field of discussion. The complexity however will be great, and one will have to have to required experience on all aspects. This development will be guided by industry and academia. The EU CTR will not be a barrier on this aspect.

Session 4: LESSONS LEARNED FROM ACCELERATION IN PEDIATRIC ONCOLOGY PROGRAMS

c4c aims to enhance the development of Better Medicines for babies, children and young people through a pan-European clinical trial network

Heidrun Hildebrand (Bayer, DE)

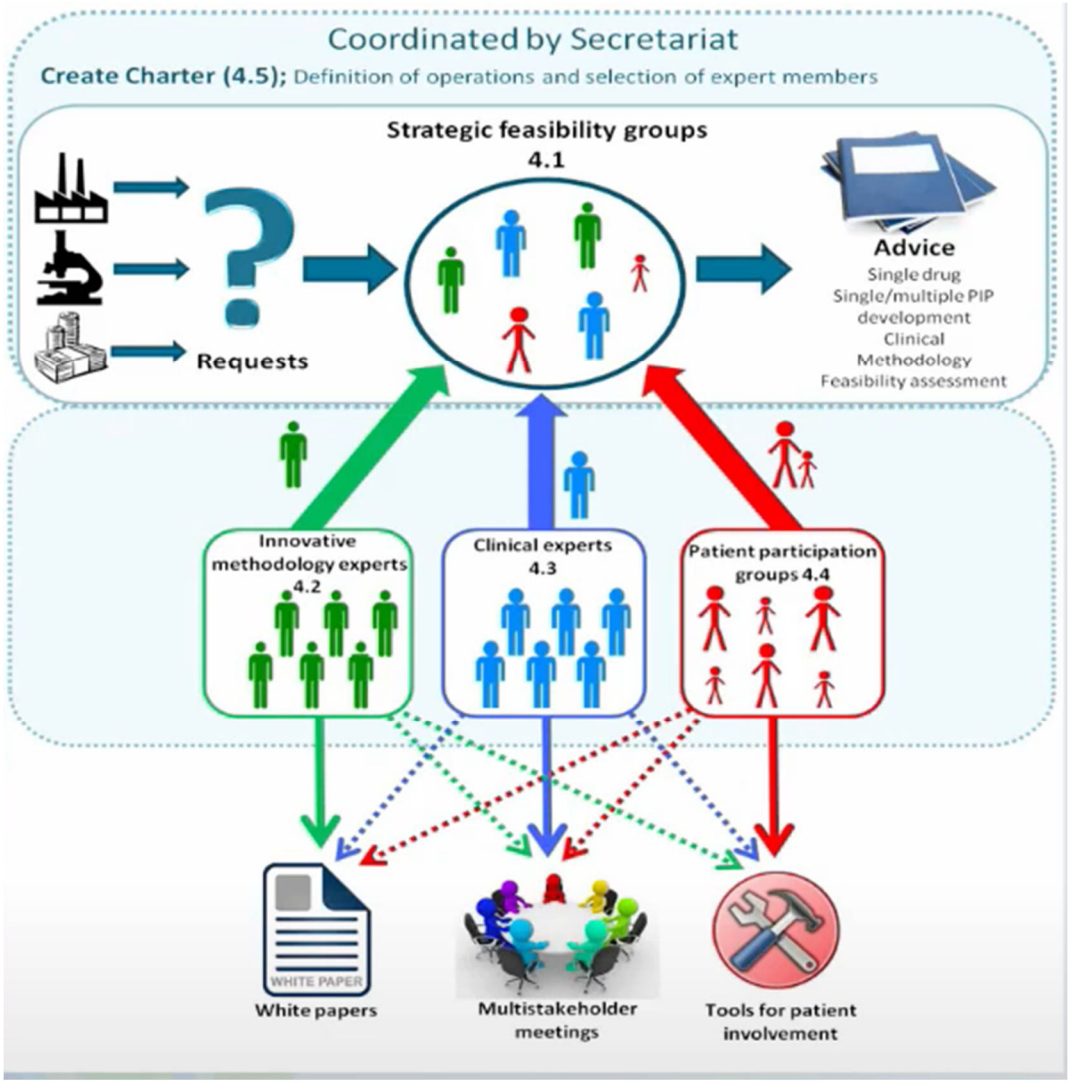
While there was progress in the number of clinical studies evaluating new medicines for children and the number of such new medicines available to children since the first implementation of the EU Pediatric Regulation, still 40% of Paediatric Investigation Plans are not completed as planned, and there is an increased competition between studies for shared resources.
This parallels the existing multifaceted challenge:

To address these challenges conect4children (c4c) was created in 2018 and is funded by the Innovative Medicines Initiative (IMI2), a public private partnership co-funded by the European Commission and the pharmaceutical industry. The vision of c4c is to enhance the development of Better Medicines for babies, children and young adults by creation of a pan-

European clinical trial network.
c4c aims to generate a sustainable infrastructure that optimizes the delivery of clinical trials in children through:

a) the implementation of a ***single point of contact*** for all sponsors, sites and investigators allowing access to trial sites across 21 European countries and more than 300 experts;
b) efficient implementation of trials, adopting consistent approaches, aligned ***quality standards*** and coordination of sites at national and international level;
c) high quality input into study design and preparation, through rigorous strategic and operational ***feasibility assessment.***
d) the promotion of ***innovative trial design*** and quantitative scientific methods;
e) collaboration with ***specialist and national networks***;
f) an education and training platform (***c4c Pediatric Medicine Academy***) to shape the future leaders of pediatric drug development;
g) the development of sustainable network beyond the IMI funding period.

c4c includes a Patients and Public Involvement team, that works closely with Patient / Parent Organisations and Young People Advisory Groups (YPAGs) to provide input on clinical trial design and study procedures. The Strategic Feasibility Advice includes 25 Expert Groups with over 300 registered experts in a wide range of disease areas.

