universität wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

Challenges and Opportunities of Oncological Drug Development in Paediatrics

verfasst von / submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2021 / Vienna 2021

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	UA 066 606
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Masterstudium Drug Discovery and Development
Betreut von / Supervisor:	Mag. Dr. Majid-Reza Kamyar, M.Sc.

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Acknowledgements

Firstly, I would like to thank my supervisor Mag. Dr. Majid-Reza Kamyar, M.Sc for his endless efforts as well as the ZAK Pharma team, especially Mag. Barbara Markhardt and Ms. Ingrid Hochmayer, M.Sc. for their support throughout the whole process. Apart from that I want to emphasize the support of my family. Five years of studies would not have been possible without my parents, Ursula and Robert, as well as my two beloved siblings, Judith and Bernhard. Furthermore, I would like to mention Marc Berger, Gertraud Hofer, Robert Hofer and Rosemarie Krydl and thank them for their encouragement all the way through.

Abstract

Preclinical and clinical development in the paediatric field has led to improvements in cancer therapy. However, most of these therapies have simply been taken from trials on the adult population while children are commonly excluded from these processes. This has resulted in extensive ‘’off-label’’ use of drugs without any clinical evidence from trials on children even though the major differences in drug disposition and action and the heterogeneity of childhood cancers are well known. Recent advances have recognized the importance of including children in controlled clinical trials and tailoring therapies to their special needs. This paper identifies the major hurdles to overcome in order to develop promising new agents for childhood cancer, the current gaps in research and development, and the steps forward to improve the process. The paper identified issues regarding regulations focusing on the indication, rather on the mode of action, a lack of consideration of age groups and paediatric formulations, small sample sizes, missing parallel developments, educational work that needs to be done and the urgency of handling paediatric drug development on a global rather than on a regional level. Last but not least, the paper makes a new proposal to capitalize on today’s science to bring new treatments to children’s cancers by making use of juvenile animal models, M&S, innovative trial designs and by revising current legislations based on their impact.

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List of Abbreviations

Fig.	Figure
PD	Pharmacodynamics
PK	Pharmacokinetics
ADME	Absorption, Distribution, Metabolism, Excretion
EU	European Union
USA	United States of America
PIP	Paediatric Investigational Plan
PSP	Paediatric Study Plan
MTD	Maximum Tolerable Dose
EMA	European Medicines Agency
IRB	Independent Review Board
ICF	Informed Consent Form
PREA	Paediatric Research Equity Act
BPCA	Best Pharmaceuticals for Children Act
Off-label	Use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration
M&S	Modelling and Simulation
MOA	Mode of Action

1. Introduction

"It is important to get results from experiments but the most important is the process in getting these results." (Dr. Ahmad Nizam, 2020)

Cancer is still one of the leading causes of death in children worldwide. One out of 285 children will be diagnosed with cancer before even reaching their 20th birthday. On a global level, 400 000 children are diagnosed with cancer annually, whereas 44% of these will die due to cancer before being diagnosed. In 2020, it is estimated that 181 000 children with cancer will remain undiagnosed. The estimated 5 year survival of children up to 19 years old with cancer is estimated to be 79.8% in high-income countries, whereas it is estimated to be only 7.4% in low-income countries. (American Childhood Cancer Organization, 2020) Therefore, paediatric cancers and their at least temporary remissions have been of utmost importance for decades already. However, only in the last decade advances have been made in clinical research in order to improve the outcomes for diseases such as childhood cancers. The rate of overall survival has been significantly improved by combining different doses and agents of chemotherapy with conventional methods such as radiotherapy and surgery. (Fig. 1) Roughly 80 per cent of children are prone to live longer when being diagnosed with cancer early on in developed countries due to the broader access to clinical trials in most of the industrialized countries worldwide. (Pritchard-Jones & Valsecchi, 2011)

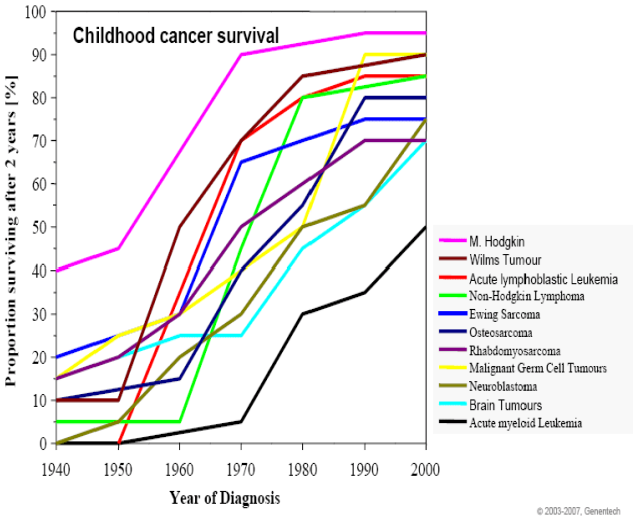

Fig. 1: Survival rates of children with cancer have been increasing over the past years. (survivor vision, 2021)

However, with every obstacle surmounted new burdens arise: How can researchers improve survival rates further and how can researchers and clinicians demonstrate comparable survival rates of a drug with a reduced side effect profile compared to agents already on the market? Apart from that childhood cancers are of extreme complexity with several molecular signatures involved, ultimately leading to the fact that there is no such thing as a miracle cure even for the same type of childhood cancer with it being such a heterogeneous disease and group of people considering the age groups. As a result, there are only small sample sizes available.

Therefore, the recruitment of new subjects is of utmost importance in order to be able to conduct clinical trials within a reasonable amount of time and retrieve valuable results in terms of efficacy and safety.

Moreover, factors such as language, culture and therapeutic preferences play a major role. Underdeveloped countries are still facing issues in regards to access to clinical trials and survival rates in paediatric cancers are significantly lower. Most of the time clinical trials in children differ from studies conducted in adults in regards to timing and also strategies employed. Minors are a fragile group of people. Prior experiences made in clinical trials and the therefore gained information as well as interactions between stakeholders, involving family members, the regulatory authorities, clinicians and the industry itself have made paediatric clinical research unique. (Pritchard-Jones & Valsecchi, 2011)

However, it needs to be considered that children need to be included into the testing of medications for their own safety and well-being. Several tragedies occurred in the paediatric population highlighting this urge. For example, in the year 1939 a new liquid formulation of sulphanilamide was invented for children who were not able to swallow the drug in tablet form. However, the solvent used in this case was later revealed to act as a toxin causing a mortality of 30% in children. Another famous example is the Thalidomide tragedy: It was marketed to treat nausea in pregnant women in the 1950s ultimately resulting in major birth defects and malformations depending on the developmental stage of the child when Thalidomide exposure took place. (Gaitonde, et al., 2020)

These are just a few examples that highlight the major risks children have been exposed to for several years and the urge to study medications in a proper way before using and approving them in children to ultimately guarantee their efficacy and safety in this fragile population by implementing proper requirements whilst also considering ethical issues. As a result, regulations have been implemented. (Gaitonde, et al., 2020)

In 2006 the European Paediatric Regulation was invented which required companies to develop a paediatric investigational plan (PIP) for drugs meant for the use by children in order to be able to receive marketing authorization. Furthermore, rules as well as incentives and rewards were implemented for the development of drugs for children such as the paediatric-use marketing authorization (PUMA).

In the USA, the PREA and BPCA were enacted in the years of 2003 and 2002 to rule the evaluation of drugs used on minors as well as to increase clinical trials in children and drug labelling in the paediatric population. (Gaitonde, et al., 2020)

To promote and conduct research, specifically in the paediatric population, is extremely crucial since children significantly differ from adults in factors such as genetics, aetiology, progression, comorbidities and prognosis. Furthermore, it is highly important to consider that childhood is a significant period of life where a lot of changes occur in a small time frame not only on a physiological but also on a physical level. These systems progress continuously, with changes occurring in pharmacokinetics such as motility and function of the gastrointestinal system, body size and composition, transporter activities and enzymes of the metabolism and renal function. In the first weeks to months of life these changes happen in a highly dynamic and nonlinear manner and ultimately slow down later. These changes in development potentially affect factors such as drug disposition which can even vary between neonates, children, adolescents and adults resulting in the paediatric population being a highly heterogeneous group to study. (Gaitonde, et al., 2020)

Therefore, often only small populations are affected which results in the issue of low enrolment rates. As a result, the interest of pharmaceutical companies is also relatively low as they are risking a low return of investment. Moreover, ethical issues arise very frequently in the field of paediatric research as well as other challenges which appear solely due to the progressive, life-limiting and threatening nature of childhood cancers. (Gaitonde, et al., 2020)

Nevertheless, several drugs that are not specifically approved for children are routinely administered to children by physicians ‘’off-label’’, even though it is well known that the paediatric population responds to drugs in a different manner than adults affecting not only efficacy but also safety. (Intini, et al., 2019) Most of the off-label use happens in children aged between 1 to 13 years, whereas there is a peak in children from 6 to 13. It mainly affects dose, duration as well as the indication. (Fig.2) (Hammer, 2021)

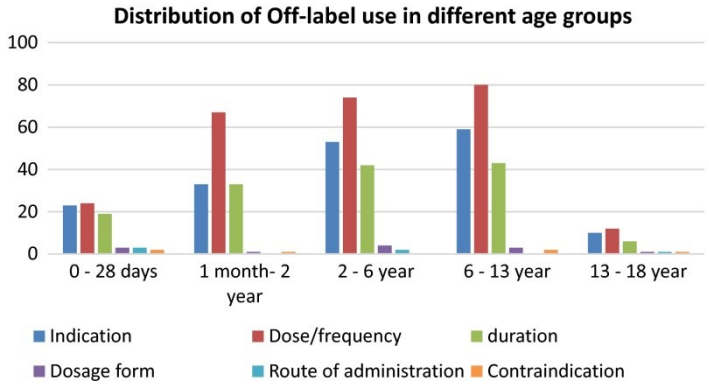

Fig. 2: Distribution of off-label use in different age groups in paediatrics. (Hammer, 2021)

Major differences in absorption, distribution, metabolism and excretion of drugs, known as ADME, can be observed. These differences in drug responses can manifest themselves anatomically, on the physiological level and in development. Furthermore, there is a major lack of information about younger children and neonates. Moreover, cancers in children are considered as highly rare diseases due to their uniqueness. Children have not been properly included in studies for several years due to their fragility which ultimately resulted in them being defined as ‘’Therapeutic Orphans’’ in the year 1969 by Shirkey. (Gaitonde, et al., 2020)

Taking the major differences between adults and children into consideration it is clear that drugs should also be tested specifically on children in controlled clinical trials. Drug discovery and development starts with target identification (discovery phase), moves on to preclinical development, which will include *in vitro* and *in vivo* research (preclinical development), to ultimately testing new therapies in the target paediatric population (clinical development) until the drugs are finally brought to the market after they received marketing authorization. The uniqueness of this population should be considered starting in the very first phase of discovery. (Gaitonde, et al., 2020)

Lack of medicines tailored to children can therefore be traced back to ethical, practical as well as economic reasons. As discussed in this thesis, differences existing in cancers between children and adults as well as the different physiologies need to be addressed. Furthermore, the different developmental stages and the potential late effects of cancer treatments will be highlighted.

Moreover, a brief insight will be given into the regulatory framework for paediatric drug development over the course of time to highlight potential lacks of regulations and to assess the usefulness of policies.

Preclinical Safety Assessment as well as the design of clinical trials in childhood cancer will be addressed and the importance of juvenile animal models will be critically assessed as well. Furthermore, a small digression about outcome measures and the importance of juvenile biomarkers will be given. Moreover, the informed consent process as well as ethical issues that arise will be presented in a separate chapter and novel strategies to improve paediatric clinical trial design will be proposed.

A balance will need to be found between avoiding exposing children to unnecessary risks and obtaining enough safety and efficacy data to prevent their endangerment and extensive off-label use of medications. Therefore, this thesis aims to increase the understanding of the drug development process in children by highlighting challenges and opportunities to invent and repurpose medicines tailored to children with the ultimate goal of finding ways to make paediatric drug research more efficient timewise and economically and ultimately more safe and available for children affected by cancer.

2. Differences between adult and children cancer causes and late effects

Children are under paediatric care until the age of 16 to 18 depending on the region. There are five major classifications: preterm new-born infants, term new-born infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years), adolescents (12 to 16-18 years). (EMA, 2021) Often clinical trials are first performed on adults before the drugs are tested for paediatric indications. Childhood specific cancers develop from embryonal cells and are able to multiply rapidly. (Adamson, et al., 2016) The most common cancer types in children in the western societies are: Leukaemia (30.9%), malignancies of the central nervous system (23.7%) and lymphomas (14.1%) (Fig.3). (Kinderkrebsinfo, 2020) These cancers derive from failed control mechanisms resulting in cells reproducing in an uncontrolled way ultimately causing cancer. Cancers such as neuroblastoma (nervous system), retinoblastoma (retina), rhabdomyosarcoma (muscle), medulloblastoma (brain) and Wilms tumour (kidney) usually occur in the first four years of life. (Adamson, et al., 2016)

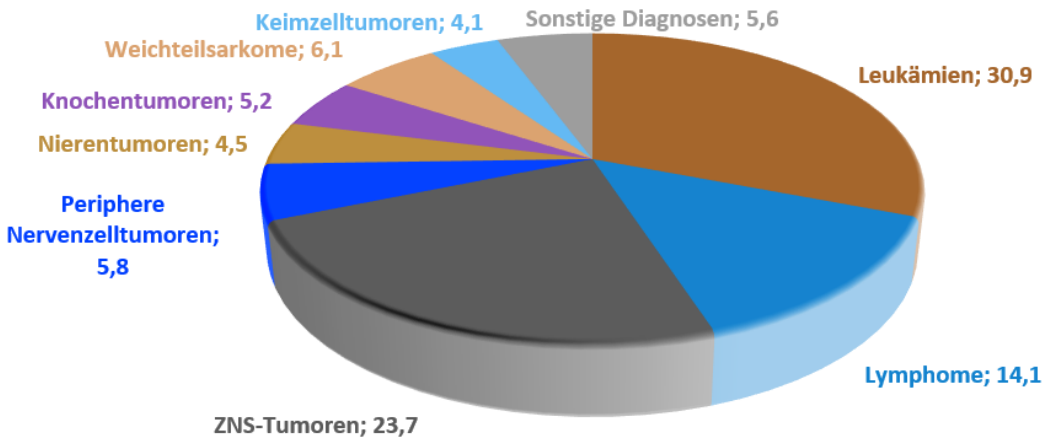

Fig. 3: Most common cancer types in children in %. (Children's Cancer Web, 2003)

Adult cancers usually arise from changes in cells as part of the tissues of the inner and outer surfaces of the body. Reasons might be environmental influences such as tobacco smoke as well as internal exposures such as hormones. (Adamson, et al., 2016)

Types of cancer seen in both the paediatric population as well as adults are acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), Hodgkin and non-Hodgkin lymphoma, thyroid cancer, melanoma, and glioblastoma (an aggressive type of brain tumour).

Even though they carry the same name they usually represent different biological subtypes revealing different genetic fingerprints such as in adult B-cell non-Hodgkin lymphomas, glioblastomas and ALL (Fig. 4). Even in cancers that are similar between children and adults, different therapy approaches may need to be applied as the juvenile body is still developing and due to differences in pharmacokinetics. Furthermore, the prognoses, the late effects, as well as the responses to a certain type of treatment might differ significantly between adults and children for the same cancer diagnosis.

Said characteristics also depend on whether the cancer is caused by mutations in certain genes, inherited genes or epigenetics. (Adamson, et al., 2016)

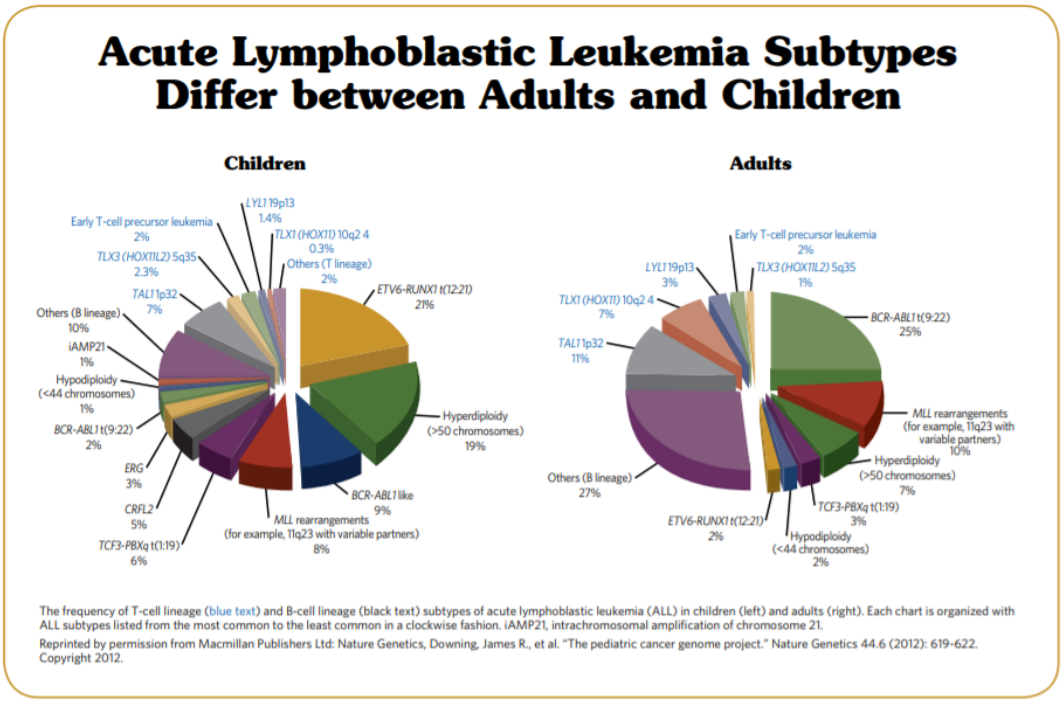

Fig. 4: Different genetic subtypes of ALL in children compared to adults. (Adamson, et al., 2016)

2.1 Genetics

Genetic cancers are caused by different mutations in the genes. The majority of cancers in adults result from genetic changes (roughly 90-95%). Mutations can occur due to internal or external factors as well as randomly. Changes in the ALK gene for example are implicated in certain cancers such as childhood anaplastic large cell lymphoma (ALCL), some subtypes of neuroblastoma as well as non-small cell lung cancer. Due to different mutations cancer can be subdivided into its genetic characteristics. Medullablastoma can be divided into 4 major groups due to its specific mutations. These subtypes may vary in terms of prognosis and treatment approaches. Genes frequently mutated in childhood cancers are evolving and continuously being discovered. (Adamson, et al., 2016)

2.2 Inherited Genes

Only about 5 to 10% of adult cancers are caused by inherited genes from their parents. All of the cells will subsequently exhibit the problematic mutation. Certain inherited mutations can result in a lifelong risk of certain cancers.

Inherited cancers do not occur more frequently in the paediatric population: Roughly 1 to 10% of cancers in children are caused by inherited mutated genes. However, in some specific cancers such as retinoblastoma roughly 35 to 45% are caused by inherited mutations. On the other side, in cancers affecting the brain and spinal cord this percentage is extremely low: only about 2% can be traced back to inherited genes. (Adamson, et al., 2016)

2.3 Epigenetics

Generally, paediatric cancers reveal fewer mutations compared to adult cancers, however these mutations can still vary significantly between individuals. Epigenetic causes are found more frequently in childhood cancers than in adult cancers. Epigenetic changes describe modifications in gene expression as opposed to alterations of the genetic code itself. Studies revealed that for paediatric high-grade gliomas, osteosarcomas and T-cell ALL tumours roughly 50% show epigenetic mutations.

This is crucial information as depending on that knowledge different treatment approaches may be applied. (Adamson, et al., 2016)

2.4 Late effects of cancer treatment in children

Efficacy has risen in the last years; however increasing efficacy often comes along with severe side effects and especially late effects. Roughly 25% of paediatric cancer survivors will suffer from late effects which are considered severe or even life-threatening as a result of their cancer treatment such as secondary cancers, damage of the heart or lungs, infertility, chronic hepatitis, growth and developmental deficiencies, impaired cognitive functions as well as psycho-social impacts. (American Childhood Cancer Organization, 2020) Due to the fact that children affected by cancer are being treated while they are still developing and growing, the late effects are especially substantial as opposed to the effects on adults. The resulting effects can range from skeletal maturation, deprived intellectuality, sexual maturation to defects in linear growth. Above all the effects on organ function can be rather severe compared to adults due to the ongoing development. Deficiencies generated by cancer treatment may appear later on in life. Recent advances have also revealed an increased frailty resulting in heightened mortality, rated 13.1% in females and 2.7% in males that have undergone treatment for cancer in their childhood.

