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Global Pediatric Drug Development Collaboration:

Part One

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Introduction

The pharmaceutical industry is highly competitive. The stakes are high, and while the costs are significant to get a drug to market, so is the potential payback. Competition is often accepted as the path to profitability. However, the pharmaceutical industry is not like any other industry in that the products of this competition can dramatically improve, and even save, lives. This is especially the case when it comes to children. Children are generally healthier and so comprise a small population of pharmaceutical consumers. However, children that are sick have a greater need for products given the paucity of treatment options specifically for the pediatric population.

How can this apparent contradiction of competition for profits be reconciled and solved with such small populations and increasingly precise and sophisticated therapeutics?

In Part One of this white paper series, we demonstrate that collaboration is a critical piece of the solution and there is already evidence of this in the industry. We consider the key stakeholders in the development pathway and provide examples to show that moving from competition to collaboration may be their answer to thrive and survive, particularly for pediatric research and especially for childhood cancer. Part Two of this series discusses the pivotal role of global collaboration and alignment between agencies in bringing safe and effective treatments to the children who need them most. Click here to read Part Two now.

Sponsor Collaboration

The National Cancer Institute (NCI) defines a clinical trial sponsor as "a company, institution, group, or organization that oversees or pays for a clinical trial and collects and analyzes the data." The sponsor "takes responsibility for and initiates a clinical investigation."[1] Government agencies, academic institutions, non-governmental organizations, foundations, private individuals, or companies can sponsor trials, but the majority of sponsors are pharmaceutical or biotechnology companies who fund over 60% of clinical studies.[2]

Pharmaceutical companies are often viewed as not trustworthy by the public.[3] As described here, collaboration with consortia, sites, and patients contributes to the need for increased transparency and accountability of sponsors who must embrace this to earn the public's confidence.[4] Further, collaboration between sponsors is critical not only to meet these demands but also to overcome the significant challenges in drug development and to get safe efficacious medicines to market within a reasonable time.

With few exceptions,[5] the primary goal of pharmaceutical companies is to make a profit. The numerous challenges of drug development culminate in one critical number: the significant cost of getting a therapeutic to market. This is not a simple calculation and estimates range up to $2.8 billion (US)[6] with a recent study calculating a median cost of $985 million.[7] Overall, drug development costs double about every 9 years.[8] Profitability is further pressured due to strained healthcare budgets and patent expirations, which have resulted in the dramatic increase in generic drug prescriptions from 40% in 2005 to over 85% by 2018,[9] and an overall decline in rate of return.

Among the many reasons for the high cost of trials and declining rates of return, such as competition from generic drugs, patent cliffs,[10] rising R&D costs, decreased budgets, and increased regulatory requirements, the industry faces rapidly increasing technological complexity and sometimes legal liability. However, the greatest contributor to the high cost of getting a drug to market is the cost of failures. Attrition rates for clinical trials remain high, with approximately 85% of therapies failing in early phases. The very expensive late stages have an estimated success rate of around 50%,[11] though this may actually be closer to 25% for novel therapies.[12] Failures at this later stage are primarily due to insufficient data to support safety and efficacy.[13]

There is a huge demand for truly innovative drugs that address unmet needs, yet greater innovation comes with higher risk and greater attrition.[14] Traditionally, business models are underpinned by intellectual property rights such as patents. Despite the wealth of scientific and technological advancements, the traditional approach inevitably results in fewer new molecular entities (NMEs) and first-in-class medicines.[15] Overall, patents are becoming less important, while sharing data and specimen repositories are becoming more so.[16] A new approach to drug development is needed to allow for innovative and urgently needed medicines to get approved. Can pharmaceutical companies survive if they diverge from the traditional competitive paradigm for drug discovery? Spreading risk through cooperative models may be the critical factor that allows sponsors to maximize the potential of scientific advancement not just to survive but to thrive.

Public-private partnerships (PPPs) have become more common as a result of the need for a more open innovation model in drug development. Distinct from research investments or joint ventures, PPPs can be defined as agreements between at least one for-profit and at least one not-for-profit organization. This can include academia, non-governmental organizations, governmental agencies, community and volunteer sectors, and health groups. These can further be classified based on the stakeholder participants, and can be broadly categorized within the precompetitive or competitive space depending on stage of drug development, which can be anywhere from pre-discovery through post-approval.[17] The Merck Mectizan® Donation Program in the 1980s was the first life science PPP.[18] Pre-competitive PPPs typically aim to optimize knowledge in the pre-discovery phase, such as creating technology platforms, shared databases, research tools, and specimen repositories.[19] Well-known examples of these include the Innovative Medicines Initiative (IMI) in Europe,[20] the Critical Path Initiative in the US,[21] and the Structural Genomics Consortium.[22] All of these are in the relatively early stages and so their impact on the drug development process is still to be determined.