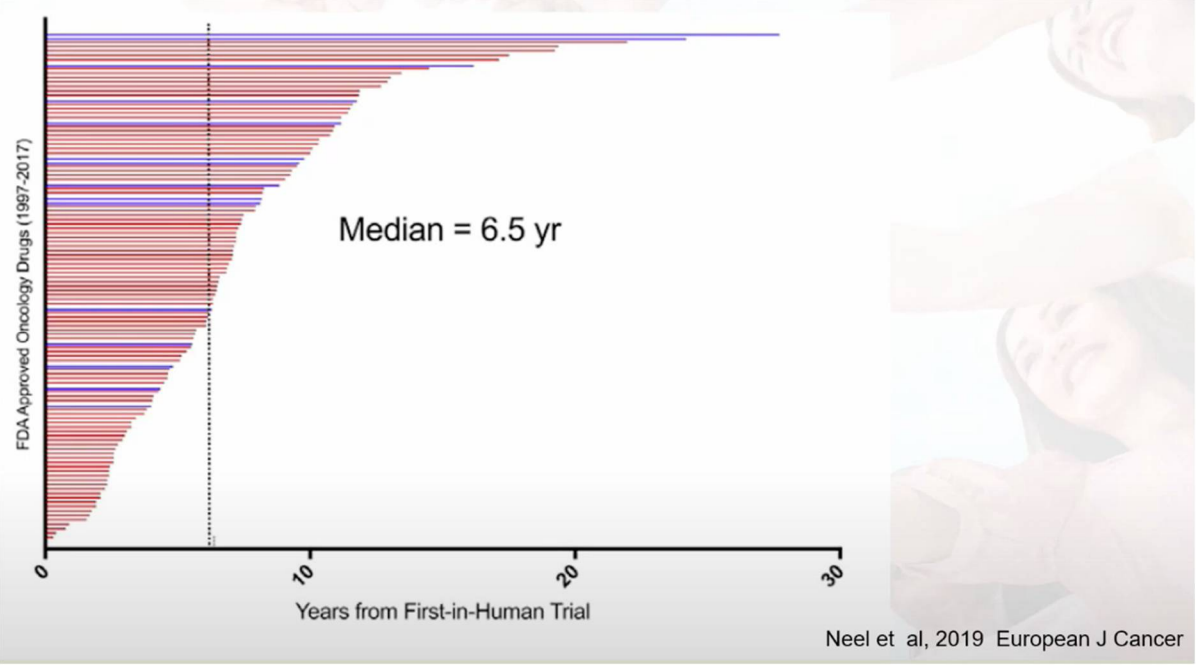


c4c now has 19 national hubs serving 21 countries across Europe, via about 250 clinical sites. The feasibility service has shown to be able to very rapidly (within 20 working days) identify appropriate trial sites for specific study purposes.
c4c work also supports data harmonization and standardization. c4c has developed a cross-cutting pediatric data dictionary, and, in close cooperation with CDISC is developing the first Pediatric Therapeutic Area User Guide (TAUG).

Lessons learned from Acceleration in Pediatric Oncology Programs

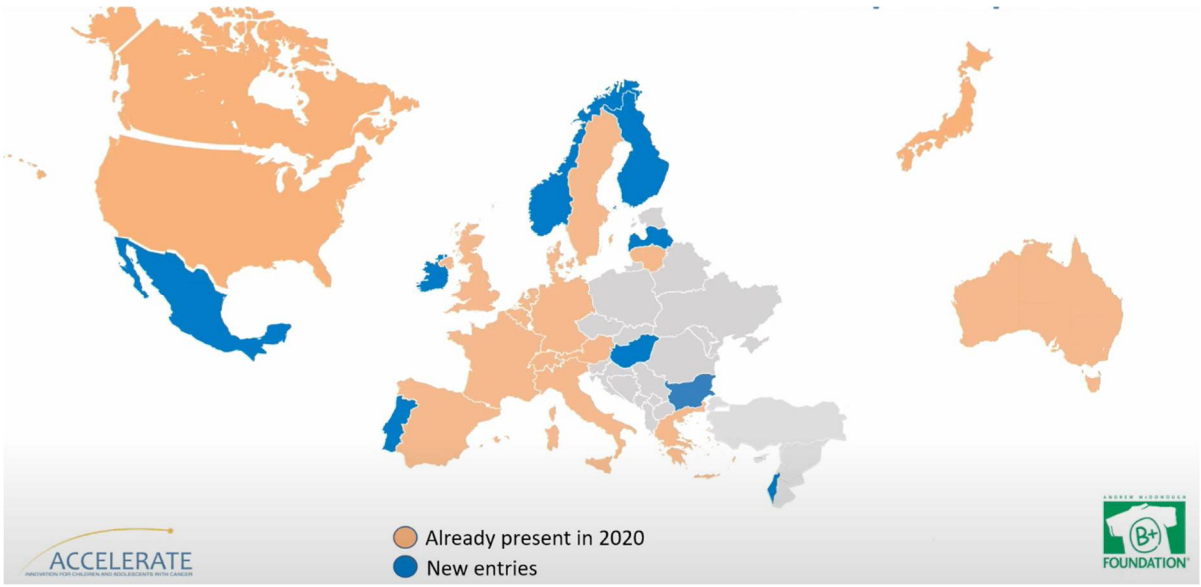
Peter Adamson (Sanofi, US)