This clinical syndrome related to aging appeared only in individuals who were 30 years older to the same extent, therefore revealing a highly expedited aging process. The treatment age of the children is exceptionally crucial as it majorly correlates with the potential health burdens that might be seen later in the patient's ongoing life. Depending on the developmental stage the paediatric population might suffer from neurocognitive injury, growth delay, musculoskeletal malfunctions and organ dysfunction deriving from the increased toxicity to immature organ systems and tissues. The latter is especially the case for infants. While in older children the same late effect can occur, they might also endure emotional deficits and problems with social maturation. This highly depends on their cognitive maturity as well as the psychosocial support they receive later on. Moreover, treating juveniles during puberty may result in an elevated risk of Hodgkin disease in females and young girls. Furthermore, exposure to higher radiation doses reveals a 4-35% increased risk of breast cancer two decades later. (Adamson, et al., 2016)

3. Paediatric cancer treatment

Paediatric cancers are relatively rare compared to adult cancers: in the United States 12 500 children are diagnosed, whereas 1.6 million adults are diagnosed with cancers annually in the United States. In the European Union 35 000 children are diagnosed with cancer annually, whereas 6000 patients die from it consequently. Nevertheless, promising survival rates of up to 80% can be achieved, due to agents already on the market and also products being researched through clinical trials. Nevertheless, despite all the efforts made, childhood cancer is still one of the leading causes of death in minors worldwide. The most commonly used agents are listed in the table below. (Fig. 5) (Mulberg, et al., 2013)

Drug	**Disease**
Antimetabolites	
Antifolates	
Methotrexate	ALL
Purine Analogues	
Mercaptopurine	ALL
Thioguanine	ALL, AML
Fludarabine	ALL, AML
Pyrimidine analogues	
Cytarabine	ALL, AML
Flurouaracil	HCC, HBL, Carcinomas
Clofarabine	ALL
Nelarabine	ALL (T-cell)
Tubulin binding agents	
Vinca alkaloids	
Busulfan regimens	CML, SCT conditioning
Temozolomide	Brain
Procarbazine	Brain, HD
Dacarbazine	NBL, STS, HD
Topoisomerase I inhibitors	
Topotecan S	TS, NBL
Irinotecan	STS
Topoisomerase II Inhibitors	
Epipodophyllotoxins	
Etoposide	Brain, STS, ESFT, NBL, ALL,
Antitumor antibiotics	
Doxorubicin	ALL, AML, most solid tumors
Daunorubicin	ALL, AML, NHL
Mitoxantrone	ALL, AML, NHL
Idarubicin	ALL, AML, NHL

Vincristine	ALL, HD, NHL, WT, STS	Bleomycin	Germ cell, HD,
Vinblastine	HD, Germ cell, Histiocytosis	Dactinomycin	WT, STS, ESFT
Alkylating agents		**Steroid hormones**	
Nitrogen mustards		Prednisone	ALL
Mustargen	HD	Prednisolone	ALL
Melphalan	SCT Conditioning regimens	Dexamethasone	ALL
Cyclophosphamide	NHL, ALL, STS, WT, NBL, ESFT	**Asparaginase preparations**	
Ifosfamide	OS, ESFT, Germ cell, STS	E. coli L-asparaginase	ALL, NHL
Nitrosoureas		PEG-asparaginase	ALL, NHL
Carmustine	(BCNU) HD, NHL	Erwinia asparaginase	ALL, NHL
Lomustine	(CCNU) Brain	**Other agents (Targeted)**	
Platinum compounds		All-trans-retinoic acid	AML(M5)
Cisplatin	OS, NBL, Brain, Germ cell	Imatinib	CML, ALL (Phþ)
Carboplatin	Brain, NBL, STS, ESFT, Germcell		

Fig. 5: Most commonly used agents in childhood cancers, adapted from Mulberg et al., 2013. (Mulberg, et al., 2013)

Nonetheless, most of the agents mentioned in Figure 5 are not officially approved for the use on the paediatric population and are therefore used off-label. The compounds used are usually highly cytotoxic agents that are rather non-selective, ultimately causing a large range of side effects and resulting in steep dose-response curves. They are usually administered at the maximum tolerated dose of the patients and several agents need to be combined in order to retrieve decent treatment outcomes. Cancers such as Leukaemia can be treated solely using chemotherapeutic agents, whereas solid tumours are treated by rather using chemotherapy combined with surgery or radiotherapy. Chemotherapeutic agents have achieved the best results for solid tumours when being used adjuvantly, as they are able to prevent metastatic spreading as well as local recurrence.

Despite all, the treatment outcomes as well as the intensity of therapy for solid tumours still highly rely on the stage of the disease as well as the tumour histology. The treatment outcomes for cancers such as acute lymphoblastic leukaemia (ALL) still exceed those of solid tumours up to this point. However, treatment options usually come at the cost of ongoing and late toxicities caused by chemotherapies. Some approaches are aiming to lower potential toxicities whilst risking an increased chance of treatment failure in order to achieve a better cost-benefit calculation. The paediatric cancer survival in common childhood cancers over the years, up until 2005, has risen constantly for most cancer types as it is captured in the figure below. (Fig. 6) (Mulberg, et al., 2013)

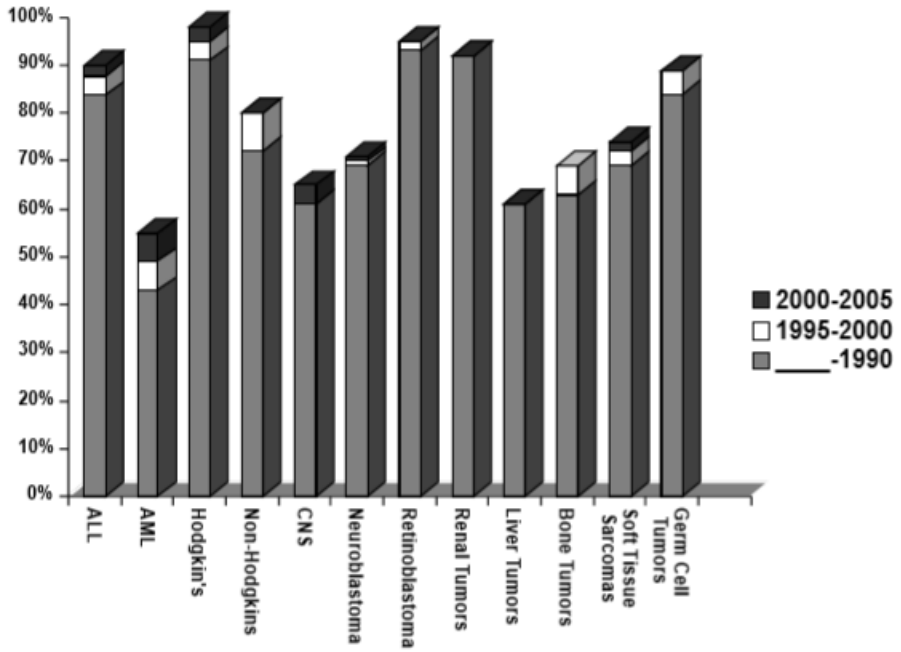

Fig. 6: Paediatric cancer survival in common childhood cancers over the years up until the year 2005. (Mulberg, et al., 2013)

Major improvements in survival rates could be achieved; nevertheless the intensification of the chemotherapy is still limited due to unreasonable occurring toxicities. Generally speaking, the number of new curative agents has decreased recently whereas new anti-cancer agents, with a lower-range side effect profile, are highly demanded. Recent advances have revealed agents prone to inhibit proteins and their several pathways directly and therefore interfering with oncogenesis, as well as other approaches focussing on containing the malignant phenotype of the cancer cells. However, most of these approaches are mainly targeting conventional adult cancer types, only a few have been applied to childhood cancers such as Imatinib. There are several reasons for this result such as the lacking identification and also validation of molecular targets in paediatric tumours. (Mulberg, et al., 2013)

Repurposing drugs, initially applied for adult cancers, for paediatric cancers raises several issues: the signal transduction pathways utilized by these drugs are very crucial in children's development and growth. Therefore, the influence of these agents on minors can result in severe long-term as well as short-term effects and risks. In conclusion, drug discovery and research should highly focus on new study designs and also endpoints, to find alternative ways of cancer treatment as the risk benefit profile urgently needs to be improved. (Mulberg, et al., 2013)

4. Major contributions to therapy development in the field of paediatric oncology over the course of time

Paediatric oncology drug development initially focused on finding agents for all common childhood cancers. The first milestone was set when the efficacy of Aminopterin (Fig. 7) was proven in the year 1947 by Farber et al. Aminopterin, a folate antagonist, was probably the pioneer of all following anti-cancer drugs developed. (Mulberg, et al., 2013)

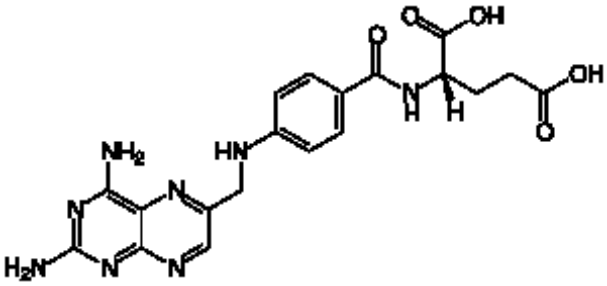

Fig. 7: The structure of Aminopterin, which was one of the first anti-cancer drugs being developed. (Wikipedia, 2021)

Only years later the use of multi-agents was observed to enhance remissions. Moreover, the average survival rate was improved from eight months to a year by adding purine antagonists to folate antagonists. Ultimately the advantages of combining multi-agents became obvious as they were targeting different modes of actions. Initially the use started to treat acute leukaemia and then expanded to all childhood cancers. These affected children finally presented some of the first ever juvenile subjects in clinical trials, ultimately impacting the fundamentals of chemotherapy. Later, in the year of 1948, Burchenal et al. revealed the positive effects of nitrogen mustard compounds used to treat leukaemia in rodents. Years later a sub-division of the NIH (National Institute of Health) supported anti leukaemia cancer research in the paediatric population by offering sponsorship for finding new agents. In the following years several children hospitals as well as university paediatric programs were incorporated by Burchenal and his study group formed in 1955. (Mulberg, et al., 2013)

In the year 1959 five multi-agent chemotherapy protocols had already been implemented at 12 institutions with an overall number of 542 children enrolled. In the year 1964 already 1485 people of the paediatric population had been accrued. The therapeutic field had finally expanded from AL to solid tumours, glioblastoma as well as neuroblastoma. Significant efforts were made by these groups known as the ‘’Children’s Cancer Group Development of Drugs for Paediatric Cancers’’. (Mulberg, et al., 2013)

Later several other groups were formed, significantly impacting paediatric oncology research, such as the Paediatric Oncology Group (POG) and the Chemotherapy Cooperative Group (CCG) which later merged with the National Wilms Tumour Study Group and the Intergroup Rhabdomyosarcoma Study Group to form the Children's Oncology Group (COG) in the year of 2000.

The historical development of the different paediatric cancer research groups is important in order to understand the close relationship between children cancer care and clinical research, which finally was one of the reasons why the cure rates for cancer in the paediatric population have risen from 10% to almost 80%. (Mulberg, et al., 2013)

These member institutions are still fundamental as almost 90% of children affected by cancer under the age of 15 are cared for at these institutions and 60% of those eligible to participate in clinical trials are enrolled in the latter. Infants and children below the age of five even achieve an enrolment rate of almost 90%, therefore contributing significantly in the development of new anti-cancer agents for children. (Mulberg, et al., 2013) However, patients suffering from hematologic cancers have only started to be represented in the past years unlike paediatric patients suffering from solid and central nervous system tumours. (Faulk, et al., 2020)

5. Regulatory framework for paediatric drug development over the course of time

5.1 Paediatric policies and legislative changes

Research has been lacking since the 1960s on the paediatric population. It finally moved forward when two new programs were introduced: the increased scientific understanding of drug disposition in children as well as the evolvement of the regulatory guidelines and legislations resulting in the laws present nowadays. The foundation of clinical pharmacology in children was set by Sumner J. Yaffe, MD by intensively studying drug disposition in the paediatric population in close collaboration with computational science group led by Gerhard Levy, MD. (Turner, et al., 2014)

Initially it was thought that including paediatric subjects in clinical trials was unethical, however in 1974 the AAP released the “General Guidelines for the Evaluation of Drugs to be Approved for Use During Pregnancy and for Treatment of Infants and Children.” by the FDA. As a result the FDA released the “General Considerations for the Clinical Evaluation of Drugs in Infants and Children.” which was supposed to be a general guidance for the pharmaceutical industry in the year 1977. (Turner, et al., 2014)

5.1.1 US labelling requirement

In 1979 the regulation for labelling prescription drugs for children was introduced to address the need for information about drugs used on children. This was one of the first benchmarks for the inclusion of paediatric subjects since rarely any studies had actually been conducted on the paediatric population by then. (Turner, et al., 2014)

5.1.2 US Paediatric Labelling Rule

Later, in 1994, the Paediatric Labelling Rule, which was a FDA regulation, demanded that pharmaceutical companies submit literature as well as data revealing additional information on the use of the agent on the paediatric population. Nonetheless this regulation proved to be not as effective compared to others. (Knutsen, et al., 2008)

5.1.3 US FDA Modernization Act

In the year 1997 a subsection for paediatric drug development studies was introduced in the FDA Modernization Act. Paediatric patent exclusivity was stated for a time period of six months for the sponsor when conducting paediatric studies requested by the FDA. This provided economic incentives for sponsors that studied their drugs in the paediatric population. (Turner, et al., 2014)

5.1.4 US Best Pharmaceuticals for Children Act

The mentioned incentive was then renewed in the year 2002 as the BPCA, also known as the Best Pharmaceuticals for Children Act, which authorized the FDA to request studies of approved and unapproved indications for children. The BPCA also results in the advantage of marketing exclusivity for sponsors, as long as the clinical studies on the paediatric population is outlined in a written voluntary request, issued by the FDA, first. The sponsor can then accept or decline this written request as it is solely voluntary.

These written requests are usually issued by the FDA when there is a public health benefit, safety data from animal studies or adult clinical trials already exist or if information is needed, for example about certain age groups. (Knutsen, et al., 2008)

On the FDAs website a published list of active moieties, that were approved, and additionally the sponsor the written request was issued for can be found. (Knutsen, et al., 2008)

5.1.5 US Paediatric Research Equity Act

In 2003 the PREA, also known as the Paediatric Research Equity Act, was introduced by the FDA which authorized the FDA to demand a paediatric assessment of already approved drugs and biologics used for specific indications. Consequently, the PREA and also the BPCA are crucial to guarantee the inclusion of paediatric subjects in most drug development processes. Both had a 5-year expiration period, but were renewed in the year 2007 and made permanent in 2012 under the ‘’Safety and Innovation Act’’ (FDASIA) by the FDA. (Burckart, 2019) (Bucci-Rechtweg, 2017) Title III or the Paediatric Medical Device Safety and Improvement Act, Title IV or Paediatric Research Equity Act (PREA) and Title V or the Best Pharmaceuticals for Children Act (BPCA) all confirmed the importance of appropriate development of products intended for use on children. (Turner, 2014) As opposed to the BPCA, in the PREA studies are required and their summaries will not be available as an open source. (Fig. 8) (Knutsen, et al., 2008)

On the 18th of August 2017 an amendment was added to PREA named the ‘’Research to Accelerate Cure and Equity’’, also known as RACE. This amendment states the requirement of early evaluations for oncology products used on children if the drug target is considered to be relevant for childhood cancer. (Ye, et al., 2020)

Moreover FDARA, the Food and Drug Administration Reauthorization Act, was introduced in 2017. This act describes that if a molecular drug target is involved in the development of one or more types of cancer in children, the orphan designation is not valid anymore. (Ye, et al., 2020)

BPCA	PREA
Studies are voluntary	Studies are required
Includes orphan drugs	Orphan drugs and indications are designated exempt
Covers drugs only	Covers biologics and drugs
Studies encompass whole moiety (active part)	Studies limited to drug/indication under development
Summaries posted on FDA website	Summaries not made available publicly

Fig. 8: BPCA versus PREA. (Knutsen, et al., 2008)

5.1.6 US and EU paediatric study plan

Furthermore, the PREA calls for a PSP (=paediatric study plan) for drugs that are about to be introduced to the market, if a new active pharmaceutical ingredient, a new formulation, a new indication or a new dosing regimen or route of administration is involved. (Turner, et al., 2014)

A major difference between the EU and the US is the timing of the paediatric development plan. Whereas in the EU the so called PIP (=paediatric investigation plan) should be agreed on by the end of Phase I, the PSP in the US is agreed on by the end of Phase II.

It can be determined if a PIP is necessary judged by the intended indication, mode of action, the unmet paediatric need and a classification of diseases relevant and recurrent in both the adult and paediatric population. The advantages of early paediatric development plans usually outweigh the disadvantages of potential deferrals of PIPs. (Turner, et al., 2014)

A globally standardized paediatric study plan would generally benefit the overall development of drugs. (Turner, et al., 2014)

5.1.7 EU paediatric regulation

The paediatric regulation was introduced in 2006 to ensure the development of drugs for minor children. Its ultimate aim is to guarantee that medicines used on the paediatric population are of high quality, researched in an ethical way, properly authorised and that essential information for medicines for the use on children is available. Furthermore it aims to not interfere with and cause unnecessary clinical studies conducted on children as well as a delay in drug authorizations for adults. (EMA, 2020) These newly authorized drugs will then be protected by the Supplementary Protection Certificate (SPC). The SPC intends to compensate for the time elapsed between patent application and market authorization and can result, if the requirements stated in the PIP have been fulfilled, in a 6 month patent protection prolongation. Generally, the paediatric regulation has resulted in an increased number of paediatric products, indications or posologies. (Fig. 9) (Bucci-Rechtweg, 2017)

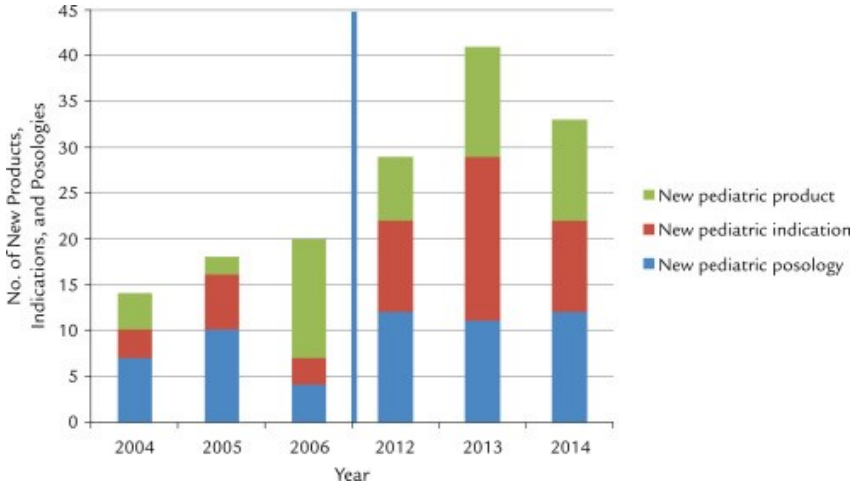

Fig. 9: Impact of the paediatric regulation on the number of paediatric products, indications and posologies 3 years before and after its implementation. (Bucci-Rechtweg, 2017)

5.1.8 EU Paediatric Use Marketing Authorization

Several off-label products are commonly used in the paediatric population; however they have not been adequately tested on this specific group of people. Therefore, PUMA, also known as the Paediatric Use Marketing Authorization, has been invented to regulate the development of off-label products in children and neonates. The development of PUMA needs to follow a paediatric study plan (PIP). However, PUMA is not used in the US legislation but solely in the EU. The Paediatric Use Marketing Authorization ensures a data protection of 10 years. (Turner, 2014)

Nevertheless, a 5 year follow-up report published by the European Commission in 2013 revealed that the implementation of PUMA was not capable of outweighing the economic risks for manufacturers. (Bucci-Rechtweg, 2017)

5.1.9 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Another highly crucial regulatory measure was when the ICH , also known as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, harmonised the regulatory requirements for pharmaceuticals between the EU, the US and Japan in the year 2000 by introducing the guideline ICH E11. The ultimate aims were to drive paediatric drug development forward on an international level in a timely manner, to outline critical aspects in drug development in the paediatric population and to introduce approaches for safely, efficiently and ethically studied drugs. Nevertheless, this guideline is not mandatory and solely a recommendation and is therefore not impacting submissions for trials in the paediatric population.

Between 1996 and 2005 almost 44%, of the 243 medicines authorised by EMA, could have been used on the paediatric population but had no experimental data available. This outlines the urge for the amount of work that still has to be done in this context and how crucial the before mentioned regulations are, as the ICH E11 cannot stand alone. (Turner, et al., 2014)

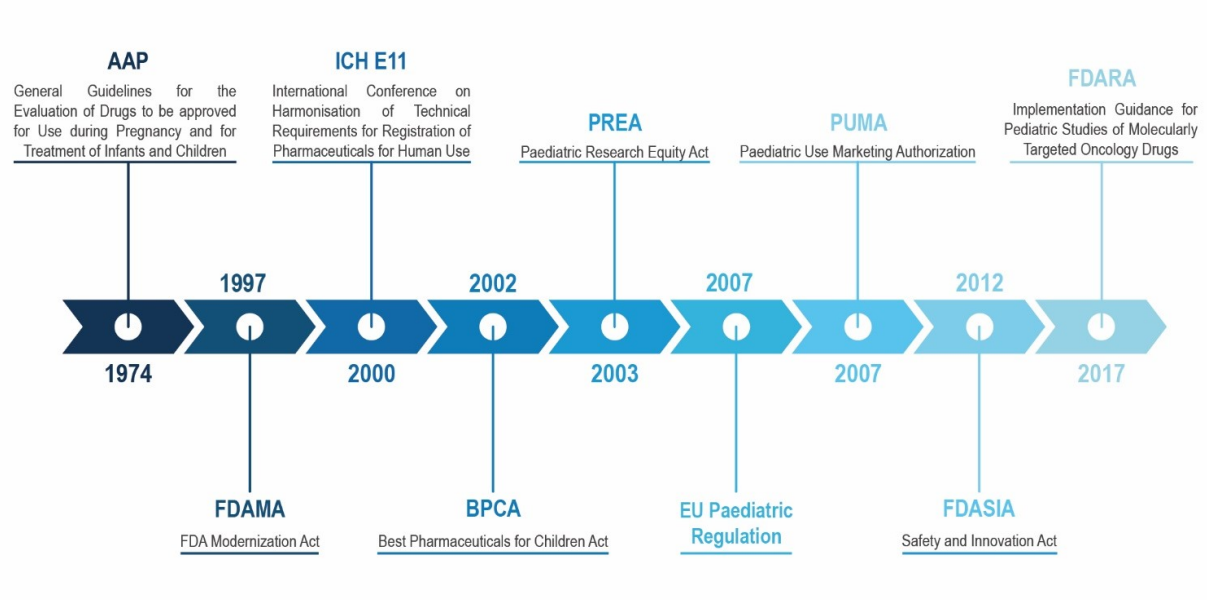

Fig. 10: Benchmarks for paediatric drug development in the US and EU.