Childhood cancers are a constellation of rare and ultra-rare diseases. Despite the progress made over the past decades, with 5-year overall survival rates exceeding 80%, cancer remains the leading cause of death from disease in children in high income countries. More than 50% of survivors experience serious long-term effects of therapy. Consequently, the 3 main challenges we face in pediatric oncology are to further improve cure rates, to diminish acute toxicity, and to minimize the risks for late effects.
Most of the advances made for children resulted from the intensification of cytotoxic therapy for certain cancers. However, children with cancer are not benefitting in timely way from today's scientific advances, despite European and US regulatory and legislative programs (such as the best pharmaceuticals for Children's ACT (BPCA), Pediatric Research Equity Act (PREA), Research to Accelerate Cures and Equity for Children Act (RACE) and the EMA Pediatric Investigational Plans (PIPs)) that provides requirements and incentives and have catalyzed discussion between stakeholders.
Yet, a recent study found that there still is a median of 6.5 years between the start of a first in human study and the start of a first in children study, an unacceptable delay.



Underlying the problem is that pediatric cancer drug development has evolved into a complex interplay of academic networks, pharmaceutical partners, and regulatory agencies. One example to highlight where the system has failed was with a novel drug for acute lymphoblastic leukemia (ALL). After showing the first relevant efficacy data in ALL in 2011, the drug was approved for adult patients with relapsed ALL in 2017, while the first pediatric studies only began that year. The incidence of ALL in children is similar to that in adults, and

thus this 6-year time lag in initiating of studies is difficult to justify and represents a **system failure** of the current landscape of pediatric cancer drug development.
In this system, industry does not want to invest significant resources in pediatric development until there is a reasonable likelihood of regulatory approval in adults, and in many circumstances seeks to minimize its financial investment in pediatric development.
Academia struggles as well. It is faced with hurdles to get drugs into the clinic faster, tends to want to do too complex trial designs, and could improve the efficiency of study development.
Regulatory agencies are face with requirements that are too granular or restrictive. One could ask itself if indeed pediatric oncology should have a greater regulatory burden than medical oncology has.
Yet progress has been made. The regulatory incentives and requirements have served as a major catalyst throughout industry to build pediatric capabilities; the full implementation of the US Race legislation that focuses on mechanism of action of drug is furthering the drive for improvements in capability. Cluster meetings between FDA and EMA are leading to better informed plans. PIPs & Pediatric Plans appear to be improving over time and perhaps most importantly childhood cancer drug development is on the radar screen of all stakeholders.
In 2015, the Accelerate platform was created. An international (global) multi-stakeholder organization to improve and accelerate new drug development for children and adolescents with cancer. It is a patient centric organisation aimed to solve problems.



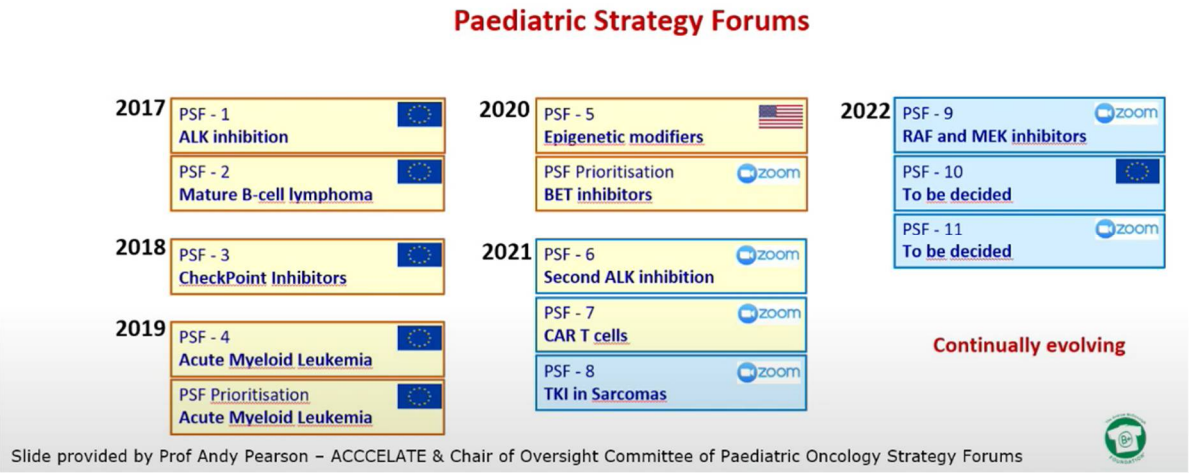
One function of such a platform is to develop Strategy Forums. In less than 5 years 13 such forums were held.
Yet, there is little evidence that we are shortening the timeline between first in human studies, and first in children's studies. And given the limitations of conducting multiple phases 3 trials in paediatric cancer, we need prioritization. And the community is also pleading for alternative avenues.

European perspective on collaborations to accelerate global pediatric oncology drug developments

Dominik Karres (EMA, DE)

To address the known challenges related to global development efforts in paediatric oncology conceptually, on content and operationally, there is a need for international cooperation and collaboration between all relevant stakeholders.

International multi-stakeholder interaction, exemplified by the ACCELERATE Paediatric Oncology Strategy Forums, organised in collaboration with the EMA and with participation of the FDA, have shown to be able to evaluate the current state of science, facilitate dialogue and discussions, and catalyse innovation and foster early, focused academia/ multi companies' collaborations.



Importantly these discussions facilitate identification of unmet medical needs and priorities of product developments based on science, able to support regulatory decision making of mandated development plans.

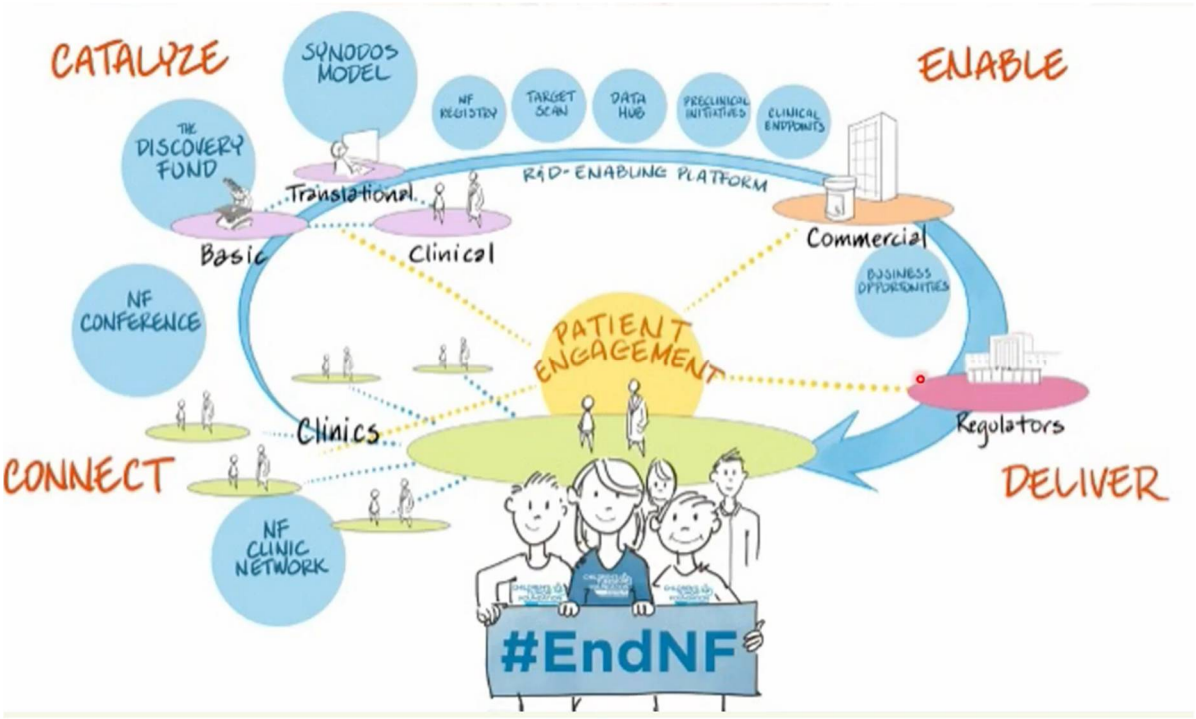
The changing regulatory landscape in paediatric oncology drug development in the US underlined the need for further strengthening of international regulatory collaboration. Recognizing that paediatric cancer drug development is a global endeavour, and using well established and efficient infrastructures, such as the monthly paediatric cluster calls involving EMA, FDA, TGA, PMDA, and HC, can support timely initiation of early-phase studies and a coordinated approach to later phase developments globally.
But this requires transparency by industry to regulators on paediatric plans (PIPs) beyond EU requirements and ideally simultaneous submissions of PIPs and iPSP to EMA and FDA respectively, taking into consideration reflections from the published generic common commentary on paediatric oncology development plans.

Research Foundation perspective: How nonprofits can be the changemakers

Annette Bakker, PhD (President of Children's Tumor Foundation US and Chair of CTF Europe)

The Children's Tumor Foundation Europe, (CTF-Europe) founded in 2018 by CTF (HQ in New York since 1978), is entirely focused on the acceleration of treatments for patients with Neurofibromatosis (NF).
NF is a family of rare genetic disorders that lead to tumors growing on nerves. The tumors can cause blindness, deafness, excruciating pain, mobility and disfigurement issues, to name a few. They can sometimes turn malignant and cause cancer. Since the NF tumor biology highly overlaps with cancer biology, CTF has been playing a unique role in the R&D ecosystem.
Beside investing in research, CTF and CTF-Europe have collaborated to develop a global R&D enabling platform to help pharma and biotech companies discover and develop drugs for the NF patients.