5.2 General considerations

In general paediatric drug development is based on the principles of reward: prolonged patient protection as mentioned above, a prolonged duration of the SPC (Supplementary Protection Certificate) as well as an additional 2 years of exclusive marketing for orphan medicinal products. However, the industry has to receive the confirmation of the PDCO (Paediatric Committee) for the paediatric development and there needs to be a mutual agreement on the paediatric development plan as well. This is required in advance of marketing authorization. The paediatric development needs to cover all paediatric age ranges: from the neonatal period to adolescence, therefore covering all age specific conditions. Furthermore, a formulation adapted to the age of the final recipient is required. Sometimes studies are first conducted on adults and studies on children are deferred to later. The highest priority is always to ensure that studies are only conducted on the paediatric population when it is considered to be ethical and safe. Nevertheless, in some cases the benefit of not deferring studies in children outweighs the disadvantages. If studies are deferred, the PIP still has to include the paediatric population and timelines.

In some cases, such as in Parkinson's disease, a PIP is not required, as it is a disease that does not occur in children. (Turner, et al., 2014)

5.3 Impact of paediatric policies and legislative changes on paediatric cancer drug development

The ultimate aim of the introduced policies as well as legislative changes was to fill the gap between adult drug development and paediatrics' unique needs. However, the significant differences in terms of biology, aetiology and the different treatment goals between paediatric and adult cancers have still not been considered properly. PREA for example intends that the new compound is used for the same indication as in adults in the paediatric population; therefore it can rarely be applied as most of the new therapies for cancer are used in adult populations for indications that do not occur in both populations, such as breast and lung carcinomas. The only approved cancer treatment that came out under PREA, and actually included paediatric labelling, was imatinib mesylate. (Bucci-Rechtweg, 2017)

The BPCA, on the other hand, considers the fact that most of the paediatric cancers are actually unique to this population. Even though the FDA can grant a written report to a sponsor if the paediatric indication differs from the intended use in adults, so far only 20 products had an update in their labels to include data for the use in paediatric cancers. (Bucci-Rechtweg, 2017)

However, after the impact of identification of cellular mechanism, genetic alterations and deletions on cancer´s growth and progression in children was highlighted in 2016 in the Report to Congress (resulted in FDASIA) by the FDA, the number of written requests increased in that year.(Fig. 11) (Bucci-Rechtweg, 2017)

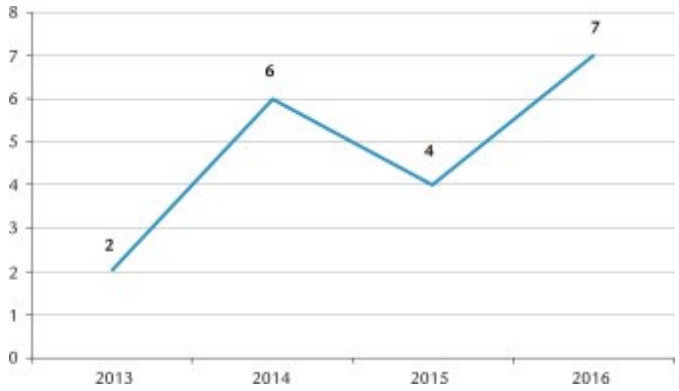

Fig. 11: Amount of written requests issued by FDA for paediatric cancers before and after the invention of FDASIA. (Bucci-Rechtweg, 2017)

After the PIP was invented in 2015, 83 PIPS for 68 different therapeutic approaches for cancer have been implemented with the sponsors as well as the EMEA.

Of the plans implemented, 41 PIPs were meant to directly address cancers in the paediatric population. Moreover, 24 PIPs (on a voluntary basis) have been agreed on for solid malignant tumours in paediatric patients.

Seven PIPs have been conducted so far, whereas five recently developed anticancer drugs and six new anticancer indications have been authorized in the EU. (Bucci-Rechtweg, 2017)

5.4 Obstacles caused by the Paediatric Regulatory Framework

Off-label use as well as unlicensed use of drugs in children is incredibly common. About 50% of the drugs used on the paediatric population are drugs with no randomized controlled trial data when compared to drugs used in adults. The first legislative changes to facilitate the conduction of more trials on children were made by the US in 1997 with the FDA Modernization Act and in the EU in 2007 with the EU Paediatric Regulation. These legislations introduced the need for safety and efficacy data for all age groups in children and that all product labels actually provided data from research in children. Furthermore, the PIP was introduced to facilitate testing in children starting at the point in time of drug application submission. This resulted in an increase of clinical research conducted on children. (Fig. 12) (Joseph, et al., 2013)

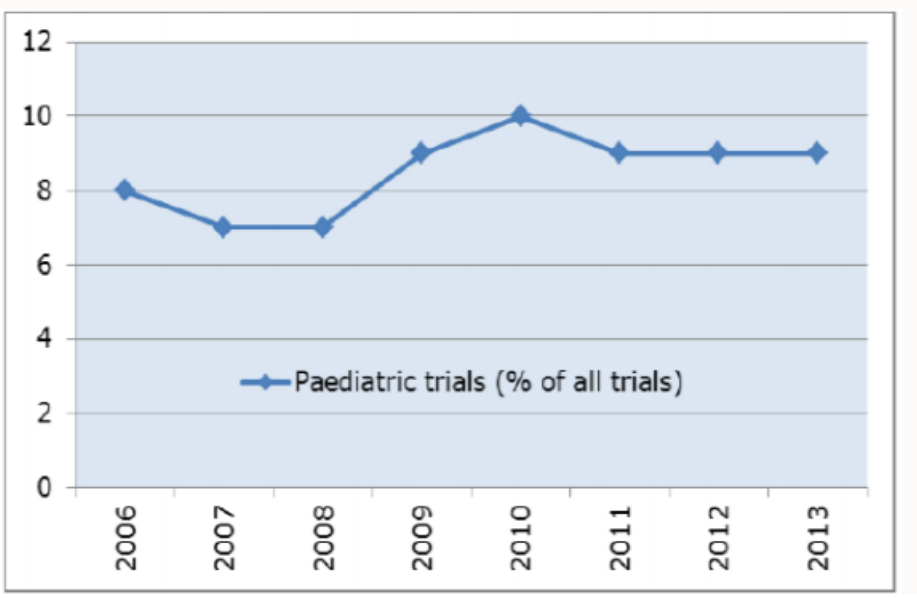

Fig. 12: Clinical trials conducted in paediatrics in the years 2006 to 2013. (Zepp, 2015)

In the year 2008 49 000 minors were already enrolled and exclusivity was recognized for 150 drugs and 842 studies for new indications of already existing drugs were permitted. Furthermore, a study analysing the impact of the PIP submitted to the European Medicines Agency (EMA) in the years 2007 and 2009 revealed an increase of paediatric trials of 1.2% (from 8.2% in 2007 to 9.4% in 2009), with an increase in paediatric oncology studies to roughly 11%.

The slight increase can be explained by the industries' interest to perform expensive clinical research for drugs with a high expected market value, which are mainly drugs commonly prescribed in adults as children cancers are relatively rare diseases affecting small populations. (Joseph, et al., 2013)

This results in the fact that drugs that are essential for children and frequently used off-label still require research. Potential causes might be that incentives that should enhance off-patent drug development are small and happen on a voluntary basis. Furthermore public funding is rather insufficient. (Joseph, et al., 2013)

There is a major need for specific labelling instructions. Both the US as well as the EU provide several frameworks which are enhancing and facilitating labelling of compounds used in children.

In the US mainly the BPCA encourages research to facilitate proper labelling by providing market exclusivity. The PUMA is the legislation of the EU which facilitates research in drugs that are regularly being used off-patent on children. Performing PUMA required studies results in 10 years of label protection of the drug in a paediatric indication for the sponsor.

Of course, agents that have obtained paediatric labelling are of major interest for the industry as they will have the reward of exclusivity extension and their image of achieving paediatric obligations. However, whilst the BPCA as well as the PREA have resulted in an overall increase of paediatric labelling of drugs, the actual number of drugs being used off-label in paediatric oncology has risen. (Fig. 13) Also PUMA has proven to be inefficient and needs to be revised based on its low impact. (Kern, 2009)

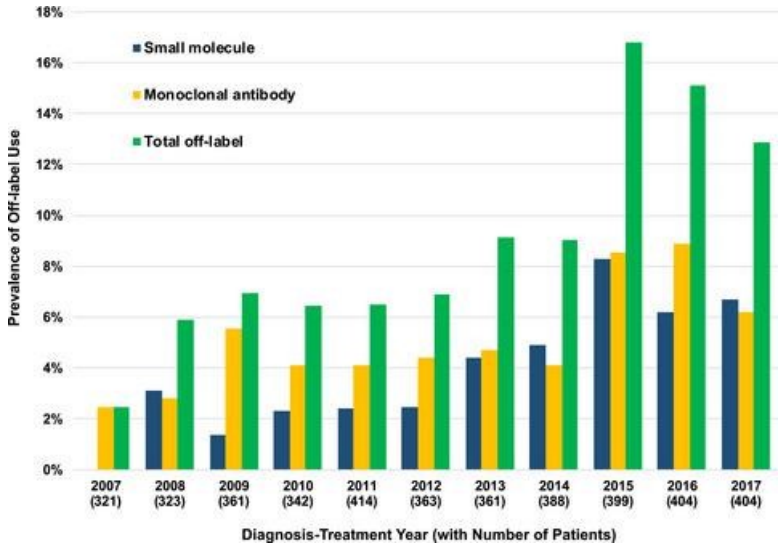

Fig. 13: Off-label use of anticancer therapies over the past years. (Lim, et al., 2020)

Interestingly, this distribution can be found in the increased amount of drugs being used in adults. (Boots, 2007) Therefore the question arises whether these programs do indeed result in safer drugs for children or solely result in economic advantages for the manufacturers. (Kern, 2009)

Of course these efforts still resulted in some positive contributions too even though they were rather limited compared to what was expected. Nevertheless, efforts could be made by prioritising the most crucial questions that arise in paediatric drug development. In order to evaluate the highest priority questions an interactive exchange and cooperation is required between the industry and clinical researchers such as physicians and health authorities. This will result in narrowing down promising candidates and not just studying a drug because it is new. More generalized knowledge could be acquired in terms of pharmacology and dose finding in children compared to adults which could ultimately result in more efficient drugs. (Kern, 2009)

Another major issue is that pharmaceutical companies show little to no interest for establishing already in the US and EU approved drugs in other countries.

Here, again, there is a major lack of incentives as well as demanding costs for registering new compounds or amending the labels of already existing medicines with new data from the paediatric population. All of these pitfalls required global harmonized processes and an intense networking and a willingness to collaborate between the industry, physicians, researchers and the government to make sure medicines are provided regarding health care needs and not economic benefits. Additionally other countries should facilitate drug development as well as the transferring process of already approved drugs from the US and EU, by introducing incentives and adopting regulations. (Joseph, et al., 2013)

6. Preclinical safety assessment in juvenile drug development

Usually only a few compounds will reach the preclinical stage of the discovery process. Preclinical assessments are performed either *in vitro* or *in vivo* and aim to retrieve insights into valuable pharmacodynamic and pharmacokinetic properties. *In vivo* factors such as biodistribution, efficacy and toxicity will be evaluated. (Gaitonde, et al., 2020) The reason why preclinical safety assessments are performed is to see if a compound used in the paediatric population might interfere with juvenile development and growth and is therefore used to identify toxicities related to the stage of development and age. Also potential differences between juvenile and mature animals can be assessed in regards to sensitivity to a drug as it can affect drug disposition as well as action. Reasons for this issue are differences in metabolism such as Phase I and Phase II activities of enzymes due to different rates of maturation, differences in receptor function and expression, organ functional capacities and growth rates as well as changes in adsorptive surfaces in the gastrointestinal tract. (U.S. Department of Health and Human Services & CDER, 2006) Furthermore, differences in biliary function as well as renal clearance affecting the elimination of compounds can be observed. (Gaitonde, et al., 2020) Usually, these tests mainly focus on the active ingredient; however it can also be crucial to assess the whole formulation which will be used in clinical testing as the inactive moieties may also interfere with distribution, bioavailability as well as pharmacodynamics. Generally, the local as well as the systemic effects should be analysed in regards to development and growth in the paediatric population to retrieve insights into pharmacological as well as potential toxicological features. Animal studies on young animals are especially crucial if toxicity in the targeted organ has been observed in postnatally developing tissues. Of course the timing and extent of preclinical safety assessment studies highly relies on whether an already approved product is intended to be used on children or if a completely new molecular entity is intended to be used on the paediatric population due to a different extent of safety concerns. Juvenile animal models can be compared to the paediatric population in humans as they reveal comparable developmental characteristics and are therefore considered as appropriate to evaluate effects of a drug on this specific population. The focus has shifted from not only performing nonclinical safety testing in the prenatal population but also in the postnatal population. (U.S. Department of Health and Human Services & CDER, 2006)

Especially neonatal and juvenile toxicity studies in animals have become more and more common due to regulations in the US as well as the EU. The ultimate aim of these is to find whether certain toxicities might arise and are linked to immature individuals and their development.

Furthermore, it can be seen if toxicities arise already at a lower dosage and which developmental stages might be of higher sensitivity in terms of toxicity. This is usually performed in addition to the standard toxicity studies that are being conducted on mature animals and can be used to support drug administration for human beings above the age of 12. These complex studies need to be adapted and designed individually for each case in regards to species, dose selection as well as dose timing and duration. Some practical considerations can be seen in Figure 14 below. (Mulberg, et al., 2013)

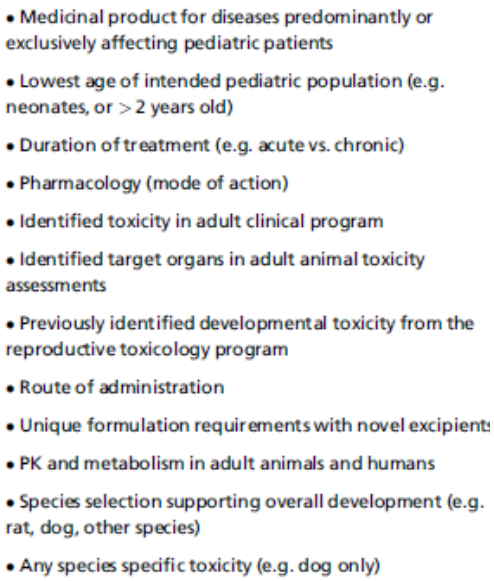

Fig. 14: Practical considerations for preclinical safety assessment for drugs which are intended to be used on children. (Mulberg, et al., 2013)

It is crucial to compare age categories of human beings with animal models, as it is done in Figure 15 for central nervous system and reproductive organ development as there are several organ systems that are especially exposed to drug toxicities as they undergo significant postnatal development: firstly the brain (development ongoing until adolescence), the kidneys (adult levels reached at approximately 1 year), the lungs (major alveolar maturation occurs in the first 2 years of life), the immune system (adult levels of IgG and IgA antibody responses are not achieved until about 5 and 12 years of age for the latter), the reproductive system (maturation until adolescence), the skeletal system (maturation until 25 to 30 years) as well as the gastrointestinal system (mature at 1 year of age approximately). Postnatal development has effects on factors such as bioavailability, clearance and the biotransformation of drugs. (U.S. Department of Health and Human Services & CDER, 2006)

PK as well as PD profiles can be affected depending on the developmental stage resulting in changes of the drug target such as expression, affinity or activity affecting the drug's response. This needs to be considered especially with younger children such as neonates as these represent a target group vulnerable to toxicities as well as adverse events by altering and adapting drug therapeutic windows. (Gaitonde, et al., 2020)

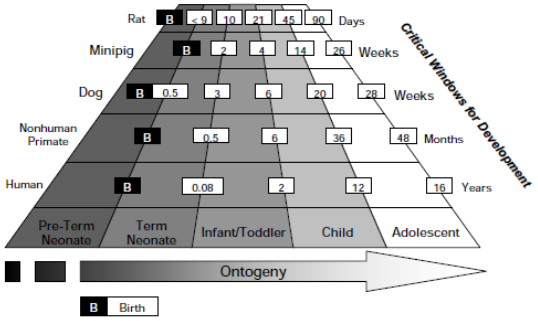

Fig. 15: Age-dependent comparison of development between humans and animals in regards to critical windows which are of major importance in paediatric drug development. (Mulberg, et al., 2013)

6.1 General toxicity screening in juvenile animal models study design

Usually, general toxicity screening represents a single dose toxicity study and a repeated dose toxicity study. Initially the dosing is performed on younger animals to also retrieve insights into the essential phases of postnatal organ development. Furthermore, endpoints are used as well as daily examinations of the animal models, body weight measurements and ophthalmology and laboratory assessments including haematology and urine analysis as well as histopathological investigations of certain tissues and monitoring of organ weights. Moreover, milestones are included to investigate the sexual development and overall behaviour including learning and memorizing capacities as well as the reproduction of offspring. (Mulberg, et al., 2013)

6.2 Targeted toxicity in juvenile animal models study design

This study design is further essential as it provides more detailed insights into certain organ toxicities of concern. Generally, from a regulatory and scientific perspective, these are considered to be more insightful compared to general toxicity screening studies. In most of the cases juvenile animal studies have been designed highly individually. After all there are some factors that need to be considered such as age at the beginning of dosing, dosing duration, recovery time, the number of animals used and many more. Generally speaking, they should be designed with a purpose and should be based on a scientific rationale. Each endpoint needs to be considered thoughtfully in terms of practicality and interpretability of the resulting data. (Mulberg, et al., 2013)

6.3 Key study design considerations

Guidance for recommended ages for nonclinical safety assessments can be found in the ICH Guidance for Industry - E11 Clinical Investigation of Medicinal Products in the Paediatric Population. The age of the respondent at the dosing start and study duration is highly important as it affects the stage of postnatal development and may influence the timing, extent and also the type of testing. Furthermore, it is extremely crucial to select endpoints to be able to address concerns appropriately. General toxicity, reproductive toxicity, genetic toxicity, carcinogenicity and special toxicities are usually being assessed. (Mulberg, et al., 2013)

Another factor to consider is the age of the model which should represent the intended paediatric population. Moreover, the sex, the sample size and the allocation of animals, usually rodents due their genetic similarity, to study groups are crucial in order to retrieve statistically sound results. Usually, both genders will be used. (U.S. Department of Health and Human Services & CDER, 2006)

Moreover, it is of utter importance to select the right animal model for the study. It is also important that developmental periods are covered in the study that are not representing the primary period of postnatal development the drug is being used in since development is a continuous and individual process. Furthermore, a target organ may be regulated by other tissues or organ system which should also be assessed in regards to the effects of a drug during the stages of development in the tested species. Certain in-life as well as post-mortem investigations need to be performed to evaluate the effect of a compound to specific target organ systems. (Mulberg, et al., 2013)

Furthermore, certain factors such as ADME, pharmacology, pharmacokinetics and toxicology of the therapeutic agent, comparative developmental status of the major organs of concern between juvenile animals and paediatric patients as well as sensitivity of the selected species to a particular toxicity should be considered by the sponsor when selecting the appropriate species. Preclinical research is usually conducted in one rodent and one non-rodent species. Rats and dogs have been very commonly used as subjects. However the drug metabolism can differ significantly in certain species and other species might have to be used such as pigs or monkeys. In some cases studies conducted on one animal species regarding toxicity in juveniles might be sufficient. Furthermore, it is fundamental to distinguish acute effects from developmental toxicities. (U.S. Department of Health and Human Services & CDER, 2006)

When performing nonclinical studies, the intended clinical route of administration, the dosage quantity, the frequency and duration of exposure and the dose selection needs to be considered carefully. (U.S. Department of Health and Human Services & CDER, 2006)

6.4 Practical consideration

In order to be able to find the appropriate design of studies in juvenile animals certain factors have to be considered such as the intentional use of the drug on the paediatric population, the dose and the timing of it in regards to the stage of growth and development in both the human and animal model. Moreover, differences in toxicology and pharmacology between adolescent and juvenile systems and also differences in development between animals and the paediatric population need to be taken into account. Furthermore, the endpoint assessment of specific target organ toxicity will be of importance as juveniles undergo a highly dynamic development. Moreover, not dependent on the duration of the therapy itself, it is crucial to consider developmentally substantial phases. (Gaitonde, et al., 2020)

6.5 Age-adjusted formulation

Pharmacokinetics is highly influenced by the age of the patient, as mentioned above, which results in different dosing adjustments for different age groups. From birth to adulthood the dose may vary as much as a 100-fold due to factors such as body size and weight, since neonates can weigh as little as 500g. Furthermore, the development and organ maturation of children is not a strictly linear process which means that is not possible to draw conclusions for a medication dose solely relying on body size and weight. (Gaitonde, et al., 2020)

In order to provide safe drugs to children the drug formulations need to be adjusted to each target age group. They do not only need to be tailored depending on the maturation process, but also depending on the development of cognition as well as motor skills since children at a very young age might not be able to swallow pills for example. Last but not least the taste of a drug might even need to be considered. (Gaitonde, et al., 2020)

The optimal formulation for paediatrics requires flexible dosing, should provide a minimal amount of excipients, should be pleasant-tasting if administered orally, safe and uncomplicated to administer and not sensitive in regards to light, humidity and also temperature of the surroundings. Furthermore, the product information needs to be easy and comprehensible for the parent and the frequency of administration should be low. (Gaitonde, et al., 2020)

7. Design of clinical trials in childhood cancer

In general, clinical trials can be sub-divided into four phases: named Phase I to Phase IV. (Fig. 16) Phase I represents the earliest stage and is relevant to assess the ultimate safety as well as the pharmacokinetics of a new product for the first time on healthy human beings rather than animals and is therefore also known as a first in man study. Furthermore, it is used to find the maximum tolerable dose. On the other hand, Phase II studies assess the activity profiles as well as the safety in a larger number of study subjects to receive a more holistic view. This helps to find disease types or participant groups that display better response rates than others. After Phase II, Phase III is initiated, in which the new agent is compared to either the “standard of care” or in some cases a placebo and is therefore also known as a ‘’Proof of Concept” study. The ultimate aim of this phase is to demonstrate enhanced efficacy or also an enhanced safety profile with remaining efficacy. After regulatory approval is obtained, Phase IV starts. This phase assesses long-term risks and makes statements about optimal usage. (Pritchard-Jones & Valsecchi, 2011)

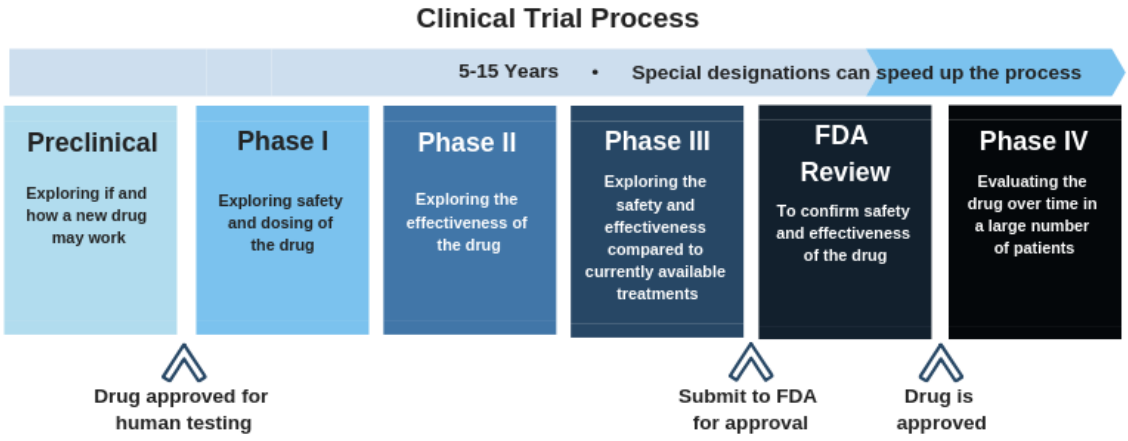

Fig. 16: Different phases of drug development. (hepbtalk, 2019)

7.1 Phase 0 trials in children

In Phase 0 studies pharmacokinetics will usually be assessed in adults. They are also known as micro-dosing studies and will not provide sufficient data on efficacy and safety. They do not belong to the conventional trials even though they are also being conducted on human beings. They are used to speed up the approval process of a drug which may result in savings ultimately regarding time and money. (American Cancer Society, 2020)

Only a few small doses are used on a small group of people for a short period of time. It may help to retrieve insights into drug-target effects and the assessment of pharmacokinetic-pharmacodynamic relationships in humans.

Some extra tests may be required such as biopsies. There is no chance that the subjects will actually benefit and therefore they are not conducted on children, even though the risk is relatively low as only a very small dose is being administered. They are relatively rare and not required by law. (American Cancer Society, 2020)

7.2 Phase I trials in children

7.2.1 Phase I trials in paediatrics

Generally speaking Phase I is the first stage of testing a drug on a human being. In adults this is being done on healthy volunteers, in paediatric studies this is rarely done except in oncological trials and some agents used in neonatology. Phase I trials on children differ from conventional studies: a new anti-cancer agent is tested on children for the first time after it has been tested on adults before and there is already some information about the dosage quantity as well as potential side effects. This fact helps to reduce the number of juvenile participants that may be exposed to a non-therapeutic dose and helps to estimate what toxicities to potentially expect. Nevertheless, the possibility of unpredicted side effects in the paediatric population is always present and this approach cannot be used in cases where an agent is uniquely designed for a target in the paediatric population. (Pritchard-Jones & Valsecchi, 2011)

Phase I trials are used to determine the MTD (maximum tolerated dose) of the agent in the investigated sub-group, to provide first insights into the toxicity profile and to determine the DLT (dose limiting toxicity). Usually, blood samples are analysed simultaneously for the pharmacokinetics. The blood levels of the active agent can then be compared to those found to be required in preclinical models. The finding of the right dose is based on the assumption that the higher the dose, the greater the activity against the tumour. However, it is worth mentioning that also the likelihood of toxicities rises correspondingly. The conventional study design used here is the “3x3 design” in which 3 patients are administered a certain dose level and if no severe toxicity occurs (DLT), the dose is elevated to the next pre-set dose level. If a DLT is experienced by a patient the cohort number is heightened to six patients. As soon as two participants of three or six suffer a DLT, the MTD is set back at the previously tested dose level. In some case, the maximum feasible dose is predetermined due to the chemical and pharmaceutical properties of the compound. To reduce the amount of time consumed for observing potential toxicity, variations of the “3x3 design” have been introduced. For example the “rolling 6” allows the participation of up to six subjects per dose level, awaiting the toxicity profile of the first three subjects participating. Furthermore, there is the “continuous reassessment method” which aim is to enrol each subject at the current best estimate of the MTD, which is then assessed again after the first toxicity occurred.

Moreover, the “time to event” approach has been proposed, which investigates the dose-toxicity relationship over the course of time. (Pritchard-Jones & Valsecchi, 2011)

Not to mention, first insights into metabolism and elimination of the drug will be provided as well as certain insights into antitumor activity. However, the effectiveness is not a primary endpoint in these studies. Children that are eligible for a Phase I clinical trials must have failed known active treatment. Moreover, they need to have proper organ function and a minimum life expectancy of eight weeks. The possible risks patients might endure are unpredictable side effects, as this is usually the first in-human test. A benefit is a potential antitumor effect. These studies are usually restricted to 15 to 30 patients and are only conducted at a small amount of specialised institutions. (Bond & Pritchard, 2006)

7.2.2 Pharmacokinetic Studies

Phase I studies are important as they help to receive insights into pharmacokinetics between the different paediatric age groups. However, a major obstacle is the still existing lack of information on pharmacodynamics and pharmacokinetics of the paediatric population, issues with number, amount and timing of the drug dose administered and the issue to determine drug concentrations at very small amounts using micro-analytics. If disease progression is comparable between adults and children, the dose extrapolated for children might be appropriate. In cases where drugs show a linear pharmacokinetic behaviour in adults, this knowledge can also be applied to single dose studies in the paediatric population. Another approach is using non-linear mixed effects which help to minimize the number and volume of samples required by using scavenged pharmacokinetic samples.

Moreover, opportunistic trials are performed which collect pharmacokinetic samples as soon as a child has received treatment. This is a relatively low risk and very efficient design which parents as well as the ethics committee most of the times agree on. Pharmacogenomics is used to retrieve insights into drug disposition, efficacy and safety. (Joseph, et al., 2013)

7.3 Phase II trials in children

Phase II studies represent the first stage of a drug being tested for efficacy and safety and is usually conducted on patients already. Knowledge obtained in Phase I studies in regards to dosage and schedule is used. These trials are used to receive an insight if an agent reveals a reasonable degree of confidence in regards to antitumor activity against a specific type of tumour to proceed with its development. (Kathy Pritchard-Jones, 2011) Moreover, it guarantees that only a small amount of patients is treated with a potential low-activity agent as these studies are usually conducted with approximately 100 patients at specialised institutions. (Bond & Pritchard, 2006)

They usually represent uncontrolled trials and are single-arm with a multi-stage recruitment scheme with the endpoint being antitumor efficacy. The null hypothesis is usually that the response rate is lower than a certain level set in advance, with P0 often set at 0.2. P1 is usually predefined and represents the lowest desired response rate to consider the drug efficient or not. Furthermore, the alpha value is highly important, as it defines the probability of rejecting the null hypothesis even if it is true. On the other hand, there is the beta value, which wrongly declares a drug as ineffective even though it actually is effective. A quite common design is the “Simon’s optimum design” that, if P0 is 0.2, P1 is 0.4 and alpha/beta at 0.1, would lead to a stop of the clinical trial if of 17 patients three or fewer are responsive to the drug. If the number is higher than three, the trial would proceed with 37 subjects. In that case, more than 10 subjects should reveal a response in order for the trial to be continued and the agent to be preliminary declared as efficient. However, when using this type of trial design it is crucial to make sure enough patients are recruited in a feasible time period of 18-24 months. This results in several hurdles, as the endpoint of response evaluation might take several weeks and might lead to waiting periods of patients and clinicians between two stages. (Pritchard-Jones & Valsecchi, 2011)

In the case of Phase II studies, minor patients that are eligible will usually need to have failed standard treatment or suffer from certain tumours that have no known effective treatment. (Bond & Pritchard, 2006) Therefore, there are only a few patients which meet all of the inclusion/exclusion criteria for early phase trials in childhood cancer since there are several good and efficient therapies on the market for newly diagnosed patients. Lastly, a lot of the patients do not have a disease state that is actually measurable, which should be a soft tissue lesion that can be measured by for example cross-sectional imaging. Considering the above mentioned obstacles, recruiting enough eligible subjects in a reasonable time frame remains difficult in early drug development studies. Often, specific cancers in the paediatric population affect only a very small sized sub-population, for example regarding ALL (acute myeloid leukaemia), and therefore benefit from tyrosine kinase inhibitors for BCR-ABL + ALL or FLT3 inhibitors as their cancer cells show FLT3 internal tandem duplications. Therefore, the common DLT approach cannot be applied since there would be an extremely low number of recruitment and also because those new agents are often combined with standard agents. In those cases it is quite difficult to assess the activity levels as the response may be unquantifiable due to the combined therapy approach. Due to the hurdles just mentioned randomized Phase II designs have been invented, such as the selection design and the screening design, which compromise smaller numbers of patients that are at high-risk and only assess activity rather than efficacy. Therefore, they are also a lot faster than Phase III studies for instance. (Pritchard-Jones & Valsecchi, 2011)

Risks of Phase II studies may include an unpredictable side effect profile as well as no anticancer activity. If the study drug or drug combination, on the other hand, reveals antitumor activity the subjects are amongst one of the first patients to benefit. (Bond & Pritchard, 2006)

7.4 Phase III trials in children

Phase III studies are conducted to see the efficacy of a drug and also the role of it in the clinical practice. Usually children that are newly diagnosed with cancer are asked to participate in Phase III trials as they are of relative low risk. Generally the child's state of health and chance to be cured are prioritised. As a comparative treatment the best available and comparable treatment is used to see if there is increased efficacy or the same efficacy with less toxic side effects. The latter are known as non-inferiority trials, which rather focus on reducing the side-effects, toxicity and generally the hurdles of treatment, while maintaining the same overall survival. However, cases in which a new drug is meant to replace an existing drug are often viewed with a lot of scepticism as people fear it may lose its therapeutic value. (Pritchard-Jones & Valsecchi, 2011) Moreover, it is highly critical that trials are set up by an interdisciplinary field of specialists such as clinicians, biologists, pharmacologists and biostatisticians. There should be a pre-specified hypothesis depending on whether a non-inferiority or a superiority trial is being conducted. In some rare cases testing for both can be possible. (Pritchard-Jones & Valsecchi, 2011)

Usually a large number of children participating is required to assure statistical power. (Pritchard-Jones & Valsecchi, 2011) Therefore, Phase III trials usually involve a few hundred to thousands of patients and are usually multicentre studies including many different community centres. (Bond & Pritchard, 2006) However, usually the number of children diagnosed per year is not that large which makes it not that easy to recruit the right amount of patients. (Fig. 17) They are usually performed in a randomized fashion.

Diagnostic subgroup	Expected no. of cases/year*	Expected no. of deaths/year*
Acute lymphoblastic leukaemia	372	71
Acute myeloid leukaemia	69	26
Hodgkin lymphoma	58	<2
Non-Hodgkin lymphoma	82	16
Medulloblastoma	70	31
Astrocytomas	155	33
Neuroblastoma	89	38
Retinoblastoma	43	2
Renal tumours	81	13
Hepatoblastoma	11	3
Osteosarcoma	31	10
Ewing sarcoma	22	6
Rhabdomyosarcoma	55	17
Malignant germ cell tumours	31	2

Fig. 17: Number of expected cases per year for common childhood cancers and the expected number of deaths per year for children below the age of 15 in a standard European country with approximately 60 million inhabitants. (Pritchard-Jones & Valsecchi, 2011)

Apart from that, the number of patients to be enrolled depends on the extent of statistical difference that is being assessed by the trial. If the difference is small more patients are required compared to greater differences. However, to accrue a significant amount of children is still one of the major issues in paediatric clinical trials. (Pritchard-Jones & Valsecchi, 2011) Only 38% of 736 trials on children from 1996 to 2002 had a larger sample size than 100 children. (Kern, 2009) These might seem like small improvements, yet they are still of high clinical importance. Several national cancer study groups in the paediatric field have helped to improve the design and conduction of clinical trials. Furthermore, a vast amount of subjects could be recruited due to the interdisciplinary teamwork between physicians and subjects in treatment centres. However, a close interaction between the different countries is still required, as it is crucial to receive the required statistical power, even for rather common cancer types in children.

Nevertheless, this requires an expanded time frame and can also result in discrepancies between the countries as what is defined as the standard arm. The current trend is to even move from national to international recruitment.

This often is the only way to really receive trustworthy evidence which is able to enhance clinical practice in the long run.

A good example for the successful execution of this approach is when the International Society of Paediatric Oncology conducted clinical trials in 1991 for a very rare childhood cancer, known as hepatoblastoma, and the overall survival rate was improved significantly in all of the participating countries. (Fig.18) (Pritchard-Jones & Valsecchi, 2011)

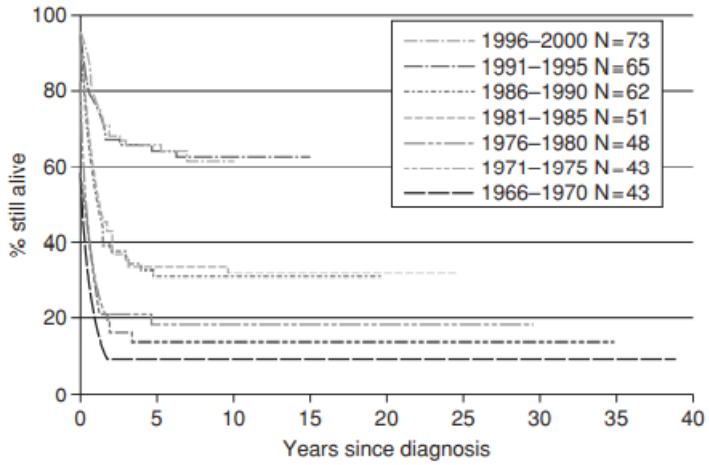

Fig. 18: Enhanced survival of the paediatric population with hepatoblastoma in the UK after participating in SIOPEL trials in the year 1991. ((Pritchard-Jones & Valsecchi, 2011)

The potential risks for subjects of Phase III studies include that the standard treatment might be better or reveal a smaller side effect profile compared to the investigational product. However, if the study drug reveals less toxicity and shows enhanced efficacy the study participants are one of the first patients to benefit from it. Moreover, it is not rare that the outcomes for these patients are improved solely due to the strict monitoring guidelines implemented in clinical trials. (Bond & Pritchard, 2006)

7.5 Phase IV trials in children

Phase IV studies are known as post-marketing trials and are performed after the drug has been approved. (Joseph, et al., 2013) This type of trial is used to gather data regarding efficacy and safety over a longer period of time to retrieve insights into long-term side effects, safety, potential risks and benefits and how applicable the drug actually is in clinical practice. (Inova Childrens Hospital, 2021) According to PREA and the Food and Drug Administration (FDA) marketed medicines require specific paediatric trials. Nevertheless, Phase IV studies are still rarely performed in children. (Joseph, et al., 2013)

8. Outcome measures

Generally, it is rather complex to determine whether a new cancer therapy is successful or not. Usually, this is determined by assessing whether the overall survival is improved or by a reduced side effect profile. However, due to the differences between children such as age, health status, random biological variations as well as the cancers they harbour, one treatment could result in several different outcomes. To overcome these hurdles a large amount of patients to be enrolled is required to rule out random variation. Another strategy is to repeat the trial on another occasion. However, only a small amount of children suffers from specific childhood cancers. Another issue is the pace of disease progression as it highly affects the time period needed to actually measure outcomes in these childhood cancers. For example DIPG, also known as diffuse intrinsic pontine glioma, is a cancer of the brain that reveals a median time period of progression of roughly six months with a median time to demise of roughly a year or even less. Furthermore, only about 25% or less of children having been diagnosed with DIPG are still alive after 2 years. Due to the rapid disease progression and low survival rates it is rather easy to assess whether an improved overall survival rate due to a drug can be seen. However, in other childhood cancers such as ALL where the five year survival is at 90% for children aged 14 or lower, it would be difficult to measure the outcome quickly as the time period needed to actually observe a difference that can be measured regarding the outcome is very long. Therefore, as the time span of overall survival increases, it will also take more time and often also more patients to actually observe if a new drug has advantages regarding survival compared to treatment options already on the market. (Adamson, et al., 2016)

8.1 Biomarkers

Due to the small amount of children diagnosed with cancer each year, which could be potentially enrolled in a trial, advances have been made in trial designs as well as outcome measures to decrease the amount of children needed in a trial and also to reduce the time needed for the conduction of it. From the introduction of how the safety of a drug is assessed, to dosage finding to new trial designs for early-phase studies a lot of advances have been made. Furthermore, single arm trials, Bayesian statistics and surrogate endpoints have been introduced, ultimately increasing efficiency. (Adamson, et al., 2016)

Besides measuring overall survival as an endpoint, other factors are assessed such as tumour shrinkage by imaging, cancer progression over the course of time, the number of patients responding to a drug or changes in other biological measurements such as white blood cells or proteins within the blood.

Therefore biomarkers can be defined as a tool to measure and evaluate processes which can be biological, pathogenic or pharmacologic. These are known as surrogate endpoints as they do not recapitulate the outcome as the highest interest. Ultimately surrogate endpoints belong to the group of biomarkers. These are biological markers which act as a tool to determine the state of health or the disease of an individual. They can give insights into tumour shrinkage, safety of a drug (disruption of cardiac rhythm e.g.) or even the chance of having late effects (cardiac troponin T e.g.). With the help of biomarkers it is possible to obtain way more information about the effect of a drug in a shorter period of time than simply measuring overall survival. If they are used as a substitution of clinical results they must be able to predict the clinical effect properly in the future.

If the TTP (time to tumour progression) is delayed, the biomarker needs to be validated thoroughly as it could also be the case that the cancer might reoccur more aggressively later on, meaning there will be no ultimate change in overall survival time. In order for surrogate endpoints to be used in clinical trials the biomarkers need to be validated and will then be listed by the FDA in a specific list for surrogate endpoints. However, pharmaceutical companies are also allowed to develop their own. In the years 2010 to 2014 40% of the approved drugs were approved due to surrogate endpoints. (Adamson, et al., 2016)

Generally, they are able to have an impact in every phase of drug development, preclinical and clinical. They are used to retrieve insights into drug doses, the dosing interval or to even find the right target population. Often, biomarker data from adults is extrapolated from adults to children which is not always appropriate since development affects not only organ function but also drug disposition. Unfortunately, children-tailored biomarker development faces several hurdles since also in this case only a small amount of children is available, sage-specific controls are required and the ethical aspect needs to be considered. (Gaitonde, et al., 2020)

9. Ethics of clinical trials in children

The aim of a clinical trial is to test a new compound which is not authorized for marketing yet. Several risks and benefits of participating cannot be foreseen. Therefore, participating has to occur on a voluntary level and participating in a trial is never a guarantee to receive the best available treatment or even a cure. Some concerns have been raised that family members as well as clinicians overestimate the therapeutic advantages of trial participation, especially in regards to Phase I and II trials. Therefore, the discussion as well as the accurate documentation is highly crucial. For that matter, the informed consent process has been established. Especially for parents this process is highly beneficial, as the verbal discussion of the several issues and benefits is often more helpful than the informed consent document itself. As the diagnosis of cancer often reveals an urge of rapid treatment, parents are often asked very early after the diagnosis if they would like to participate in a study. However, it is of major importance that the risks and also the benefits that might come along with participating in a clinical trial are clarified by their trusted physician as well as by their oncologist of choice. Approval needs to be obtained by the Ethics Committee (independent review board (IRB)) from all parts participating in a study. These boards' obligations are to ensure the patients' rights are protected in terms of the conduct of a trial as well as the informed consent process. The ECs (IRB's) approval is required in order for a patient to be enrolled. (Bond & Pritchard, 2006)

9.1 Informed consent

The informed consent builds the base of ethical research on human beings. The article three of 2005/28/EC states that research should be conducted in compliance with the so called Declaration of Helsinki, adopted in the year 1996 by the General Assembly at the World Medical Association. Principle 9 captures hereby that reasonable information and understanding of the research that is about to be conducted is required in order to participate in a trial, regardless of whether it is therapeutic, diagnostic or even preventive. This includes the major questions: Why is the research being conducted, what actions will be performed during the trial and how long is the treatment going to last? Furthermore, what are the risks that are involved and if there are any suspected benefits, what are they? Moreover, it is crucial for the subjects to understand what other interventions might be available. (Costello, et al., 2007)

Subjects are allowed to terminate their participation at any time without justifying their reasons for it. IC (=informed consent) should be documented by using the ICF (=informed consent form), which should be signed, dated and usually witnessed by a third party.

This process is crucial in order to ensure that the participation is solely voluntary and in favour of the person's own interests. In the case of under aged people, their personal interests and values might be of unknown nature in which cases research proxy is used or the legal guardian is allowed to permit the participation and represent the children's interests, as stated in principle 11 of the Declaration of Helsinki. SI 2004 1031 Schedule 1 Part 4.1 states that a person with parental responsibility can provide informed consent on behalf of a minor. Interestingly, the child's mother automatically has parental responsibility, whereas the father only has parental responsibility when being married. (Costello, et al., 2007)

Moreover, in some cases, children are asked to give assent for the treatment of the trial if they are considered to be of appropriate age to understand medical discussions. This means the child is asked for its disagreement or agreement to participate in a trial for a particular treatment and its procedure. Children might be as young as 7 years. Generally, assent is demanded voluntarily by the institutions and not required by law as it is favoured that the child participates in the decision making if it is able to do so in regards to development and cognition. Often these discussions are assisted by psychologists or social workers. (OncoLink, 2019)

9.2 Protection of minors § 42 AMG

Clinical studies of drugs can only be conducted on minors if certain criteria are met:

- The drug is only to be tested in minors if it can help to diagnose, cure, relieve or prevent disease and if it is urgently needed to validate data of clinical studies performed on adults or data obtained by other research methods.
- If it can diagnose, cure, relieve or prevent disease specifically in minors and the benefits outweigh the risks for the study participants.
- If the legal guardian has consented to the participation of their child on a written form after the whole process has been explained to them.
- If the minor has received a proper explanation of the study and its procedures adjusted to their capabilities of an investigator experienced with minors.
- If the consent of the minor has been obtained and if the minor is capable of understanding the nature, the meaning, the risks as well as the impact of the clinical study and if it is made sure that the expressed denial of participating in the study or terminating it at a certain point of time of the minor has been acknowledged by the investigator.
- If the consent can be withdrawn at any point of time without any disadvantages occurring for the minor.
- If no incentives, which can be of financial or other nature, occur due to the study participation, except expense allowances.