The platform is composed of an NF patient Registry, NF Clinic network, key opinion leader network, agreed clinical trial endpoints, preclinical test service, NF data portal, target-drug scanning service, biobank, to name a few.
Since 2019, CTF is IMI associated partner and co-leader of the NF work package within an IMI grant, EUPEARL, aimed at developing an innovative platform trial infrastructure for all manifestations of NF.
Moreover, CTF has a strong track record in developing multi-stakeholder communities (patients, researchers, clinicians, industry, policy makers and regulators) that drive research, expand knowledge, and advance NF care and support the NF community.



Our value proposition is to be the global connector as we are convinced that by connecting the unconnected, we can end NF faster, together.

Early experience of the RACE for Children Act: Accelerating initiation of pediatric investigations of novel cancer drugs

Gregory Reaman (FDA, US)

A few years ago, a FDA Advisory Committee Consensus statement stressed that pediatric oncology drug development should generally be coordinated with oncology drug development for adults, as part of an overall drug development plan. Yet, there is still room for improvement, with delays in initial pediatric evaluation. The impact of the legislative initiatives (PREA, BPCA) which support pediatric drug development, has been markedly less obvious in oncology than in other clinical areas.
Genomic/proteomic profiling of human cancers has resulted in highly specific targeted agents with major treatment effects in small subsets of patients. Which has given rise to precision medicine. In addition, there has been a tissue/histology agnostic drug development, that offers expanded opportunities for pediatric cancer.
The RACE for children act was incorporated as part of the FDA Reauthorization Act and went into full effect in the USA on August 18, 2020. It requires evaluations of new molecularly targeted drugs and biologics, also in pediatric cancers. Studies need to be described and agreed in an Initial Pediatric Study Plan (iPSP). There is a requirement for FDA to work with

NCI on a regular update of relevant targets, and a guidance was issued. There was also a requirement of early advice meetings, to clarify issues, scheduled and held within 30 days of the request. 28 Of such meetings have been held since, and there have been agreed iPSP on 26 NME's since August 2020.

Type of Review	Number
Agreed iPSPs for initial applications of NMEs	26
Products directed at non-relevant targets (Automatic Full Waivers)	8
Products directed at relevant molecular targets	18
Pediatric studies: 1 focused pediatric development; 11 proposed (1 extrapolation, 2 studies in progress)	12
Deferrals	7
Partial Waivers	6
Full Waivers*	6

*Same in Class

The past year has shown a significant increase in NME's involving pediatrics, which shows a promising trend for commitment to early pediatric studies.
Obviously global collaboration is essential. The recent AAADV-CDDF satellite meeting (Sept. 2021) focused on the need to develop such a global network, in this case for Pediatric Neuro-Oncology. There are obviously several challenges, but also opportunities, for instance provided by telemedicine tools.
The Accelerate platform also involves a multi-stakeholder based global platform

Panel discussion

Q: Molecularly targeted agents are selected for the program under the RACE act. Why are criteria such as high unmet need not reason for selection?
A: High unmet need spans the entirety of pediatric oncology. The legislation however required specific criteria.

Q: Will a waiver still be possible for the targeted drugs on the RACE list?
A: This is indeed the case for multiple same-in-class drugs, and if a product is not in a formulation for pediatric use, or in case of specific developmental toxicity that might require a partial waiver for specific age groups.

Q: What is the best approach to get joint EMA and FDA advice on pediatric study design and pediatric development outside of a parallel FDA/EMA scientific advice procedure.
A: If the question focuses on parallel discussions related to paediatric requirements (PIPs, iPSPs), sponsors can specifically request discussions at the paediatric cluster and issuing of a common commentary. The comments are not binding but represent

a coordinated approach. Agreement of discussion at the cluster and issuing a common commentary remains by FDA/EMA.

Q: How did c4c and CTF experience the issue of prioritization and how could one prevent that prioritization for pediatric development does not jeopardize development in adults?
A: The first c4c experience is outside of oncology, so the question is yet difficult to answer from their end. For CTF the priority will be to find drugs with long-term safety, so also appropriate for adults, since the diseases are life-long. Obviously, in case of development of tumors, the issue is somewhat different.

Q: Is there exchange among patient advocacy groups for rare conditions, such as CTF?
A: There is indeed a very collaborative community, with exchange of views.

Q: When, in the development of a drug, should pediatric associations be involved?
A: This will also depend on the type of association, and the knowledge they have built and activities they stimulate. If there is an R&D platform in an association, they should be involved from the beginning.

Q: Is it possible to present various options on trial designs to EMA, in order for the agency to help select the most optimal one?
A: If the aim is to get advice on novel trial designs, then this is indeed the case. If it is part of the discussion within the PIP to help identify how to best move a product forward towards the target population of highest unmet needs, the opportunity also exists.

Q: Is a master protocol conceivable that includes all age ranges, for diseases that affect all age ranges?
A: The simple answer is yes. Also, in case of tissue agnostic developments. For NF there is actually a protocol such as this in development in c4c.

Q: Precompetitive data-sharing has shown to be a challenge. CTF seems to have this activated. How was this achieved?
A: It took an enormous and difficult discussion. It started by a consortium, in which by contract, the contributors were basically forced to accept data-sharing. The experience obtained, smoothened the discussion, albeit there is still some resistance. More recently the International neonatal platform has started a similar initiative.