- If the study is planned in a way that the disease, the maturity and the developmental stage of the minor is being considered and that as little as possible pain, complaints as well as fear and other unforeseeable risks occur for the minor. This needs to be re-evaluated regularly.
- If the study plan has been approved by the ethics committee, which have substantial knowledge in the field of paediatrics or which have been advised externally in terms of clinical, ethical or psychosocial paediatric questions.
- If there are any doubts about the willingness and interest of the minor to participate, as its own well-being should always stand above the public interest and the scientific interest. (jusline, 2021)

Apart from that, clinical studies on minors are also allowed if:

- The clinical study is seen as something that will add significant value to the condition, the disease or the disorder of the child and can therefore create a substantial benefit for the specific group of people.
- The clinical study only presents a small risk and a minor burden for the minor, if it is expected that this risk or burden will only be temporary and if the symptoms or the impairment will also be temporarily and marginally. (jusline, 2021)

9.3 Suggestions for the informed consent process with minors in Austria

After the 8th year of life children, if they are in a physical or mental state to declare their consent, should be included in the process by asking for their consent and explaining the study by a written form. Therefore, two documents need to be available: one informed consent form signed by one of the parents and one informed consent form signed by the minor itself. These informed consent forms need to be adjusted to the maturity and the age of the potentially participating child, which results in the fact that the document needs to be written in a more comprehensible manner for children below the age of 10, whereas for minors aged above 15 the written document can be the same as for adults. It is not allowed to combine the information for adults, parents and adolescents. Furthermore, it should be considered that children that have been under treatment for a long time, as it is often the case with chronic diseases, have already a vast amount of knowledge regarding their disease and can be addressed differently in the informed consent process. Regardless of the age, minors should always receive a proper clarification in a comprehensible manner regarding the aim of the research, the risks and the inconveniences that might come along with participating in a trial. (Ethikkommission, 2021)

9.4 The informed consent process with children and its hurdles

Several hurdles come along with the informed consent process. It highly depends on the emotional stress and also the education of the person that holds parental responsibility. (Costello, et al., 2007) A study revealed that up to 20% of the parents would not consent on their child participating in a clinical study. (Fig. 19) (Zepp, 2015) Therefore, misunderstandings can arise as well as the feeling of powerlessness due to the diagnosis of the child and the authority of the physician. (Costello, et al., 2007)

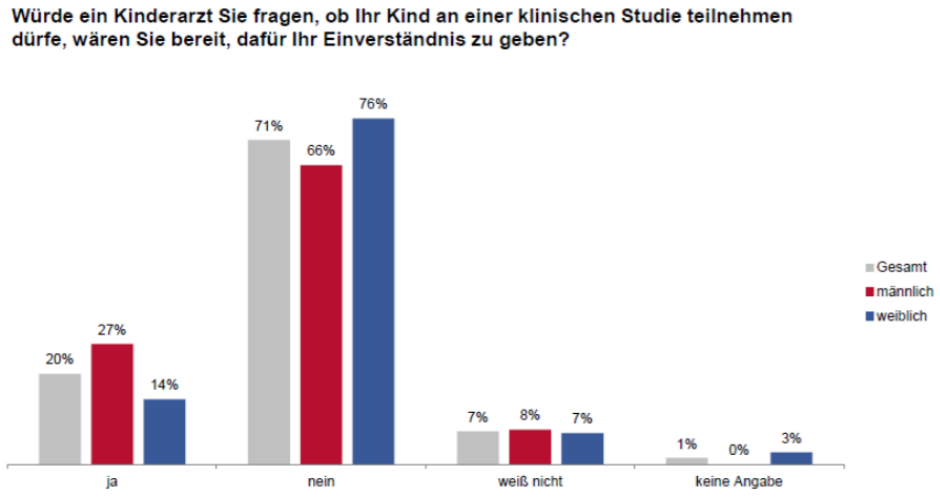

Fig. 19: 20% of parents would not consent on their child participating in a clinical study. (Zepp, 2015)

Interestingly, some studies have revealed (Mason and Allmark, 2000) that up to 2.5% of parents even tend to forget that they have given informed consent. Additionally, a common issue is that parents often feel a lack of discussion of alternatives to the potential treatments and scopes of the research protocol investigated in clinical trials. This is especially present in oncology trials of the paediatric population as these are fundamentally protocol driven. (Kupst, 2003)

Some parents even feel the obligation to participate (up to as many as 25%). (Van Stuijvenberg, 1998). These parents seem to not have given informed consent on a truly voluntarily basis.

Furthermore, guilt plays a major role as parents often question their decisions if their child dies. Nevertheless, clinical trials are often the only way to receive certain treatments that are not yet available. In trials in neonates the influence of exhaustion or sedatives and analgesia might also come into play when the mother decides for her child whether to participate or not.

An interview with mothers whose children had received ECMO (=extracorporeal membrane oxygenation) in the UK revealed that their decisions were driven by fear, pressure, stress and also anger when their neonates were randomized for conventional treatment. (Snowdon, 1997) (Costello, et al., 2007)

These interviews and studies really outline the urge to consider the emotions and dynamic thought processes of parents that come into play when giving informed consent. (Costello, et al., 2007)

10. Novel strategies for clinical trial design

10.1 Statistical design

As already mentioned, the characterisation of the several different subgroups of childhood cancers is of major importance as gaining an understanding of molecular basis becomes increasingly important in drug discovery and development. Diseases such as ALL could be sub-divided into even smaller subgroups such as Philadelphia chromosome-positive. This distinction even within one cancer type could result in better treatments with increased response rates due to heightened target sensitivity. Different sub-groups raise different therapeutic questions and therefore statistical designs need to be adapted. Increased efficacy for poor survival rates as well as improved designs of Phase I to II studies are required since only a small amount of patients is available and because of the increased amount of new drugs approved for testing of side effects and antitumor activities. As a result, designs have been adapted. However, these adapted designs might be rather useful in cases where drug activity as well as the general response to a therapy is evaluated rather than in cases where efficacy is measured in regards to event-free overall survival over a long period of time such as in Phase III studies. These adapted trials are usually data driven and will re-evaluate sample size, exclusion of certain treatment arms or even different primary measurements of treatment response. These trial designs usually use interim findings to adjust the sampling plan. They are being criticised for the introduction of bias as well as imprecision as a result. Furthermore, using adaptive designs in the late phases of drug development such as Phase III studies, in which confirmation is being sought in order to approve a new drug, these designs might be questionable. However, in the case of a problematic situation where for example uncertainty is caused due to a lack of available knowledge, it might be of advantage to implement adaptive approaches. Of course, uncertainties must be acknowledged in advance and need to be justified in the protocol beforehand. They should not be used to deal with poor trial planning. A good adaptive trial design must be able to control bias by preserving type I errors and introducing proper confidence intervals for the treatment effect as well as estimates. Moreover, for interim analysis it needs to be ensured that the integrity of the adaptive design is preserved by limitation of the data access as well as the results. Heterogeneity in the treatment effects needs to be detected by performing heterogeneity tests to avoid any discrepancies caused by monitoring designs. A good example for adaptive design is the ‘’seamless design’’. Two phases of drug development are combined in one. It is split up in two stages, whereas the first one is the learning stage where data is gathered and is then used to adjust the trial plan of the second. Still data from both stages is later used for the final analysis.

It avoids discontinuation of the preferred arm and the need to start a new trial. An endpoint is required for the learning phase with immediate continuation of the confirmation stage. It will later be a primary endpoint and also used to answer questions of the study. (Pritchard-Jones & Valsecchi, 2011)

10.1.1 Bayesian Designs

This design is used to learn from evidence and is applied in the analysis as well as the design of the trial. A mathematical model is used that combines prior knowledge with accumulating evidence. As a result the ‘’posterior distribution’’ will be obtained which will give insights into the endpoint of interest. Applying this model might result in a shorter and smaller study, however good prior information is required so it can be incorporated. This method can also be used in cases where information is provided but remains questionable, as it allows a flexible type of study design in which interim analysis can be performed to modify the ongoing trial. Sample size is usually not predetermined as it mainly focusses on a specific endpoint to stop the trial. During the trial the required number of observations to reach the stopping criterion can be updated. As sample size is not directly included, trials can be terminated as soon as sufficient information is gathered to answer the study questions.

The sizing however should be adjusted and predetermined in regards to safety and efficacy endpoints. The final analysis includes the testing of the hypothesis and interval estimates. Using the posterior probability distribution, it can be calculated whether a certain hypothesis, concerning an endpoint, is true in regards to the data being observed.

Interval estimates can be used to determine the intervals in which the true unknown treatment effect is included regarding the posterior probability to a certain percentage. These Bayesian designs could be implemented in Phase II trials by comparing several therapies resulting in a randomized selection. In rare subgroups it is proposed to include prior information gathered in earlier studies. These small trials might otherwise be underpowered, which could be avoided by implementing the Bayesian framework. (Pritchard-Jones & Valsecchi, 2011)

10.2 Pharmacometrics

Pharmacometrics is also known as modelling and simulation. This means that mathematical models of pharmacology, biology disease and physiology are used to describe and also quantify interactions between drugs and patients, which involves describing side effects as well as efficacy resulting from these interfaces. A common approach is the “top-down” approach of empirical equations which makes use of only a few parameters. The probability parameters in these cases are not used to obtain insights into physiology and anatomy but rather to receive insights into the distribution of these parameters.

The model will be evaluated based on bias, imprecision and the distribution of predictions referring to the independent data provided. This way of proceeding is therefore also known as “population modelling”. The second option is known as “bottom-up” or PBPK (physiologically based pharmacokinetic) approach. This alternative utilizes a few hundreds of parameters and equations which will retrieve insights and reproduce anatomic distributions as well as physiological functions as opposed to the first approach. The parameter values for the probability distributions are usually obtained from independent sources of data such as published clinical trial data or *in vitro* experiments. The model is subsequently considered to be evaluated if the simulation output is similar to the data set used. (Neely, et al., 2018)

Apart from helping to predict PK and PD observations, pharmacometrics has also been utilized to transfer knowledge from preclinical and clinical data into drug exposure/disease models ultimately setting the foundation for novel clinical trial design by simulation of varying designs and therefore controlling design and trial selection decisions.

Furthermore, pharmacometricians can help to not only model and simulate human-drug relationships, but also quantify them to improve and optimize drug dosing and achieve the correct concentrations. Last but not least, effect targets of an individual patient can be targeted with high precision as well as accuracy, also resulting in effective drug management rather than just monitoring. (Neely, et al., 2018)

An example for the usefulness of the implementation of pharmacometrics is a proof of concept PK study performed for the drugs omeprazole and pantoprazole. In this case DNA was harvested for CYP2C19 genotyping. Both revealed the same genotype and phenotype (assessed by drug plasma clearance) for CYP2C19, however after reassessment of the data it became clear that the inclusion of CYP2C19*17 allele that there was a gene dependent dose effect for pantoprazole, whereas this was not the case for omeprazole. This reveals that the inclusion of pharmacogenomics, since gene polymorphism has been shown to affect drug clearance, can beneficially influence clinical pharmacokinetic trials in a significant manner as it might explain outliers for drug plasma clearance and elimination. Furthermore it might provide support in terms of compound-dependent differences in drug disposition during development. (Laughon, 2011)

10.3 Opportunistic studies in paediatrics

Opportunistic studies represent studies in which a child receives the standard-of-care as part of its therapeutic treatment. After obtaining the informed consent investigators are allowed to compile in addition to their routine blood draws also samples for pharmacokinetic analysis. This has already resulted in highly meaningful data ultimately resulting in improved dosing recommendations for drugs used in paediatrics.

Samples were obtained from children already receiving drugs rather than performing studies where drugs are being administered for children for that matter. Data obtained from opportunistic studies have already guided the design of Phase I to Phase III studies and have supported research applications. (Laughon, 2011)

Another variation of opportunistic studies is real-time monitoring. This approach is used in cases where dosing has not been entrenched for children. Therefore, sample collection at informative time points is promoted as well as it facilitates enrolment of subjects as physicians might see a benefit from receiving direct feedback of drug concentrations. Nevertheless, additional resources are required as rapid analysis samples as well as their thorough interpretation are crucial. A proof of concept is the example of zidovudine: an opportunistic real-time study design was applied to obtain information of pharmacokinetics as well as safety in preterm infants. The ultimate aim was to use ZDV prophylaxis to prevent HIV exposure and transmission from their birth givers. A reduced dose was administered due to immature renal function as well as glucuronidation. In weeks 1,2 and 4 two to three blood samples were drawn for pharmacokinetic analysis of ZDV and ZDV-glucuronide. Depending on ZDV drug concentrations doses were adjusted individually. Large differences were found in pre-term and full-term infants. Infants born at 30 weeks or earlier required a major delay in ZDV dose increase due to different ZDV clearance capacities. This example reveals that incorporating opportunistic study design into clinical care can generate valuable pharmacokinetic as well as dosing information and should as well be applied in paediatric clinical research in the field of oncology. (Laughon, 2011)

10.4 Precision trials

10.4.1 Basket trials

Basket trials focus on genetic alterations which cancer types have in common rather than on a specific cancer type. In basket trials people with any cancer type such as breast, lung or colon cancer can be enrolled as long as they share the same genetic irregularity. (Fig. 20) They fall under the category precision trials and can be single- or multi-arm trials. Each treatment arm is seen as a basket and cohorts of subjects are assigned to these baskets. It is a target based approach which focusses on finding treatments for specific targets rather than just focusing on the disease type itself. With the help of basket trials the effectiveness of new medications can be tested for several different cancers simultaneously. Due to the union of different cancer types they are called basket trials, as they focus on similarities on the molecular stage rather than organ or histological origin. (Strzebonska & Waligora, 2019)

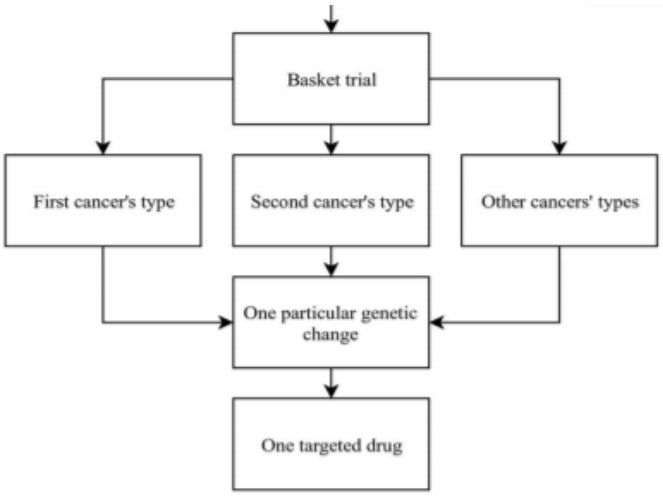

Fig. 20: Scheme of a basket trial. (Strzebonska & Waligora, 2019)

An example for a basket trial was initiated by the COG (=Children's Oncology Group) which is known as a paediatric MATCH trial (=Molecular Analysis of Therapy Choice). It started in July 2017 and was initiated after the counterpart study on adults. Subjects were enrolled that either had NHL (=non-Hodgkin Lymphoma), histiocytoses or recurrent or refractory solid tumours and were 1-21 years old. Samples of the tumours were sequenced to see whether the mutation of interest is present or not. The screened for mutations were predefined for each study arm in advance depending on whether there was already evidence available for a specific target response to the therapy. If there is only limited information available, preclinical studies are required to ensure that these genetic aberrations are response biomarkers to a certain therapy. The hypothesis states that this response evidence does not necessarily need to be linked to cancer therapy, but whether or not the genetic variation is able to predict a response to a specific target therapy, inconsiderate of the cancer type itself. In the paediatric MATCH trial, the goal is to enrol at least 20 subjects for each trial arm with the primary outcome measure being the objective response rate. If the objective response rate is ≥16% then the targeted therapy is seen as promising and worth testing further. (Forrest, et al., 2018)

10.4.2 Umbrella trials

In contrast to basket trials umbrella trials are based on enrolling subjects that suffer from one particular cancer type which are then, with the help of biomarkers, divided into sub-groups based on the genetic aberration they are suffering from. (Fig. 21) Therefore multiple agents are tested at the same time. These drugs are adjusted to the genetic change of each sub-group. These trials are named umbrella trials because they focus on dividing a particular cancer type into several different sub-groups due to their molecular particularities.

In these trials a control group, also known as default arm, can be used as well to simply receive the standard of care without a biomarker. Furthermore, there are cohort specific control groups which receive the standard treatment. (Strzebonska & Waligora, 2019)

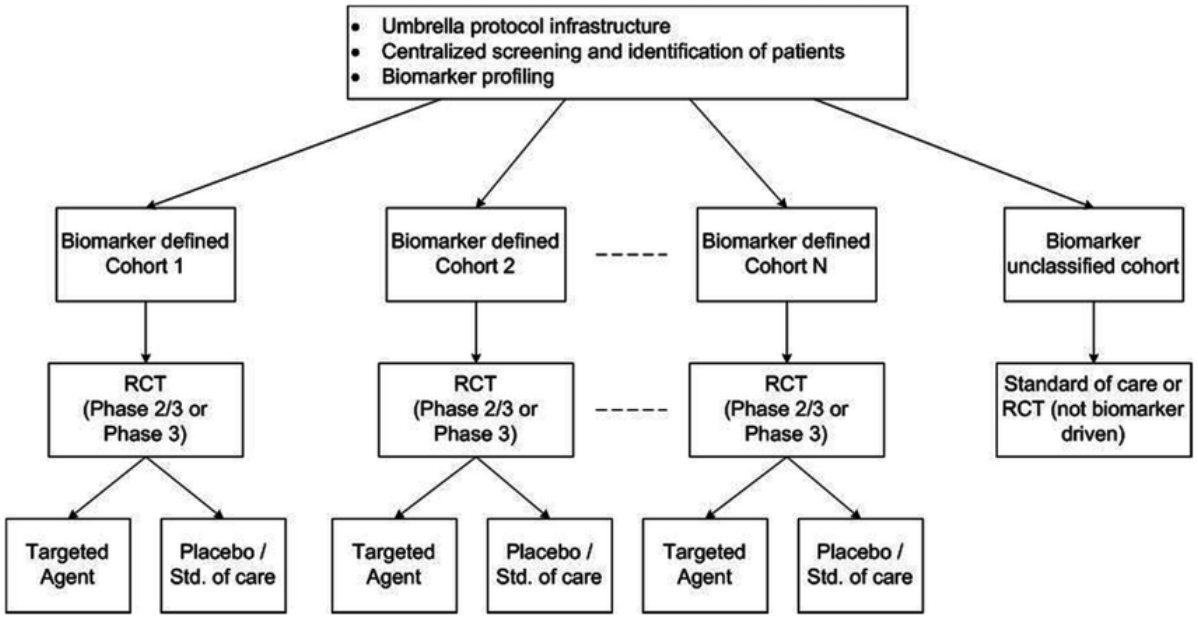

Fig. 21: Schematic example of an umbrella design. (Mandrekar, et al., 2015)

Umbrella trials are commonly used when the studied mutations are well known to be susceptible to the specific medication and they occur often enough so the study on the specific cancer type alone is sufficient. Umbrella designs are utilized in paediatric cancers that have a specific number of recurrent mutations that have already been discovered by sequencing, such as neuroblastoma and leukaemia. In ALL, as mentioned in a prior chapter, the Philadelphia chromosome-like ALL is a highly represented molecular subtype that occurs in 15% of children suffering from ALL and commonly results in a worse disease progression. This subtype always includes genetic variations that activate kinase or cytokine signalling causing changes in ABL1/2, CSF1R, PDGFRB and changes and mutations in CRLF2, JAK2 and EPOR. Research suggested that JAK as well as tyrosine kinase might be an interesting target to inhibit. A single institution took up the idea and performed an umbrella trial with subjects that were 10 years and older, with relapsed or refractory ALL and Philadelphia chromosome-like genetic alterations or CRFL2 positivity. In this study reinduction chemotherapy was combined with either Ruxolitinib, which is a Jak inhibitor, or Dasatinib, which is an Abl/Src kinase inhibitor, dependent on the gene variants that were identified beforehand.

It is worth emphasizing, that this early Phase 2 umbrella study driven by biomarkers allowed patients as young as 10 and above to participate, which is supported by statements from the FDA as well as the American Society of Clinical Oncology. (Forrest, et al., 2018)

Another mutation is the ALK gene which affects 10% of the neuroblastoma patients. Eight agents were screened in vitro in 17 patient-derived neuroblastoma cell samples, whereas combining two agents, CDK4 inhibitor ribociclib and ALK inhibitor ceritinib, could be identified to be sensitive to cell lines with the ALK mutation. Based on this knowledge the Next Generation Personalized Neuroblastoma Therapy trial, an umbrella trial, was set up. Subjects eligible for the study were patients with relapsed or refractory neuroblastoma aged 1 to 21 years. Based on their genetic alterations they were split into several groups: ALK pathway mutation positive subjects received the combination of Ceritinib and Ribociclib, whereas RAS-MAPK positive patients received Trametinib. Patients without any of these mutations received HDM201, an oral HDM2 inhibitor, and represented the 3rd treatment arm. (Forrest, et al., 2018)

11. Research

The method used for the thesis is based on a qualitative interview with the use of an interview guide. The manner of the questionnaire represents a problem-based approach and focusses on an expert's opinion. The interview is evaluated with the help of a qualitative content analysis. The questions are asked in an open manner and the expert is allowed to talk freely as long as there is no major digression.