Q: How can we best achieve adequate pediatric prioritization?
A: Designing the phase 3 trial before having any early pediatric data, is not a good investment. Also, in most of pediatric oncology one can only perform 1 randomized phase 3 trial at the time. So, prioritization of choices, based on actual early pediatric data, makes more sense.

Q: The delay between first in human trials and first in children's trials, is a true concern. How could we work to close this gap?
A: The delay underscores that, while regulators have solved the awareness, they have not been able to solve the timelines that relates to it. It is clear that not all drugs are created equally, and the pediatric field has to decide on which drugs it wants to move quickly on, and which drugs are important but do not rise up to the highest level. In fact, this is a prioritization issue, in which it is important to get rid of the concern on parallel de-prioritization for the development of adults. It will have to become a multi-stakeholder data-driven global process.

Q: If an iPSP exist and PIP has not yet started, how high is the likelihood that EMA/PDCO will accept to treat the US iPSP as basis for the EU PIP without major change?

A: The submitted PIP will be discussed and assessed based on its own merits. The better recommendation is to submit simultaneously, in which case the likelihood ofan aligned development is higher.

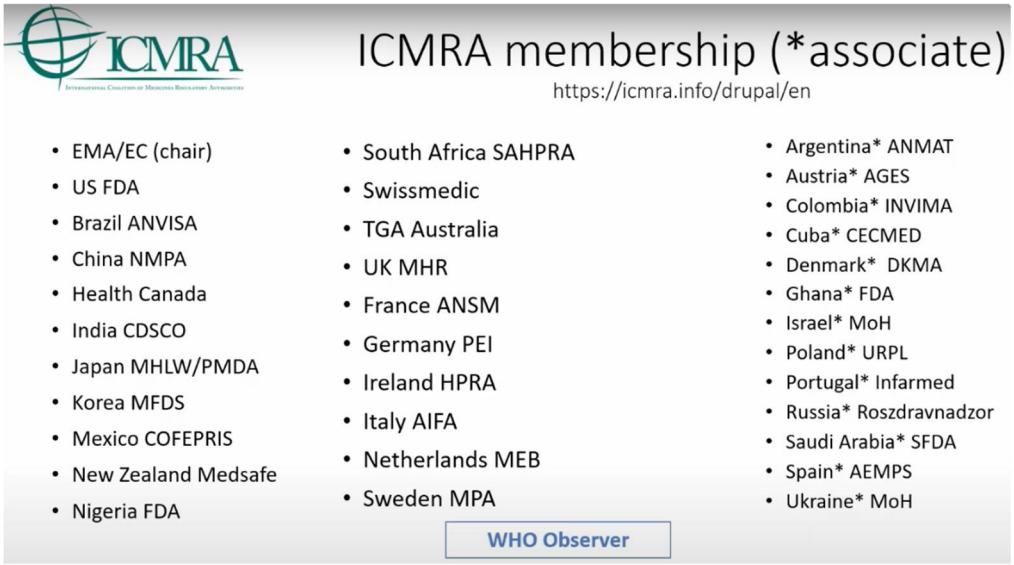
Session 5: COLLABORATION IN THE POST-COVID REGULATORY ENVIRONMENT

Boosting international regulatory collaboration

Agnes Saint-Raymond (Former EMA Head of International Affairs Division, FR)

When faced with nitrosamines contamination of some products in August 2018, EMA initiated international collaboration with FDA, Health Canada, Japan, WHO (and more). This was the model used to agree, harmonise and speed up the regulatory requirements for trials, vaccines and therapeutics against SARS-CoV2 as early as Feb 2020. But also, to share information, and share data.

Using the existing structure of the International Coalition of Medicines Regulatory Authorities (ICMRA), originally created in 2012 as an informal group, and active with 27 members but until 2020 poorly known, up to 34 regulatory authorities were able to work together in a flexible and informal setting. ICMRA is a strategic voluntary group of regulators from all regions, including WHO as an observer with the initial aim to identify common topics and common issues and common solutions.



The COVID-19 pandemic has further boosted this international regulatory collaboration. Together ICMRA quickly built consensus on criteria for vaccines and therapeutics development, Real-World Evidence and data sharing. The only topic on which there was no full consensus, was on the definitions of vaccine effectiveness, which in hindsight was a non-issue, since all initially assessed vaccines had a much higher effectiveness, than any of the regulators' bars required for approval.

The various ICMRA meetings held since, were chaired by a rotating chairmanship. All partners were considered as a valuable participant. All regulators contributed information and exchange in real time on progress of trials and therapeutics or vaccines development and reviews. They built consensus, and issued statements and recommendations, for example on

large, well-powered multinational trials, showing capacity to adapt and collaborate in such a crisis situation.
ICMRA is a regulators-only group, using agile approaches and deliverables. The main benefits were sharing information and data in real time while collaboration with patients, academics and industry took place in different settings.

In parallel, EMA set up the **OPEN** initiative in December 2019, allowing for the first time other non-EU regulators (Health Canada, Swissmedic, Japan MHLW/PMDA and TGA) and WHO to participate as peers in the scientific evaluation made by the Committee for Human Medicinal Products (CHMP). The idea was not to have one single assessment, but to learn from each other, and make use of each other's experience. This was impactful with for example, approvals by more than 100 countries within 2 weeks, using the WHO Emergency Use Listing based on the OPEN evaluation of one vaccine. OPEN will now be extended to non-COVID areas.
Other ways of collaboration that are explored are joint GMP inspections, including remote participation.
In contrast to project ORBIS, where the assessment of other countries is not leading for FDA, in OPEN that various opinions are weighed in the balance and accepted by all participants. In ACCESS, another initiative, a work-sharing approach is used whereby different parts of the assessment can be performed by selected authorities, all bringing in their findings into an overall assessment that is used by all.