11.1 The expert interview

The expert interview is a certain kind of guided interview, in which the interview partner that is being questioned is a highly qualified person in its subject which often also has had a scientific education. These experts are usually part of organisations and the expert usually represents this group. The interview questions will be asked in an open manner and the guide will guarantee that the conversation will not digress. This way of interview presupposes that the expert has sufficient knowledge on the research subject.

11.1.1 Selection of the expert

The expert that was chosen is a professor at the St. Anna Children Hospital in Vienna, which is the leading hospital for paediatric cancer research as well as treatment of children in Austria. The first contact was via email and telephone. The interview was conducted via telephone and recorded, due to the current COVID-19 restrictions. The expert that was chosen will be represented shortly:

- Assoc. Prof. Dr., MBA, cPM Ruth Ladenstein is president of the European Society of Paediatric Oncology, leader of the coordination centre for clinical trials and statistics of the St. Anna Children's Hospital in Vienna and member of the Mission Board for Cancer in the parliament. She is a certified paediatrician with a special focus on haemato-oncology.

- The interview was performed on the 4th of February 2021 at 9:35 am with a duration of 31 minutes.

11.1.2 Selection of the categories for the expert interview

The categories were selected by theoretical considerations and according to chapters of the prior literature research. The following categories were selected:

- ➢ The history of clinical trials in paediatric oncology in Austria
- ➢ The uniqueness of the conduction of clinical studies in children: Differences between adults and children
- ➢ Regulatory pitfalls
- ➢ Obstacles to overcome to decrease paediatric labelling
- ➢ Paediatric Extrapolation
- ➢ Biomarker development
- ➢ Innovative clinical trial designs
- ➢ Future of paediatric drug development

12. Evaluation of the interview

12.1 The history of clinical trials in paediatric oncology in Austria

Professor Ladenstein talked about the importance of the history behind the development of clinical studies in paediatric oncology in Austria. This history started in the late 1960 with a strategic, consecutive work of the GPOA, in which the former leader of the St. Anna Children Hospital played a major role. What followed was a step by step evolution as new medications came to the market and randomized trials were implemented. As a result highly standardized treatment concepts evolved which also led to a major increase of success rates in paediatric oncology therapies. According to Statistic Austria the newest numbers are 85%, says Prof. Dr. Ladenstein

12.2 The uniqueness of the conduction of clinical studies on children: Differences between adults and children

According to Prof. Dr. Ladenstein clinical studies performed on children of several age groups are highly fundamental as organisms differ significantly depending on the age. However, what most people do not consider, as stated by Prof. Dr. Ladenstein, is that dealing with children is far more complex. There are major differences between a newborn child and an adolescent, ultimately affecting volume distribution, ways of metabolization, hormonal influences and potentially causing changes in efficacy as well as dosage. Her major point was that age-specific testing is urgently required for each drug as there are severe backlogs.

There is an off-label use of 80% in paediatric oncology, even 90% in neonatology, which means that the drugs have never been tested for this certain indication in this specific age group.

Prof. Dr. Ladenstein mentioned that due to our history there has always been a major fear of experiments on the human being, which led to the outcome that children were protected from research instead of them being protected through research.

Clinical studies on children are highly complex and not comparable to studies on adults. She pleaded that as soon as the intended use is for children the consideration of the different age groups is required. As stated by her, 16-year old adolescents can still be included in the adult population as there are no major differences in terms of metabolism anymore. However, if one is seeking an approval for the paediatric population, at least four age groups need to be considered: 12-year-olds, elementary school children, kindergarten children as well as children in their early childhood and infancy.

Using age groups results in different dose findings, a decreased market, and a decreased trial population for each group. Last but not least the overall effort increases by a fivefold.

„Das heißt schlagartig, wenn Sie sagen Sie lassen etwas für Kinder zu, Sie konfrontiert sind mit zumindest vier unterschiedlichen Altersgruppen, die unterschiedliche Dosisfindungen haben. Das heißt, obwohl der Markt kleiner ist und die angesprochene Population kleiner ist, haben Sie den vier oder fünffachen Aufwand." (Interview line 203)

12.3 Obstacles to overcome to decrease paediatric labelling

Prof. Dr. Ladenstein mentioned that there are several statutory regulations, such as the paediatric regulation or the orphan drug regulation, that have not resulted in the expected outcomes. No significant changes could have been observed in drug discovery and development. Due to the fact that children have been treated off-label, data for efficacy and side effects has still been gathered. The decreasing division rates have proven the efficacy of drugs used off-label as well. Prof. Dr. Ladenstein mentioned that if she had been diagnosed with cancer in her childhood, she would have been a death candidate within the next few weeks.

"Ich sage immer, wenn ich im Kindesalter Leukämie gehabt hätte, wäre ich ein Todeskandidat innerhalb der nächsten Wochen gewesen, nur um das greifbar zu machen, welchen Sprung wir da eigentlich erlebt haben." (Interview line 40)

She stated that there are standards available; however they all derived from off-label use. The price that we are paying is high, as a lot of treatments are performed in a hidden area with a lack of knowledge in terms of dosage, pharmacokinetics, pharmacodynamics and many more, according to Prof. Dr. Ladenstein. The late effects caused by drugs are higher than they would need to be: 70% of the children will have late effects affecting their organ systems which will even increase through the course of life. She stated that the industry, the regulatory authorities, the European and American medicine agencies and the local admission boards should all be encouraged to test drugs specifically on the paediatric population, in the best-case scenario parallel to pursuing adult drug development.

Often the whole adult development process is completed, which takes several years, and then children drug development is started. In the last years 150 new innovative drugs have been brought to the market for adult indications, whereas the number for children was 9. Prof. Dr. Ladenstein stated that 3 of them were immunotherapies and that she was involved in the development of one of them.

Furthermore, she mentioned that she is part of the European committee, where she and other people are working on implementing fundamental changes in paediatric drug development, which includes early stage studies and a lot of trial and error. Moreover a lot of educational work is required, so people understand that they are in a safe environment when entering a trial.

“Das bedeutet aber auch viel Aufklärungsarbeit, dass man in einer Studie eben kein Versuchskaninchen ist, sondern dort bestmöglich aufgehoben und versorgt ist, beobachtet wird und dort eigentlich in einem sichereren Netzwerk ist.“ (Interview line 62)

Moreover, her opinion is that people assume that if they are buying something within a package it is specifically tailored to them. They are not aware that only 60% are approved for the specific age classes.

She clarified that even if it is a fever suppository or a cough syrup specific testing for the different age groups is required and that specific approvals for them are required. Prof. Dr. Ladenstein mentioned that society has learned to perfectly close their eyes.

12.4 Paediatric extrapolation

Prof. Dr. Ladenstein stated that extrapolation is a commonly used practice which is also required for admissions. She explained that what is essentially done is that through a square metre dose for a child, if one for example assumes this is 30 kg per square metre, this knowledge can be used to convert from child to adult and vice versa. One can always extrapolate smarter; however one will soon reach the point of only a few targeted blood draws where the issue of a few distribution volumes with a lot of different age groups arises. It is known, due to the exploration of children diseases, that sometimes it is not of major importance whether half a dose or a quarter a dose is administered, and that often the starting values can be similar between adults and children due to metabolic differences. Usually “first in man” studies are performed on adults. Whether a healthy or diseased subject is used however always depends on the medication that is being tested. For a cough syrup or a vaccination it can be easily justified to test them on healthy human beings - nonetheless this is not the case for chemotherapies or enzyme replacement therapies for instance. In this case one would intentionally harm healthy subjects, thus one has to make use of the already affected populations.

12.5 Regulatory pitfalls

The purpose of the paediatric regulation, that includes the paediatric investigation plan as well, was to have paediatric drug development run simultaneously to adult drug development.

According to Prof. Dr. Ladenstein this has not fully resulted in the expected outcomes. The issue she stated is that it was mainly focussed on the indication. She brought up the example where a drug was developed for lung or breast cancer, which both do not occur in children, which meant for the industry that they had a waiver to skip paediatric development. Prof. Dr. Ladenstein pleaded that for example signal transduction pathways would allow several connections between adult and childhood indications.

She mentioned the practical example of ALK inhibitors, which can, due to mutations in the ALK pathway, be used not only in lung cancer but also in neuroblastoma, which is the second most frequently occurring cancer in children worldwide. In roughly 10% of children with these malignancies an ALK mutation can be found. In most cases however, there are no drug development processes performed on children simultaneously to adult drug development. There have been cases where only 10 to 15 years later an approval could be achieved. Prof. Dr. Ruth Ladenstein emphasized that matters are evolving slowly, but way too late.

“Was ich sagen möchte ist, die Dinge kommen ganz langsam in Gang, aber sie kommen viel zu spät.“ (Interview line 105)

According to the professor, the most important part is the so called “mode of action” (MOA), whose implementation would enable a broader development in paediatrics. In basic research there is still a huge lack of information. Even though most of the basic mechanisms are already known, they are just being ignored by solely focussing on the indication itself. As she illustrated before with lung and breast cancer, if the focus was the mode of action, parallels between adults and children could be drawn. Prof. Ladenstein considers the incorporation of the MOA one of the big game changers in the field.

A lot of changes have to happen from a regulatory perspective. The industry needs to become more involved, for all of the urgently needed parallel developments to actually be achieved. In accordance to Prof. Dr. Ladenstein only global and local changes on the regulatory level can lead to improvements, which she and her colleagues are trying to accelerate at the moment. The networks are continuously evolving and even the World Health Organisation stated the need for action for paediatric drug development. 80% of cancer incidents are not in Europe, which implies it to be a global problem. What the world has attained as of today, in terms of available medications for children, is a reflection of incapability. In this case she even refers to the wealthier countries, as poorer countries have achieved even worse results.

„Das, was wir heute erreicht haben, kann eigentlich mit einem Armutszeugnis, bezüglich welcher Medikamente, welche wir für Kinder verfügbar haben versehen werden. Da reden wir aber trotzdem noch immer von den Luxusstaaten.“(sic!, Interview line 115)

In paediatrics only 60% are properly approved medications for all age groups and all indications. In oncology, even 80% of the drugs are used off label, especially in neonatology. For the professor, the main categories that need to be improved, are not only in oncology but also in all of the other special disciplines of paediatrics, such as diseases of the metabolism or innate diseases.

According to Prof. Dr. Ladenstein patent prolongation, an incentive, is very controversial, especially in the USA, as companies even receive a so called “priority voucher” which can result in large amounts of money if one can prove a certain medical need or an orphan status. This priority voucher can nevertheless be used for other developments as well, meaning that companies are not obligated to use it for paediatric drug development. Professor Ladenstein mentioned that these incentives have been exploited and that they have not resulted in the intended outcomes. The biggest mistake for her was that all of these incentives were based on the indication and not on signal transduction. She pleads that rework is urgently required in these areas.

„Dann konnte man so einen „priority voucher“ einsetzen, aber auch für eine ganz andere Entwicklung. Man ist sozusagen nicht gezwungen das in eine Kinderentwicklung zu investieren. Man hat sich also in diesen Anreizsystemen sehr wohl vergnügt. Sie haben nur nicht ausreichend gegriffen, um dies korrekter zu formulieren. Einer der größten Fehler war, dass dieses ganze System an der Indikation aufgehängt wurde und nicht an der Signaltransduktion. Sprich, es braucht jetzt die Nachschärfungen in diesen Bereichen.“(Interview line 122)

12.6 Biomarker

Prof. Dr. Ladenstein sees biomarkers as something indispensable, that she and her group have made use of for decades already. They can enhance diagnostics, risk assessment and can help to identify whether a drug is druggable or actionable. They allow researchers to retrieve insights into potential starting points in drug development.

12.7 Innovative trial designs

According to Prof. Dr. Ladenstein Bayesian designs are very common and something that has been implemented for years already. However, she pleaded that in order to obtain useful information, an informative prior action is required – meaning that one has to use data from earlier study groups. This helps to reduce the required number of patients.

As a consequence, if this is not done, the trial is no different from a classic design with lower significance limits and less certainty while calculating. In her opinion, it is nothing world changing.

She believes that opportunistic trial design's usefulness highly depends on the setting, as an ethic committee's vote is required as soon as blood is drawn, especially from a child. To summarize, one needs to explain and argue what they are studying and why and where they are studying it. Her point is that an industry partner is required and only then it could be a useful approach to study for example pharmacodynamic parameters and metabolism. However, the performed research should be bound to a specific dosage recommendation for example. This is what the industry professionally does when initiating studies in the paediatric population. The information gathered needs to be applicable.

„Das macht die Industrie ja dann professionell, wenn sie Kinderstudien aufsetzt. Natürlich kann ich so auch Wissen vermehren, aber dann ist es quasi nicht umsetzbar und anwendbar." (Interview line 175)

What Prof. Dr. Ladenstein considers an interesting approach, are so called ''Basket trials''. She explained that in these trials people make use of different signals such as molecular genetic parameters. They are then collected in the so called "basket", which can be for example different solid tumour childhood cancers, which all have the same signal pathway. These will then show some similarities signal-wise. These signals can then be clustered into molecular genetic groups for instance. In theory one will then have one medication per group available.

"Was in der frühen Entwicklung recht spannend ist, sind zum Beispiel solche Szenarien wie die sogenannten „Basket trials". Das ist nichts anderes als dass man sozusagen in einer Struktur die unterschiedlichen Signale abgreift, von zum Beispiel molekulargenetischen Parametern, macht quasi einen Topf, wie zum Beispiel Kinderkrebserkrankungen aus gewissen soliden Tumoren, wo man weiß diese Signale haben die alle, auch wenn unterschiedlich ausgeprägt, diese Signale überkreuzen sich dann über drei oder vier Entitäten. Dann mache ich einen Basket trial, wo ich die alle hineingebe und clustere die einfach in molekulargenetische Gruppen. Dann habe ich quasi für jede Gruppe ein Medikament parat. Das ist ein sogenannter Basket trial. "(Sic! Interview line 180)

What she mentioned to be very new and innovative is that a lot of industry partners are collaborating through these basket trials, which would not have been imaginable in the past due to the natural competition among them.

„Dann kommt dann noch dazu, das ist relativ neu, das war früher unvorstellbar, dass durch die verschiedene Medikamentengabe, sich mehrere Industriepartner in so einem Basket trial wiederfinden, was wirklich neu und innovativ ist und früher eigentlich undenkbar war. Natürlich hat man sich wegen dem Markt und der Konkurrenz voneinander abgegrenzt. Und jetzt wird sozusagen grenzübergreifend in Europa Gesundheitsversorgung gemacht, um auch in der Industrie hier sozusagen neue Partnerschaften zu schließen." (Interview line 188)

12.8 Future of paediatric drug development

What Prof. Dr. Ladenstein expects in the future is that the standard of testing these drugs becomes the same as in adult drug development.

„Ich erwarte mir von Medikamenten, die in Zukunft für Kinder auf den Markt kommen, das was man für Erwachsenenmedikamente für selbstverständlich hält." (Interview line 209)

Ideally, drugs used on children are specifically tested and approved for children, for each indication and for each age. In her opinion this should be out of the question. Another factor to consider is that drugs are not only administered intravenously but also orally, which is the bigger obstacle according to her. Formulations need to be adjusted to the paediatric population, which means that the pills should have a reasonable size for children and in the case of a syrup it needs to be palatable. These are additional pharmacokinetic and pharmacological developments that need to be considered, as a normal pill of an adult cannot be swallowed by a child. The shredding of pills is also not an option as this would change the galenics of the drug, since drugs are coated in a way that the active ingredient is released within a certain time frame. These are complexities that need to be dealt with in addition to the different age groups.

13. Key findings of the expert interview

- ➢ Regulatory guidelines focussed too much on the indications rather than on the signal transduction. The mode of action (=MOA) was neglected and incentives were exploited. Regulatory frameworks need to be revised.

- ➢ Age groups need to be urgently considered as children are undergoing major changes during development that may interfere with pharmacokinetic and pharmacodynamic parameters.

- ➢ Paediatric formulations need to be taken into account early in development as they differ significantly from adult formulation and might affect drug disposition.

- ➢ Parallel development between adults and children should be facilitated. Processes need to be accelerated urgently.

- ➢ Educational work should be promoted to assure patients and their environment understand that they are in a safe environment and that children should not be protected from but rather by research. Off-label use of drugs results in increased risks for children.

- ➢ Paediatric drug development needs to be handled on a global rather than a local level. Intensive collaboration is needed.

In the past, regulatory incentives have mainly focussed on the indication which led to major exploitations of the system. If the regulatory framework would rather focus on the mode of action, more similarities could be found between adult and children cancers. Frameworks, such as the Paediatric Investigation Plan, have not led to the promised results. Therefore, revisions of the regulatory guidelines and policies are urgently required. Parallel development is required as there are, if one is rather focussing on the signal transduction than on the indication, a lot of cases where mutations are present in different cancer types in children and adults. In this case Basket trials might be a very interesting approach as this approach facilitates precision medicine. Furthermore, networks should be built that focus on involving the industry, the regulatory authorities as well as other parties involved in the drug development and approval process. Also the consumer should be made aware of the presence of off-label use of drugs and what this means. Off-label use facilitates the presence of avoidable risks for children. The misperception of people that the conduction of research on children is something unethical and risk-bearing should be clarified.

Children are not protected enough due to lacking research. If research takes place it is usually delayed to a later point in time which is preventable. There is a major time delay between research performed on adults and children. Processes should be accelerated by promoting parallel developments by revising regulatory frameworks that actually draw parallels between children and adults populations regardless of the indication. These changes should follow on a global level, as paediatric cancer is a global problem and the majority of cases are outside of Europe. Moreover, the differences between drug development for the paediatric and the adults' population need to be considered very early on. Trials on children are highly complex as they go through a highly dynamic development process, resulting in the fact that a four year old cannot be compared to a 14 year old.

Age groups need to be urgently considered and make the drug development process one of a kind. If a drug is approved for a certain indication but not tested in all of the relevant age groups there is major lack of information regarding dosage, efficacy and ADME due to dynamic development processes happening. Last but not least, specific paediatric formulations are required as children differ significantly from adults. They need to be adjusted to the children's needs and should, as already mentioned, consider factors from tablet size, way of administration to even palatability.

14. Discussion

There has been a significant shift in the last few years in paediatric drug development. The children's right to benefit from clinical research while still being protected as well as new policies and solutions have been a major focus. Nevertheless, there are still several obstacles to overcome in order to guarantee innovative, high quality, effective and safe cancer treatments to which children can access quickly. This is especially the case with rare paediatric diseases such as childhood cancers. Therefore, these challenges, which can be financial, ethical, methodological or operational; need to be discussed and innovations need to be explored. This will allow paediatric drug development to move forward.

14.1 Adaptions of legislations

The implemented legislations were crucial as they overall resulted in an increase of labelling therapeutics for paediatric use. Some issues could be observed coming from badly conducted implementation, which ultimately had an impact on paediatric drug development as well as on the patients. The regulations main focus is still on performing clinical studies on children additionally to adult studies, whereas they should not be considered as add-ons but rather as part of the development process from the beginning on. This also explains why a lot of progress has been made specifically in diseases which affect both populations but not in diseases specific to children and diseases that differ significantly between adults and children on a pathological level. Existing regulations and legislations need to be re-evaluated taking into consideration the existing policies that had a positive impact on public health. These reviews and considerations should be performed by independent boards to reduce bias and risks in quantitative as well as qualitative analysis. Moreover, it is highly crucial that fewer exceptions will be made for postponing or not even conducting paediatric clinical trials and that companies will be required to complete paediatric trials and properly report them.

Incentives of the USA, PREA and BPCA, have not resulted in the expected improvements in drug development for children as off-label prescription of drugs in children is still increasing in the USA. A suggestion could be adjusting those requirements in a similar way the EU has done, to achieve better results. In the EU obligations as well as incentives are combined in one legislation, whereas in the US the obligations are included in the PREA and the incentives are included in the BPCA. Furthermore, the EU has also focused more on establishing clinical trial networks. In addition, summaries of the research performed under both the PREA and BPCA should be made public to create more open access sources and to improve and speed up paediatric drug development processes.

A solution might be, to make the written reports from the FDA public in order to create more transparency in terms of what had been required and what was actually done by the sponsor to meet these criteria. More transparency is also required in cases where the Paediatric Advisory Committee reviews adverse events for BPCA but not for PREA trials. Furthermore, it can be criticized that the PREA requires the paediatric study of the drug to be conducted only for the same implications as in adults. This is highly limiting, as literature has reported some major advancements in drug discovery regarding drugs being repurposed for children for a completely different indication as intended in adults.

Generally speaking, legislative changes will never be able to address all of the recurrent issues in paediatric drug development. Some factors to consider include expanding public and private communications to find gaps in medical needs, improve clinical trial design and identify unique approaches for data generation.

Additionally, it is crucial to facilitate data sharing by creating international databases to make better use of already existing data and to implement better preclinical as well as clinical research infrastructures in order to drive forward innovative drug development for children. Generally speaking, more hospitals should be equipped to perform clinical studies in children, as units for paediatric clinical research are rare and in hospitals resources are often lacking. All of the factors mentioned should be incorporated into the legislative framework in a flexible and meaningful way to enhance the paediatric drug development of tomorrow.

When changing and adapting paediatric policies and legislations, it needs to be carefully considered that they will not just have an impact on the regional public health systems but also globally. These policy proposals should always ensure, on a regional level, that drug development is not hindered due to the fact that they do not conform to global regulatory requirements for paediatric drug development. Consequently, the aim should be to generate global rather than regional solutions.

The small numbers of trials able to succeed take a long time to be completed, which often results in immense time spans between the indication in adults and paediatric labelling. Even though new regulations have been set up, certain guidelines and clarifications are still missing to increase parallel developments.