The COVID-19 pandemic is responsible for major disruptions and serious consequences worldwide but has allowed to boost international regulatory collaboration to an unprecedented level. Lessons learned from this model can be used for oncology.

Project Orbis, experience and expansion

Angelo DeClaro (FDA, US)

Project Orbis is part of the Oncology Center of Excellence (OCE). The OCE fosters a unified interaction between the 3 FDA centers CBER, CDER and CDRH. OCE was established in 2017.
Since its establishment, OCE has supported approvals for 76 New Molecular Entities (NME), and 185 new indications, with an average review time of 6 months.
FDA has several expedited programs:

FDA Expedited Programs	Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
Program	Designation	Designation	Designation	Approval Pathway
Qualifying Criteria (all require condition to be serious)	• Nonclinical or clinical data demonstrate potential to address unmet need	• Preliminary clinical evidence demonstrates substantial improvement over available therapies	• If approved would result in significant improvement in safety or efficacy	• Demonstrates effect on endpoint reasonably likely to predict clinical benefit over available therapies
When to Submit	IND or after	Ideally no later than EOP2	With (s)BLA, (s)NDA	Discuss during development
Features	• Expedite development and review • Rolling review	• Intensive development guidance • Organizational commitment • Rolling review	• (6) 8 month vs. (10) 12 month review clock for regulatory action	• Approval based on effect on endpoint that is reasonably likely to predict clinical benefit

The oncology field (OCE) is a major user of the FDA expedited programs.
The various OCE review programs can be summarized as follows:

	Real-Time Oncology Review (RTOR)	Assessment Aid	Project Orbis
Start Date	February 2018	April 2018	May 2019
Objective	Increase efficiency of review through earlier submission of critical efficacy and safety data	Focus review on critical assessment, decrease administrative time	Facilitate faster patient access to innovative cancer therapies in participating countries
Key Elements	Early submission of datasets	Template with distinct sections for data, Applicant position and FDA Assessment	Direct collaboration between FDA and partner countries
Qualifying Criteria	Substantial improvement over available therapy Straightforward study designs and well-understood endpoints	Any oncology drug application	High impact and clinically significant applications

Project Orbis, the global collaborative review program launched in May 2019, with current participation of Australia, Brazil, Canada, Israel, Singapore, Switzerland, and the UK, requires confidentiality agreements with all other Orbis countries, application submission in the English language with sponsor authorization letter to share information across Orbis countries, and availability of the partners to participate in product-specific meetings as well as the quarterly general meetings.
FDA serves as primary coordinator of project Orbis. In the process each country retains full independence in regulatory decision and labeling negotiations.
Project Orbis has 3 types of projects, classified according to the submission gap to the FDA timeline:

		Sharing of AAid	Multi-country teleconferences	Concurrent review with FDA	Concurrent action with FDA
Type A	Regular Orbis	Yes	Yes	Yes	Yes
Type B	Modified Orbis	Yes	Yes	Possible	No
Type C	Orbis Written Report Only	Yes	No	No	No

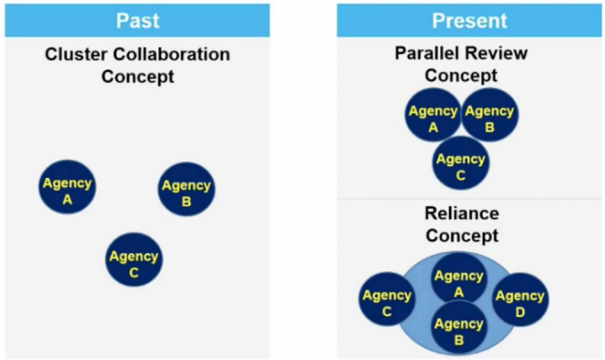
Project Orbis reported a 2-fold increase in application submissions in Year 2 of the program (with a total of 181 submissions) compared to Year 1. New molecular entities comprised 32% of the workload. Approximately one third of the FDA oncology workload is being referred for Project Orbis collaboration. In Year 2, the United Kingdom and Israel joined Project Orbis bringing in total the number of Orbis participants to 8 (U.S., Australia, Brazil, Canada, Israel, Singapore, Switzerland, UK).
Due to increased workload, Project Orbis teleconferences were changed to issue-based discussion format. In addition, the Assessment Aid is now shared with the partner countries at conclusion of the FDA review.
Challenges to future expansion to other countries include logistical considerations with coordination of multi-country teleconferences as well as ability of Sponsors to submit near-concurrent marketing applications.
Due to differences in regulatory framework with regards to companion diagnostics, the diagnostic test component of the marketing application has not been conducted under Project Orbis.
Finally, FDA continues to explore application of Project Orbis to oncology products with complex issues such as radiopharmaceuticals and advanced biological therapies.