Parallel developments need to be driven forward and need to be planned early on. The PIP is mandatory at the end of human pharmacokinetic studies, whereas in the US the PSP is required at a later point of time after Phase I and II are completed. (Fig. 22)

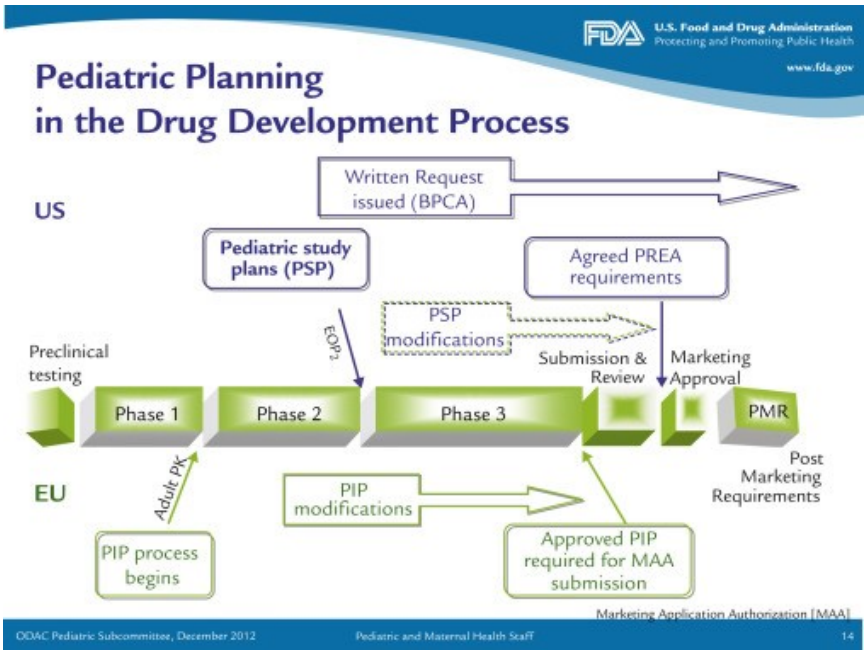

Fig. 22: Planning of the paediatric drug development process. (Milne, 2017)

The correct planning and preparation is of major importance as the PIP as well as the PSP need to be submitted in time. However, if they are submitted too early, the workload might increase as later modifications might be required. If the submission takes place too late it may result in a blocked submission.

Another obstacle that needs to be faced is the fact that waivers and deferrals can be obtained without major efforts as the main focus is on the indication. They can be obtained for all children of all age groups. Waivers can also be obtained if a drug is most likely ineffective and unsafe, if the disease does not occur in children or there is not a clear therapeutic benefit. Waivers enable companies to postpone their paediatric studies and developments to a later point in time if there are concrete measures. The main issue with this is that waivers and deferrals can easily be demanded when the assessment of paediatric and adult drug development is based on the indication. Several regulatory guidelines are based on the cancer type or indication the drug is used for, rather than the signal transduction.

This way, research in children is avoided, as there are several cancer types that are specific to the adult population even though similarities may be present in terms of MOA. A common example that has been mentioned before is breast cancer, which does not occur in children. Companies can easily obtain waivers and save a lot of money and time by not developing drugs for children. The focus should move from the indication to the mode of action (=MOA).

14.2 Preclinical considerations required for paediatric research

Children are not considered to be small adults on a physiological and pharmacological level. Liberation, absorption, distribution, metabolism as well as elimination significantly differ between adults and children and so do dose-drug exposure relationships. Moreover, pharmacodynamics are different in adults and children which ultimately alter exposure-response relationships. Thus, the ultimate aim is to retrieve more knowledge about adult-child differences and not to only work with what is already known. There is already more available knowledge about drug metabolizing enzymes and their activity which allows predicting drug metabolism differences. However, there is still a huge lack of knowledge about drug transporters and their impact on, for example, biomembrane crossing of a drug. Nevertheless, this could reveal huge insights into pharmacodynamic and pharmacokinetic differences between adults and children which could promote efficient drug design for the latter.

There are no appropriate animal and cellular models for childhood cancers yet as these models cannot replicate the differences in physiology as well as pharmacology between adults and children as observed in humans. The lifespan of the animals used in research is short in comparison; they mature and develop in relatively short time periods - ranging from days to months. In human beings lifespans of several months to years can be expected. This negatively affects the assessment of appropriate dose-exposure-responses which results in a lack of useful clinical information. Tailored technologies need to be invented to find better cellular models, make more use of juvenile animal models or apply micro-dosing in the first studies on the paediatric population to retrieve insights into PK. Examples might be pluripotent stem cells, the use of 3D cell cultures, organs-on-a-chip, patient-derived cell assays, more target validation, high-throughput cell image analyses, non-invasive drug delivery systems, and devices to measure drug safety or efficacy as minimally invasive as possible.

The increased usage of juvenile animal models could be used to better understand the differences between adults and children and to retrieve insights into specific toxicities for development as well as maturation.

As mentioned before, there are several factors that could influence the safety profile of a drug used on children such as weight, target organ development and growth, immune system development, and differences in receptor expression.

Furthermore, the importance of differences in body mass or the percentage of total blood volume between adults and children should not be underestimated to retrieve valuable insights into dose-effect relationships.

Even though exposures to a compound in plasma of children and adults are comparable, this does not automatically mean that the same percentage of the compound actually reaches the target organ in both. This is especially the case for non-systemic cancers in children.

Another aspect that should be taken into account are pharmacogenetics. Especially cancer can be caused by genetics. It is important to know the effects of ontogeny and the variable genetic interactions with drug response. An approach could also be the development of pharmacogenetic biomarkers.

All of the differences between adults and children also result in the urge to address paediatric formulations early on. Drugs used specifically on children require adjustments in terms of tablet size, if being administered orally, taste and potentially galenic properties.

14.3 In silico approaches as additional tools

Data obtained from juvenile animal models can be extrapolated for child cancer research, due to its correlation to growth in children. It can then be applied in modelling and simulation approaches. As a result knowledge about diseases, characteristics of drugs, *in vivo, in vitro*, target patient populations and certain trial parameters to enhance study design can be generated. This data can be used supplementary. For instance age-specific differences in drug effects as well as their implications for children can be assessed. Furthermore, these approaches can be of help for using *in vitro* data to generate potential outcomes and complexities in the clinical surroundings for ADME as well as PD/PK. Experimental protocols can be optimized, the number of animals can be reduced, and the efficacy, as well as accuracy, of the data extrapolation can be improved.

Physiologically based pharmacokinetic modelling is also a good example, as it can optimize already present information to predict and guide future paediatric clinical trial design. Dose-response modelling of pharmacokinetic and pharmacodynamic data provides an appropriate dose selection for paediatric trials in advance. Real world evidence can be used to check the feasibility of trials conducted on children while also providing the data required for the appropriate selection of the study design. This real world evidence can then be combined with actual trial data to confirm and solidify results.

It is known that innovative approaches will never be able to stand alone without actual clinical trials, especially from a regulatory perspective, but they can make trials more efficient and safe by including prior information and knowledge into the planning and ultimately the analysis of studies conducted on children.

14.4 Differentiation between age groups

Drug development for paediatric cancers equals orphan drug development. There is a huge issue in regards to cancer heterogeneity in children. Several sub-categories will need to be considered which can be divided by age, developmental stage or pharmacokinetics and pharmacodynamics.

Ultimately only a few paediatric patients are available for each specific cancer type. Worth mentioning is that response patterns might vary between patients of each sub-category which, combined with inclusion and exclusion criteria, may narrow down the patients' eligibility and enrolment rate even further resulting in low statistical power. Consequently the recruitment process is very challenging and inefficient. These underpowered trials might result in a lack of conclusions as well as an incapability to produce clinically significant outcomes regarding favourable as well as adverse events. Conclusively, these deficiencies cause a waste of resources and children to participate in trials that do not show scientifically relevant results. Nonetheless, on a statistical level efforts were made to address these issues. Possible approaches that have already been implemented include novel test designs requiring smaller sample sizes and collaborations of multi-national groups and trial networks which share their data and resources to ultimately join forces. Due to the differences in weight, organ maturation and body composition children should be subdivided into at least four categories depending on their age: age 12 to 18, age 2 to 11, age 28 days to 23 months and birth to 28 days (neonates). These groups can also be adjusted depending on different countries or research groups. It always needs to be assured that there is a similarity between the children in a treatment group and that they are comparable, whereas the specific age limit of the treatment groups is not as important as long as comparability is assured within the subgroups.

It is a fact that especially for the neonatal period research is desperately needed. Not all of the paediatric sub-groups have benefited from changes in regulations equally and especially the younger groups of the paediatric population are still suffering because of extensive off-label use of drugs. For them, and their specific physiology, an even smaller amount of different therapies exist. New policies and reforms as well as possible solutions to financial and operational concerns are needed to address this issue.

All of the above mentioned difficulties require an intense cooperation between clinicians, manufacturers and regulators as well as patients and their parents in order to enhance clinical trial design and to adjust trials to the specific and unique needs of the neonatal subgroup.

14.5 Outcome measure adaption

The same outcome measurement methods cannot be used for each age group since children are continuously growing and maturing through the different developmental stages. Several reactions can occur following drug intake such as nausea, pain, dizziness, different sedation levels, visual as well as auditory responses. All responses need to be measured according to the age of the child being examined. Age-appropriate tools need to be implemented such as the Faces Pain Scale instead of simply asking the child verbally. Due to different body compositions the pharmacokinetic properties may also differ a lot between the age classes. Several studies have resulted in incomplete or incorrect conclusions for this very reason. In studies involving different age classes, which is often the case due to the small sample sizes in paediatric clinical research, the doses need to be adjusted to the patient's weight or body surface area. Moreover, qualitative outcome measurement techniques such as observing the impact of the illness and treatment on the quality of life are growing in importance as they are crucial for the family and the child. After all, it needs to be carefully considered whether the response of the parents is used, just the feedback of the child itself, or even both.

Generally speaking, it would be a step in the right direction to include parents as well as children in outcome measurements since this might also impact their willingness to participate in a trial.

14.6 Biomarkers tailored to children

There is a major issue regarding biomarkers as they are most often extrapolated from adult data and not tailored to children's needs and developmental processes and changes. The heterogeneity between the paediatric patients results in a low prevalence of specific cancer types which leads to a small study group. Considering multicentre collaborations might be the way to obtain a significantly larger study population to generate sufficient data sets and reach a certain statistical power. Moreover, age-specific control samples need to be provided in order to closely monitor the influence of developmental changes on the biomarkers behaviour and vice versa. This is clearly a sensitive topic given that it requires conducting research on healthy children. Only procedures that represent a very low risk for the subject should be allowed.

Several factors should also be considered, such as simplifying the consent process for biomarker development and making retaining samples as long as possible, for future research, more efficient. Genetic predispositions to adult-onset diseases caused by inheritance from family members also need to be given thought to.

Fortunately advances have recently been made in the “omics” fields, which range from genomics to transcriptomics, metabolomics and proteomics, and can be used to obtain insights into the underlying biology of a healthy or diseased organism. Nevertheless, ample work on translating and applying these techniques into the paediatric clinical field is still needed, a process that has been remarkably slow so far.

14.7 Informed consent process considerations

A major issue, even though numbers of enrolled paediatric patients have risen due to new regulations, is that carrying out clinical trials on children is still not accepted by society due to the fear of unnecessary exposure of the paediatric population to unknown treatment effects. Furthermore, an issue still is the attitude of parents towards their children participating in clinical trials. They tend to be afraid of exposing their children to unknown side effects. A major concern is that the doctors may not see their child’s health as a priority. To counteract this, some efforts were made to support parents in their decision making process, for example by enhancing the readability of the consent form. Additionally, the research context, the maturity in terms of emotions, and the cognitive abilities of the child and the family system should be taken into account. There should be more communication between the trusted investigators and the families to ensure that common misperceptions can be diminished, therefore time as well as attention are required to really educate parents and also children on clinical trials and their aims. This will lead to parents understanding that trials are fair tests of treatments which should never jeopardize the child’s health. The use of placebos or the standard of care is also a controversial subject. Many parents are reluctant to give their permission assuming that, if their child receives the drug of the control group, it would serve no end. This concern can be mitigated by assuring them that, if the treatment is proven effective, every child in the control group will receive it.

The fears of the children participating in a trial also need to be considered. Children tend to fear needles, for example, which makes obtaining blood samples rather challenging for physicians. Therefore, alternative approaches need to be introduced, such as finger or heel pricks or salivary samples to decrease the discomfort experienced by children.

A child-friendly environment needs to be ensured and additional stress factors need to be minimized beyond routine clinical care. Furthermore, it is crucial to guarantee that investigators are properly trained to conduct trials on children, that the facilities are adapted to children’s needs and that recruitment and trial conduction is facilitated by a well-educated trial coordinator. The importance of involving children and parents in the recruitment process, the consent process and the design of the trial itself should never be underestimated.

The informed consent process for children is rather difficult as parents, acting as their child's guardians, have the responsibility to protect them. Parents feel uncomfortable with this situation since they need to make a decision for their child. However, decision making could be improved by enhancing their knowledge of research ethics, monitoring the safety of their child and governance procedures. Some other parental concerns are the threat to their child's condition, trial risks, personal values and experiences, and the nature of the trial. These concerns could be addressed by enhancing positive interactions during the recruitment and also tailoring the clinical treatment and trial procedures to the child's and parent's needs as long as trial data is not affected, such as adjusting techniques for necessary blood draws as has been mentioned before. Therefore, trial staff should be made aware of the parents' needs and also probable misconceptions that can arise. This tailored trial information should be included in the informed consent process. Trial information should also be made comprehensible in an age appropriate way so the child can be incorporated in the decision making process as much as possible. Having said that, it is important to acknowledge and respect a child's dissent. Moreover, what could enhance informed consent procedures is to allow parents to take more time for their decision making progress and provide them with additional material to read at home.

14.8 Paediatric extrapolation to reduce the amount of children and time

Adolescents should be included in Phase I adult studies of most cancer treatments by the US legislation. In a lot of cases efficacy and safety can be compared between children in their adolescence and adults with the positive effect of decreasing ethical concerns. Therefore, information needed for younger patients can be extrapolated from data obtained from adolescent studies. Subsequently, waiting periods, between adult program approval and paediatric labelling, of usually 9 years can be reduced. Therefore, drugs can be approved faster and patients receive quicker access to information regarding dosage and side effects.

By using paediatric extrapolation, efficacy data obtained from adults can be extrapolated to the paediatric population. However, this is only the case if the responses to the treatment as well as the course of the disease are comparable between adults and children. Adult patients should be used in cases where data obtained from them can be used to sufficiently answer any study specific questions, as children represent a vulnerable population that needs to be protected. Therefore, paediatric extrapolation should be used whenever adult and paediatric indications are identical. This approach also requires extensive planning in advance and during adult development, if the data is to be used as supportive data in paediatric drug development.

As an example, including the dose range in adult programs, specifically in biomarker development, can result in extensive exposure-response profiles which can be subsequently applied to child drug development. Extrapolation of efficacy data from studies on adults, with more and wider dose ranges, can therefore reduce the amount of data needed.

Combining these approaches covers finding the right dosage and safety information as well as obtaining efficacy data. This will ultimately reduce the time needed for the development of drugs for children whilst also reducing the risks children are potentially exposed to. However, the study design should allow to use extrapolation as a process, since adjustments will need to be made during the development process as knowledge is gained.

In cases where it is uncertain whether a drug will work for children to the same extent as for adults, Bayesian statistics are a great option. They represent an analytical tool that allows smaller paediatric studies with increased efficacy and sound statistical conclusions. This methodology also represents a variant of extrapolation as it uses data from adults, adolescents and placebo experiments and ultimately combines them with newly obtained paediatric response data to arrive at an estimate for a treatment response. It can provide evidence which allows reducing sample size significantly and helps to decrease trial duration as well as slow enrollment resulting in study delays.

14.9 Innovative trial designs to improve research in children

Precision trials are a good tool to follow the mode of action approach and increase parallel developments. Designs such as basket trials should be implemented more, as they are based on similar mutations between children and adult cancer types and finding appropriate treatment options for each. Furthermore, they often provide the opportunity to also include younger populations. Researchers, physicians, the industry and regulatory authorities should start to think outside the box and implement new trial designs that allow to move away from simply considering the indication itself. The consideration of the mode of action will allow to decrease sample sizes and time to retrieve statistically sound results, learn more about diseases and their target and to find similarities between different cancer types and their control mechanisms.

14.10 Key challenges and opportunities

- ➢ Drugs are commonly used off-label on children, with lack of knowledge in terms of dosage, efficacy and safety

- ➢ Research is however urgently required as there are important characteristics that distinguish children from adults regarding clinical pharmacology

- ➢ These differences do not only show between children and adults but also between children of different ages and maturity, even further distinction is needed between neonates and adolescents

- ➢ M&S can help to gain valuable insights into the clinical pharmacology of the different age groups of children and adults, Modelling and simulation can be combined with clinical data and provide additional support for new submissions

- ➢ Regulatory guidelines and legislations should be adapted, instead of drawing parallels between childhood and adult cancers simply by the indication, the focus should shift to finding similarities regarding mode of action and signal transduction (increased number of parallel developments)

- ➢ Developments for children should be started early on, as a parallel process to adult developments

- ➢ Age specific formulations need to be considered early on

- ➢ Innovative approaches that are moving away from the indication and the cancer type and focus on the signal transduction itself should be implemented, designs such as basket trials can help overcome the hurdle of small sample sizes and limited time and generate statistical power, efficient baskets can be aggregated and inefficient ones can be dropped

- ➢ For all of the issues mentioned, an intensive collaboration between drug developers, the health authorities as well as academia is required

15. Conclusion

Drug discovery and development is a long process that starts at the discovery phase, moves on to preclinical development - *in vitro* and *in vivo* - and ends at the clinical stage where the new medicine is first tested on the paediatric population. If safety and efficacy is proven it will be authorized for the market. Taking into account the major differences between children and adults, it becomes clear why drugs that are intended to be used on children should also specifically be tested on children, in a controlled and safe environment and not used off-label. Furthermore, one should not forget the ethical obligations present when dealing with children, as they should only be enrolled in trials if studies on adults cannot provide the information sought and in studies that have shown high probabilities of completion. We are therefore faced with a strong ethical responsibility to find appropriate alternative solutions to provide children with safe and effective treatments in time.

It is highly crucial to start thinking differently and not only translate results, obtained from adults, to children - due to the major physiological and also pharmacological differences within the development process. Of course there are advantages in repurposing drugs and the use of extrapolation; however, this should rather be seen as a complementary measure than the routine way to proceed.

Research should evaluate targets unique to the mode of action affected in the paediatric population and should not be solely driven by knowledge obtained from adult indications. Animal as well as cellular models should be used and significantly improved by implementing novel technologies. Cancers are considered rare diseases in children and are often unique to this population - progress in basic research is therefore desperately needed. It is crucial to understand disease mechanisms for the development and manifestation of medications and in order to select drug targets and validate them. *In vitro* and *in vivo* models that properly represent forms of childhood cancer are therefore indispensable. The specifications of paediatric drug development, such as formulation and toxicities, should be considered very early on, starting in the discovery phase and continuing in the operational phase.

Novel methods, such as basket and umbrella trials, should be implemented in order to reduce the number of children needed compared to conventional trial design (which is based on pre-set numbers). The use of modelling and simulation will also help to find proper dosing regimens for both the preclinical and clinical phase.

Innovative approaches just like these will help to overcome issues highly present in paediatric clinical research: small sample sizes (due to the high heterogeneity), the urge for age groups, a stronger focus on the MOA, the need for parallel developments, decreasing the exploitation of waivers and ethical concerns such as general acceptability. Another important factor to consider is that due to the small sample sizes and the rarity of childhood cancers, global networks are essential. Physicians, researchers as well as patients should work together collaboratively on a global rather than a regional level.

Last but not least, more work needs to be done on quantitative and qualitative assessments specific to paediatrics, such as finding proper endpoints and outcome measures, assessments for psychophysical parameters, such as questionnaires and scales, and methods for assessing adverse events. Tools such as biomarkers should also be used to support clinical trials.

All of these factors combined will help to improve the planning, the initiation as well as the execution of trials performed on vulnerable subjects such as children and ultimately decrease off-label use and provide a safe and controlled environment for children dependent on medications as it is the case in paediatric cancers.

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Appendix

Zusammenfassung

Präklinische und klinische Forschung im pädiatrischen Bereich haben zu signifikanten Verbesserungen in der Kinderkrebstherapie geführt. Nichtsdestotrotz wurden die meisten dieser Therapien durch Studien an Erwachsenen entdeckt, da Kinder üblicherweise nicht einbezogen wurden in diese Prozesse. Bis heute werden die meisten Medikamente „off-label“ genutzt, das heißt ohne klinische Daten von Kindern, obwohl die Unterschiede in Medikamenten Disposition, Aktivität sowie die Heterogenität von Kinderkrebs allseits bekannt sind. Fortschritte in der Medikamentenentwicklung und Kinderkrebsforschung haben gezeigt, wie wichtig es ist Kinder in kontrollierten klinischen Studien miteinzubeziehen und für sie angepasste Therapien zu entwickeln. Diese Arbeit zeigt die Probleme auf, die es zu überwinden gibt, um neue Therapien für Krebs in der pädiatrischen Population zu entwickeln, welche Lücken es derzeit gibt in Forschung und Entwicklung und die Schritte, die gemacht werden müssen, um den Prozess zu verbessern. Die Hauptprobleme, die identifiziert werden konnten, waren, dass die pädiatrischen Verordnungen darauf basieren, für welche Indiktion ein Medikament genutzt wird und nicht auf die Wirkungsweise, das nichteinbeziehen von Altersgruppen und pädiatrischen Formulierungen, kleine Patientengruppen, fehlende Parallelentwicklungen zu Erwachsenenstudien, fehlende Aufklärungsarbeiten bezüglich klinischen Studien an Kindern und die Dringlichkeit pädiatrische Medikamentenentwicklung auf einem globalen und nicht auf einem regionalen Level zu betrachten. Diese Arbeit stellt einen Ansatz vor, um die heutige Wissenschaft zu kapitalisieren und neue Medikamente für Kinder mit Krebs zu entwickeln mit der Hilfe von juvenilen Tiermodellen, M&S, innovative Studiendesigns und Überarbeitung von aktuellen Verordnungen basierend auf deren bisherigen Einfluss.

Hofer: Guten Tag Frau Prof. Dr. Ladenstein. Könnten Sie mir einen kleinen Einblick geben in die Entwicklung von klinischen Studien in Kindern in Österreich, speziell am St. Anna Kinderspital in Wien?

Ladenstein: Das wichtigste an unseren Studien ist, dass sie eine Geschichte haben, die in den späten 60er Jahren begonnen haben, also das ist mehr als ein halbes Jahrhundert. Das war eine strategische konsekutive Arbeit getrieben durch die Deutsche Forschungsgemeinschaft in der pädiatrischen Hämato-Onkologie, auch GPOA genannt, wo der frühere Chef des Sankt Anna Kinderspitals, Professor Gardener, auch ein Mann der ersten Stunde sozusagen war, da er bei einer der ersten Therapien der Leukämie, der häufigsten Krebsart im Kindesalter, beteiligt war. Was dann gekommen ist, war quasi eine Stufe für Stufe strategische Weiterentwicklung, mit Einführung immer wieder neuer Medikamente, in der Folge dann Randomisierungen, das heißt offene Vergleiche von zwei verschiedenen Ansätzen, oder das Zuführen eines Medikaments das so geprüft wird. Aus dieser sehr strategischen Therapieentwicklung haben sich jetzt mittlerweile sehr standardisierte Behandlungskonzepte entwickelt, auf welche die Erfolgszahlen der Kinderkrebstherapie rückzuführen sind. Diese liegen laut den neuesten Zahlen der Statistik Austria derzeit zum Beispiel in Österreich bei 85%.

Hofer: Was sind die Besonderheiten bei der Durchführung von klinischen Studien in Kindern im Vergleich zu Erwachsenen?

Ladenstein: Die Besonderheiten bei der Durchführung von klinischen Studien in Kindern sind fundamental, weil normalerweise, wir gehen zurück auf die Medikamentenentwicklung, braucht man, damit man eine Zulassung bekommt, wie man jetzt auch an Corona sieht, dass das an bestimmten Altersgruppen getestet wird, weil die Organismen unterschiedlich sind. Was man sich oft nicht bewusst macht ist diese Komplexität im Kindesalter, in der Pädiatrie, weil sich hier vom Neugeborenen bis hin zum Adoleszenten, jetzt kann man sich vorstellen welche Entwicklungen hier vonstattengehen, nicht nur optisch und äußerlich, sondern das betrifft auch Verteilungsvolumina, andere Formen der Verstoffwechselung, die ganze Pubertät, wo sich natürlich auch durch Hormoneinflüsse wieder gewisse Dinge ändern im Körper, sodass die Wirksamkeit und die Dosierung von Medikamenten all diese Dinge berücksichtigen muss. Man braucht eigentlich eine altersspezifische Testung jeglichen Medikaments. Da gibt es einem unheimlichen Rückstand. Wir haben in der pädiatrischen Onkologie über 80% off-label use, das heißt das wurde nie in der speziellen Indikation durch die Industrie und in der speziellen Altersgruppe getestet. Das sind aber auch sogar in der Neonatologie 90%. Und weil man immer aufgrund unserer Geschichte Angst hatte vor dem sogenannten Versuch am Menschen, dann hat man immer mehr über das Ziel hinausgeschossen und Kinder vor der Forschung geschützt anstatt Kinder durch die Forschung zu schützen. Es gibt sozusagen gesetzliche Verordnungen, sowie die pädiatrische Regulation, das ist eine Verordnung die üblicherweise durchgreift über die Gesetzesebene oder auch eine „Orphan Drug“ Verordnung, die aber

nicht so gegriffen haben, dass wir eine signifikante Änderung bis dato sehen bei diesen Medikamentenentwicklungen. Was bedeutet das jetzt genau? Das bedeutet, dass wir strategisch über ein halbes Jahr Kinder behandelt haben im off-label use Bereich, dadurch wir natürlich die Wirkungen und Nebenwirkungen mittlerweile sehr gut kennen und die Teilungsraten uns recht geben. Ich sage immer, wenn ich im Kindesalter Leukämie gehabt hätte, wäre ich ein Todeskandidat innerhalb der nächsten Wochen gewesen, nur um das greifbar zu machen, welchen Sprung wir da eigentlich erlebt haben. Jetzt gibt es sozusagen über all diese Zeit Standards, aber sie sind alle vom off-label use. Der Preis den wir dafür zahlen, hat sicher auch damit zu tun, dass wir hier auch behandeln in einem gewissen Dunkelbereich, was jetzt die Dosierungen, pharmakokinetics, pharmakodynamics etc. anbelangt. Das heißt manche Medikamente haben natürlich Spätfolgen, aber die müssten aus unserer Sicht nicht so hoch sein, weil wir bei bis zu 70% der Kinder Spätfolgen in den Organsystemen sehen und das wird im Laufe des Lebens immer mehr. Deswegen halten wir im Moment ein großes Plädoyer, dass die Industrie, letztendlich die ganzen Regulatoren im pharmazeutischen Bereich, die europäischen, die amerikanischen Arzneimittelbehörden etc., aber auch die die dann letztendlich Medikamente in den eigenen Ländern zulassen, die Gesundheitsbehörden, das wir hier über einen Schulterschluss erzielen, dass mehr Medikamente dann ganz speziell für Kinder getestet werden über die Forschung, aber in einer Parallelentwicklung zum Erwachsenenalter. Oft ist es so, dass eine ganze Erwachsenenentwicklung abgeschlossen wurde, das dauert dann 10 Jahre, und dann kam irgendwie die Kinderentwicklung. Wir hatten in den letzten 10 Jahren zum Beispiel in der Erwachsenenonkologie über 150 neue innovative Medikamente am Markt, in der Pädiatrie sind davon genau 9 angekommen. 3 davon waren Immuntherapien und eine davon habe ich selber entwickelt, genau 18 Jahre von „Bench to Bedside“, das ist sozusagen das Drama welches wir hier haben. Ich sitze auch im Europäischen Komitee wo wir dann auch unsere Plädoyers halten und lobbyieren, um da einen fundamentalen Wechsel einleiten zu können, mit einer Aufmerksamkeit zur Medikamentenentwicklung. Das bedeutet dann natürlich auch Studien im frühen Bereich und testen, testen, testen. Das bedeutet aber auch viel Aufklärungsarbeit, dass man in einer Studie eben kein Versuchskaninchen ist, sondern dort bestmöglich aufgehoben und versorgt ist, beobachtet wird und dort eigentlich in einem sichereren Netzwerk ist.

Hofer: Was ist eine der größten Fehlwahrnehmungen in Bezug auf Medikamente die für Kinder genutzt werden?

Ladenstein: Die Leute glauben, wenn man etwas in der Verpackung kaufe und bekomme, dann ist das für mich gemacht. Die Menschen sind nicht aufgeklärt darüber, selbst im niedergelassenen Bereich der Pädiatrie, auch dort haben wir in Bezug auf die Altersgruppen nur 60% der Medikamente zugelassen. Dann in Bezug auf orale Antibiotika, hier herrscht sozusagen eine „Wald und Wiesen“ Pädiatrie. Selbst in diesem speziellen Bereich ist es oft nicht bekannt, dass selbst bei einem Fieberzäpfchen oder bei einem Hustensaft, man in die speziellen Altersgruppen hineingehen muss und es zugelassen

werden muss. Das ist niemandem so richtig bewusst, die Gesellschaft hat gelernt perfekt wegzuschauen.

Hofer: Was ist Ihre Meinung zur Extrapolation von Daten? Macht es Sinn von Erwachsenen auf Kinder zu extrapolieren und vice versa?

Ladenstein: Wir extrapolieren ja jetzt, das ist quasi unsere Gangart, dass wir extrapolieren, auch für die Zulassungen. Man rechnet quasi über eine Quadratmeterdosis vom Kind um und sagt ein Quadratmeter ist 30kg und dementsprechend kann man das dann umrechnen. Man kann natürlich auch schlauer extrapolieren, aber damit sind sie schon im Forschungsbereich mit wenig gezielten Blutproben, wo sie dann sehr wenige Verteilungsvolumina in den verschiedenen Altersgruppen haben. Man kann auf jeden Fall intelligenter extrapolieren. Man weiß ja aufgrund von den Erkrankungen im Kindesalter, das nicht immer eine halbe oder eine viertel Dosis so bedeutsam ist und man oft mit vergleichbaren Werten starten kann aufgrund der Verstoffwechselung. Im Grunde genommen wird eine „first in man““ Studie, es kommt darauf an um welches Medikament es sich handelt, am Erwachsenen durchgeführt. Das ist ganz unterschiedlich, man kann natürlich nicht alle Medikamente am gesunden Probanden testen. Bei einem Hustensaft kann ich das noch ganz einfach machen oder auch bei einem Impfstoff, kann dies aber nicht mit einer Chemotherapie oder einer Enzymersatztherapie machen. Hier würde ich ja aktiv einem gesunden Menschen schaden. Ich kann nur in die betroffenen Gruppen hineingehen, die auch spezielle Konstellationen haben. Aber der Sinn der „Paediatric Regulation“ die den „paediatric investigation plan“ vorgeschrieben hat, war ja auch die Entwicklung bei den Kindern parallel und zu den frühen Entwicklungen zu schalten. Es hat mehr oder weniger gut funktioniert. Da gab es Schwierigkeiten in der Verordnung, weil es leider an der Indikation per se festgemacht wurde. Zum Beispiel es wurde ein Medikament für Lungenkrebs oder Brustkrebs entwickelt, dann war das ganz einfach, denn Lungen- und Brustkrebs gibt es nicht im Kindesalter, dann hatten sie sozusagen eine Befreiung, einen „Waiver“ und mussten nicht für die Kinder entwickeln. Hier weise ich auf die Transduktionssignale hin, da gibt es eigene Wege die Parallelschlüsse zulassen. Ein praktisches Beispiel ist, es wurden für Lungenkrebs ALK-Inhibitoren entwickelt. Es gibt beim Lungenkrebs, sowie auch den Lymphomen genetische Mutationen oder auch Amplifikationen und da kann man mit Inhibitoren entgegenwirken. Vor ca. 10 Jahren, beim Neuroblastom, der 2. Häufigste kindliche Tumor, bei sehr jungen Kindern ist es so, dass wir dort bei bis zu 10% auch diese ALK Mutationen finden. Es gab jedoch überhaupt keine Medikamentenentwicklung parallel dazu. Das heißt der erste Einsatz war wieder aus dem akademischen, wissenschaftlichen Bereich. 10 bis 15 Jahre später konnte erst die Zulassung angestoßen werden. Was ich sagen möchte ist, die Dinge kommen ganz langsam in Gang, aber sie kommen viel zu spät. Da müssen in der Gesetzgebung auch noch Veränderungen passieren, dass auch die Industrie nicht so leicht aus der Schuld gelassen wird, auch die notwendigen Parallelentwicklungen, auch aus dem Verständnis der regulativen Zellabläufe, das man hier auch über

den Tellerrand schaut und das hier auch ganz anders regulatorisch aufsetzt. Dorthin wird die Reise gehen und das ganze wird das hoffentlich beschleunigen. Das sind die Dinge die wir versuchen massiv zu beschleunigen in den neuen politischen Foren und Gremien, weil man das auch nur durch Gesetzesänderungen, für Europa aber letztendlich auch weltweit, schaffen kann. Die Vernetzungen schreiten mittlerweile voran. Es gibt viele Bereiche wo die WHO dann auch schreibt, dass etwas beim Kinderkrebs passieren muss, es sind ja 80% der Inzidenzen außerhalb von Europa. Da gibt es ja weltweit ein riesengroßes Problem. Das, was wir heute erreicht haben, kann eigentlich mit einem Armutszeugnis, bezüglich welcher Medikamente, welche wir für Kinder verfügbar haben versehen werden. Da reden wir aber trotzdem noch immer von den Luxusstaaten.

Hofer: Was halten Sie von den Belohnungssystemen die eingeführt wurden, um klinische Forschung in Kindern voranzutreiben?

Ladenstein: Diese Patentverlängerung, das ist interessant, in den USA auch nochmal interessanter, da bekommen sie einen sogenannten „priority voucher“, da kann man dann wenn man eine „medical need“ oder „orphan“ Zulassung hat, hohe Geldsummen, über 100 Millionen Euro bekommen. Dann konnte man so einen „priority voucher“ einsetzen, aber auch für eine ganz andere Entwicklung. Man ist sozusagen nicht gezwungen das in eine Kinderentwicklung zu investieren. Man hat sich also in diesen Anreizsystemen sehr wohl vergnügt. Sie haben nur nicht ausreichend gegriffen, um dies korrekter zu formulieren. Einer der größten Fehler war, dass dieses ganze System an der Indikation aufgehängt wurde und nicht an der Signaltransduktion. Sprich, es braucht jetzt die Nachschärfungen in diesen Bereichen.

Hofer: In welchen Bereichen sehen Sie Nachholbedarf in der pädiatrischen Medikamentenentwicklung?

Ladenstein: Es ist überall Nachholbedarf in der pädiatrischen Medikamentenentwicklung. Selbst in der breiten Pädiatrie haben wir nur 60% ordnungsgemäß zugelassene Medikamente in allen Altersklassen und dann natürlich in allen Spezialdisziplinen. Die Highlights sind „off label use““, Onkologie, 80% sind in off label use, dann Neonatologie. Jetzt gehen sie mal weiter in die ganzen seltenen Erkrankungen der Pädiatrie, Stoffwechselerkrankungen, alle angeborenen Erkrankungen, die letztendlich dann oft durch Enzymersatztherapien gesteuert werden können. Es gibt wahnsinnig viel zu tun.

Hofer: Was sind die maßgeblichen Faktoren die man berücksichtigen muss in der klinischen Forschung in Kindern?

Ladenstein: „MOA“, also mode of action, das ist diese Signaltransduktion die ich angesprochen habe. Das ist eine der wichtigsten Ansatzpunkte, um zu einer breiteren Entwicklung im pädiatrischen Bereich zu kommen. In der Grundforschung muss noch viel getan werden, wobei das spannende ja ist,

dass wir alle diese Grundmechanismen schon kennen. Es war nur so, dass man sie nicht berücksichtigen musste, weil man sich rein nach der Indikation gerichtet hat, mit dem griffigen Beispiel der Onkologie mit Lungen- und Brustkrebs, wo man dann quasi ausgenommen war von der Verpflichtung, da diese Karzinome nicht in Kindern auftreten. Wenn man aber auf diesen „mode of action“ geht, dann kommt man sofort in ein völlig anderes Szenario. Das ist einer der größten Treiber, die hier einen Unterschied herbeiführen könnten.

Hofer: Für wie relevant halten Sie die Anwendung und Entwicklung von Biomarkern für Kinderkrebs?

Ladenstein: Wir wenden Jahrzehnte lang schon Biomarker an, das ist enorm wichtig für uns. Einerseits einer der entscheidenden Faktoren bezüglich Biomarkern ist eine verbesserte Diagnostik, aber dann auch für die Risikoeinschätzung, weil wir auf Basis von Biomarkern stratifizieren, aber auch weil Biomarker uns dann natürlich die Option geben zu sehen ob ein Medikament „druggable“ oder „actionable“ ist. Das heißt, dass wir über die Biomarker ja das Verständnis bekommen wo wir bei neuen Medikamentenentwicklungen ansetzen können. Das heißt das ist das sogenannte „Schlüssel-Loch“ Prinzip. Das heißt dementsprechend hat das die breite Bedeutung.

Hofer: Was ist Ihre Meinung zu sogenannten „Bayesian Designs“?

Ladenstein: Bayesian Designs sind etwas was wir schon immer gemacht haben. Es ist keine Zauberformel. Es ist nur eine andere Form der Interpretation. Im Grunde genommen ist ein Bayesian Design nur dann von einem Mehrwert, wenn man tatsächlich einen „informative prior“ mitverwendet, das heißt man muss frühere Studiengruppen konzeptionell miteinbeziehen. Man hat dadurch dann weniger Fallzahlen. Wenn man das nicht macht, entspricht dies eigentlich einem klassischen Design, nur dass man die Signifikanzgrenzen massiv absenkt und unsicherer kalkuliert. Man drückt es dann nur anders aus, das ist eine der spannenden Kommunikationstücken. Es ist nicht eine Zauberformel.

Hofer: Inwiefern sehen sie „opportunistic trial designs“ als relevant an?

Ladenstein: Bei „opportunistic trial design“ ist immer die Frage in welchem setting sie das machen. Man braucht heutzutage, gerade wenn man bei einem Kind Blut abnimmt, zuerst ein Ethikvotum und muss sagen was sie studieren, wie sie es studieren und wo sie es studieren. Idealerweise macht man so etwas mit einem gemeinsamen Industriepartner. Aber natürlich kann ich pharmakodynamische Parameter studieren, wenn ich sie jetzt nicht nur völlig losgelöst von allem habe. Ich muss es ja dann irgendwo einpflegen in zum Beispiel eine Dosierungsempfehlung und das heißt wenn ich das im „stillen Eckchen“ mache, dann kann ich viel erforschen, aber es wird nichts bringen. Wenn ich das aber in einem gewissen Setting mache und sich die Kreise hiermit schließen, dann kann ich Informationen bekommen über die Verstoffwechselung. Das macht die Industrie ja dann professionell

wenn sie Kinderstudien aufsetzt. Natürlich kann ich so auch Wissen vermehren, aber dann ist es quasi nicht umsetzbar und anwendbar.

Hofer: Was sind Ihrer Meinung nach die interessantesten Studiendesigns in der pädiatrischen Medikamentenentwicklung?

Ladenstein: Es gibt viele spannende Designs wo man heute schaut. Was in der frühen Entwicklung recht spannend ist, sind zum Beispiel solche Szenarien wie die sogenannten „Basket trials". Das ist nichts anderes als dass man sozusagen in einer Struktur die unterschiedlichen Signale abgreift, von zum Beispiel molekulargenetischen Parametern, macht quasi einen Topf, wie zum Beispiel Kinderkrebserkrankungen aus gewissen soliden Tumoren, wo man weiß diese Signale haben die alle, auch wenn unterschiedlich ausgeprägt, diese Signale überkreuzen sich dann über drei oder vier Entitäten. Dann mache ich einen Basket trial, wo ich die alle hineingebe und clustere die einfach in molekulargenetische Gruppen. Dann habe ich quasi für jede Gruppe ein Medikament parat. Das ist ein sogenannter Basket trial. Dann kommt dann noch dazu, das ist relativ neu, das war früher unvorstellbar, dass durch die verschiedene Medikamentengabe, sich mehrere Industriepartner in so einem Basket trial wiederfinden, was wirklich neu und innovativ ist und früher eigentlich undenkbar war. Natürlich hat man sich wegen dem Markt und der Konkurrenz voneinander abgegrenzt. Und jetzt wird sozusagen grenzübergreifend in Europa Gesundheitsversorgung gemacht, um auch in der Industrie hier sozusagen neue Partnerschaften zu schließen.

Hofer: Was sind die größten Unterschiede zwischen Kindern und Erwachsenen, die man berücksichtigen muss, in Bezug auf klinische Studien in Kindern?

Ladenstein: Klinische Studien in Kindern sind komplexer als in Erwachsenen. Sie lassen es quasi für einen Erwachsenen zu, wenn sie es jedoch für Kinder zulassen, müssen sie sich sofort über die Altersgruppen Gedanken machen. Das heißt ich kann entweder sagen ich nehme in eine Erwachsenenentwicklung noch 16 Jährige mit, da sie ab 16 in der Regel so ausgereift sind, dass quasi vom jungen Erwachsenen vom Stoffwechsel her kein großer Unterschied mehr ist. Das ist quasi eine „low hanging fruit". Das wird jedoch schon bisschen anders, wenn ich dann schon die 12 Jährigen mitnehme, dann müssen sie überlegen, dann hab ich die Population der Volkschulkinder, dann haben sie die ganzen Kindergartenkinder und dann haben sie das frühe Kindes- und Säuglingsalter. Das heißt schlagartig, wenn Sie sagen Sie lassen etwas für Kinder zu, Sie konfrontiert sind mit zumindest vier unterschiedlichen Altersgruppen, die unterschiedliche Dosisfindungen haben. Das heißt, obwohl der Markt kleiner ist und die angesprochene Population kleiner ist, haben Sie den vier oder fünffachen Aufwand.

Hofer: Was erwarten Sie sich von Medikamenten die in Zukunft auf den Markt kommen für Kinder?

Ladenstein: Ich erwarte mir von Medikamenten die in Zukunft für Kinder auf den Markt kommen, dass was man für Erwachsenenmedikamente für selbstverständlich hält. Idealerweise ist es für Kinder, für jede Indikation, für jede Altersgruppe, für jeden Patienten ordnungsgemäß geprüft und zugelassen ist, dass das eine Selbstverständlichkeit ist. Was bei den Kindern dann noch dazukommt ist, dass wir ja nicht nur von intravenösen Medikamenten, da hat man es ja einigermaßen in Griff, sondern es gibt ja auch eine Reihe von Medikamenten die oral einzunehmen sind, und da genau haben sie bei Kindern ja wieder das Spektrum, dass man es in eine Formulierung bringen muss, die kindgerecht ist. Das heißt es sind entweder ausreichend kleine Tabletten, oder sie müssen eben einen Saft haben, und der Saft muss schmecken. Das sind andere pharmakokinetische und pharmakologische Entwicklungen, die sie dann zusätzlich noch machen müssen, weil die große Erwachsenentablette ein Kind einfach nicht schlucken kann. Wenn man das dann zerbröselt, dann passt das von der ganzen Galenik nicht mehr. Tabletten sind ja auch ummantelt, dass sie den Wirkstoff in einer gewissen Zeit freisetzen. Das sind die ganzen Komplexitäten, also nicht nur die ganzen Streuungen in den Altersgruppen, sondern auch die Formulierung.