Swissmedic: Current Status & Future Considerations on International Regulatory Collaborations

Ulrich Peter Rohr (Swissmedic, CH)

Historically, regulatory collaborations took place in clusters. In these “cluster collaboration” concepts, different agencies came together to exchange their perspectives and views on specific scientific topics. In the context of application review, the clusters were specific to disease areas. The first cluster started in 2004 and joined together the FDA and EMA on hemato-oncology.

In the present time, 2 additional collaboration concepts emerged: the “parallel review concept” and the “reliance concepts”.



In the "parallel review concept," different agencies work independently and in parallel on a drug application. They share their views in joint meetings during the ongoing assessment of the drug. Based on the same baseline of knowledge each agency takes an independent decision and action. Project Orbis, initiated by the FDA in 2019 is a poster child for the parallel review concept. It has the aim to reduce the submission gap between the FDA and smaller agencies and consequently allow faster access for patients to innovative cancer treatments.
The "reliance concept" is a work-sharing model between agencies. These decide amongst each other who will take the lead on the assessment for a given drug application. The particular leading agency will conduct the assessment and the others rely on or peer the assessment of the leading agency. Depending on the strategic setup of the collaboration, the other agencies may follow the recommendation of the lead agency.
The ACCESS consortium initiated in 2007 is an example of the reliance concept. A work-sharing model between 5 regulatory agencies of Australia, Canada, Singapore, Switzerland and the United Kingdom. For the various modules during submission, one agency is in the lead of a submission module and does the assessment for the other agencies. The other agencies serve as peers.

Swissmedic, the Swiss regulatory agency for medical products, participates in Project Orbis and in ACCESS. These international collaborations perfectly match with 2 of 7 strategic objectives of Swissmedic: 1). The acceleration of time-critical processes to meet the expectation of patients in order to have rapid access to innovative therapies, and 2). An work-sharing approaches.
Swissmedic joint Project Orbis in 2020. Project Orbis engagement led to a significant shortening of the submission gap between FDA and Swissmedic by 71%, and further enabled to reduce the assessment time of a dossier by 33%.

Swissmedic, as mentioned, is also part of ACCESS. ACCESS has various different work-streams. In the rather new "New Active Substances" working group, which was initiated in 2019, 17 dossiers have been entered and 7 have been completed until the end of 2021. The consortium has jointly set its own assessment times which are shorter than Swissmedic regular timeline for New Active Substances. For the completed dossiers the agreed timelines between ACCESS partners were met and the work sharing model has been an efficient and successful collaboration between the agencies.

In summary, the two presented international working modes are successful, fully met the strategic objectives of Swissmedic and will be continued in the future.

Panel discussion

Q: Is EMA-OPEN competing with Project Orbis?
A: It is complementary covering different therapeutic areas. All partners are peers. Having several peers involved, is a benefit to both projects.

Q: After marketing-authorization actual patient access is delayed in many countries. Is there any way in better harmonizing this?
A: Early involvement of HTA or equivalent in the process, will help. The assessment is actually a small part of the total development time. The rolling review option will also enable shortening of the development time.

Q: Do different opinions from different countries in the projects, create challenges?
A: Having multiple opinions actually enriches the review experience and is perceived as a positive.

Q: Where does (or should) the assessment of the appropriate study design and/or use of comparator for the ultimate study occur, in the total development time?
A: Orbis currently focusses on the marketing application stage. This could be extended to the pre-marketing area. That might, however, affect the timing of advice.

Q: Have approvals resulting from Project Orbis, been the same in respect to indication, wording in the label etc., in the countries involved?
A: The concordance rate on type of action, and approval, is approximately 95%. But there can be differences in indication and label-wording.

Q: How has industry perceived the Project Orbis process?
A: Swissmedic has a regulatory-round table with industry representatives. There is a great interest into Orbis and a lot of attention, also from academia.

Q: Does the requirement of a companion diagnostic pose any challenge for either of the processes?
A: At European level this was not the case, given the EMA remit. In Orbis, this is part of the discussion on the clinical trial design. Given the fact that partner countries can have different labels after approval, it is difficult to harmonize this up-front.

Q: Are patients involved as stakeholders in any of the discussed processes?
A: The programs themselves are basically also a resultant of listening to the patient voice to get more rapid access to good novel therapies. How best to involve patients' needs to be balanced against the inevitable potential of a biased opinion, and yet the patient voice is crucial and needs to be integrated in the total drug life cycle. We can learn from the COVID experience on agility. In addition, we should welcome the variation in patient views, to get the best total scope.

Q: Looking forward a decade, what kind of review would be the best for patients globally? Also given the fact that, due to fragmentation of populations with improved diagnostics, we have to do global clinical trials, and the introduction of AI tools.
A: AI needs to be used; it is already available. We have to learn, but there is no way we can avoid it.
We need to try and break the confidentiality problem among regulators, in the interest of public health. Obviously, quality of data is important, and there may be different levels in

different parts of the world. In addition, priorities in Low-Income Countries may be totally different from those in high-income countries.

Given the results of deep-sequencing, and the fact that a single tumor may have different drivers, it will be a challenge to optimally design studies that apply for any individual patient.

Key take-home messages

- Clinical trial design will have to be adapted to the needs of both marketing approval assessment and health technology assessment (HTA)
- Clinical trials will increasingly be patient-centric, and organized in a decentral way.
- Multi-stakeholder collaboration proofs to be key in accelerating drug development
- The COVID-19 pandemic has strengthened international regulatory collaboration