Imatinib (Gleevec or Glivec) is a groundbreaking success story for numerous reasons, from being the first successful targeted drug by rational design to remarkable improved overall survival rates for its usage in appropriate patient populations diagnosed with CML. Imatinib transformed the diagnosis of Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) from a death sentence to one with the potential for long term survival.[23] However, perhaps less recognized, it is also notable as the result of years of partnerships between public and private organizations such as Novartis (then Ciba-Geigy), the Dana-Farber Cancer Institute, The Friedrich-Miescher Institute, the Oregon Health Sciences University, the NCI, NIH, and FDA.[24]

Advancements with the various '-omics', data analysis, specimen banks, and more, can now fulfill the potential for personalized, or precision, medicine.[25] Progress in precision medicine is by far the most advanced in translational oncology with over 90% of approved precision treatments in 2018 being cancer therapies.[26] The heterogeneity of cancer and its genetic complexity are significant challenges and have made it a key target for understanding the molecular basis of the disease, thus advancing targeted treatment for adults.[27] Now we stand on the cusp of enacting change for pediatric oncology through the imminent implementation of the Research to Accelerate Cures & Equity (RACE) for Children Act. Initial forays with innovative partnerships demonstrate exciting potential, especially in the pre-competitive space. We anticipate seeing more of these becoming necessary in order to both comply with such legislative requirements and successfully develop new therapies.

Attrition at the later stage efficacy studies is expensive and a significant amount of this can be avoided by thorough validation of biomarkers and companion diagnostic assays early in the drug development process. This is where collaborations, such as Proof-of-Concept PPPs, between academic medical centers and industry are shifting to address the challenges and opportunities presented by the advent of 'omics.' Academic medical centers benefit from the rigor of industry quality standards for therapeutic decision making, and industry benefits from the depth of expertise, specimen repositories, and data commons[28] required to drive the discovery and analysis of biomolecular determinants for study success.[29] The key challenge in these types of collaborations is the shift from some of the aspects relevant for the traditional business model, such as material transfer agreements and intellectual property in the form of patents.[30]

Collaborations are growing and evolving quickly, and recent data demonstrate that the impact of these collaborations in the area of precision medicine, especially in oncology, are yielding an increase in R&D productivity.[31] More specifically, this impact has been observed for *adult* oncology, though a great advantage for drug development for pediatric cancers is that they are typically less molecularly complex than those of adults.[32] Well-characterized models will have great potential for downstream success.

Pediatric oncology has not yet benefited from the boom in precision medicine. However, there are a number of initiatives and stakeholders devoted to molecular characterization of childhood cancers by collaboratively developing and sharing preclinical testing data. These PPPs include the Pediatric Preclinical Testing Consortium[33] and the ITCC P4 platform.[34] With greater emphasis on the development of pediatric oncology therapies due to the upcoming RACE for Children Act, these collaborative efforts will be critical to enable faster identification of promising treatment options.

Precision medicine exacerbates what is already a key challenge for most trials: identifying and recruiting patients. Looking for a smaller sub-population that fits a particular profile is more challenging. A key approach that sponsors will need to embrace for pediatric oncology is master protocols. The FDA defines master protocol as a protocol designed with multiple sub studies which may have different objectives and involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure.[35] The very definition of coordinated efforts is to work together.[36] With childhood cancer being rare, master protocols should be an effective and efficient way to assess multiple products in small subpopulations. While rare, pediatric cancer is a significant unmet need, with only 12 NMEs ever developed (from 1953 to 2019) and FDA-approved specifically for children's cancer.[37]

Master protocols require collaboration on a variety of levels, as there is one protocol, and ideally a central governance structure, IRB, repository of data and specimens, and screening platform, to name a few. To fully realize the potential of master protocols, it is critical that sponsors take into account the challenges of sites in particular so that the trial reaches patients in a seamless manner. We describe this in more detail further on.

The NCI-sponsored pediatric Molecular Analysis for Therapy Choice (MATCH) trial (NCI, 2016) is a basket trial and an example of a PPP involving 10 pharmaceutical companies with the goal of early phase safety and signal seeking assessments.[38] The Leukemia & Lymphoma Society (LLS) is currently initiating its ground breaking PedAL (Pediatric Acute Leukemia) master umbrella trial for children with AML, again with multiple industry partners.[39] Figure 1 illustrates a simple graphical representation of basket, umbrella, and platform trials.

Necessity drives innovation, and the need is great for pediatric cancer. More than 80% of pediatric patients survive past five years after treatment, which is a dramatic improvement in outcome compared to 60 years ago when this was closer to 10%.[40] However, cancer remains the leading cause of death by disease in children in developed nations, with the rates of cancer actually rising over the past few decades.[41]

Success in treatment of the most common childhood cancer, acute lymphoblastic leukemia (ALL), has been especially impressive. A child diagnosed with standard risk ALL now has a 90% chance of being cured compared to 10% in the 1960s.[42] However, successes such as these are variable depending on the type of cancer. Brain cancer comprises 15% of the malignancies in children. Brain tumors are especially difficult to treat for a number of reasons, including challenges with getting targeted therapies past the blood-brain barrier. An innovative collaboration that is in development addresses the aggressive brainstem tumor, diffuse intrinsic pontine glioma (DIPG), and is an example of the types of innovative collaborations that are needed. DIPG is almost always fatal, but DIPG tumors have been found to be specifically associated with ACVR1 mutations, which suggests that the encoded protein receptor kinase (ALK2) could be a drug target. A couple of preclinical models have supported this association. However, due to it being in a small pediatric population, the challenges with location of the tumor, and the high failure rate of those studies that have previously been conducted, the potential financial return for investors is so low that the traditional approach to drug development for this tumor is not likely.

Enter a new approach that has proven attractive to governments, foundations, and even industry partners: a virtual company, M4K Pharma, founded to develop existing pre-clinical ALK2 inhibitors into a drug candidate. M4K Pharma has aligned various academic and industry research into a drug development program.

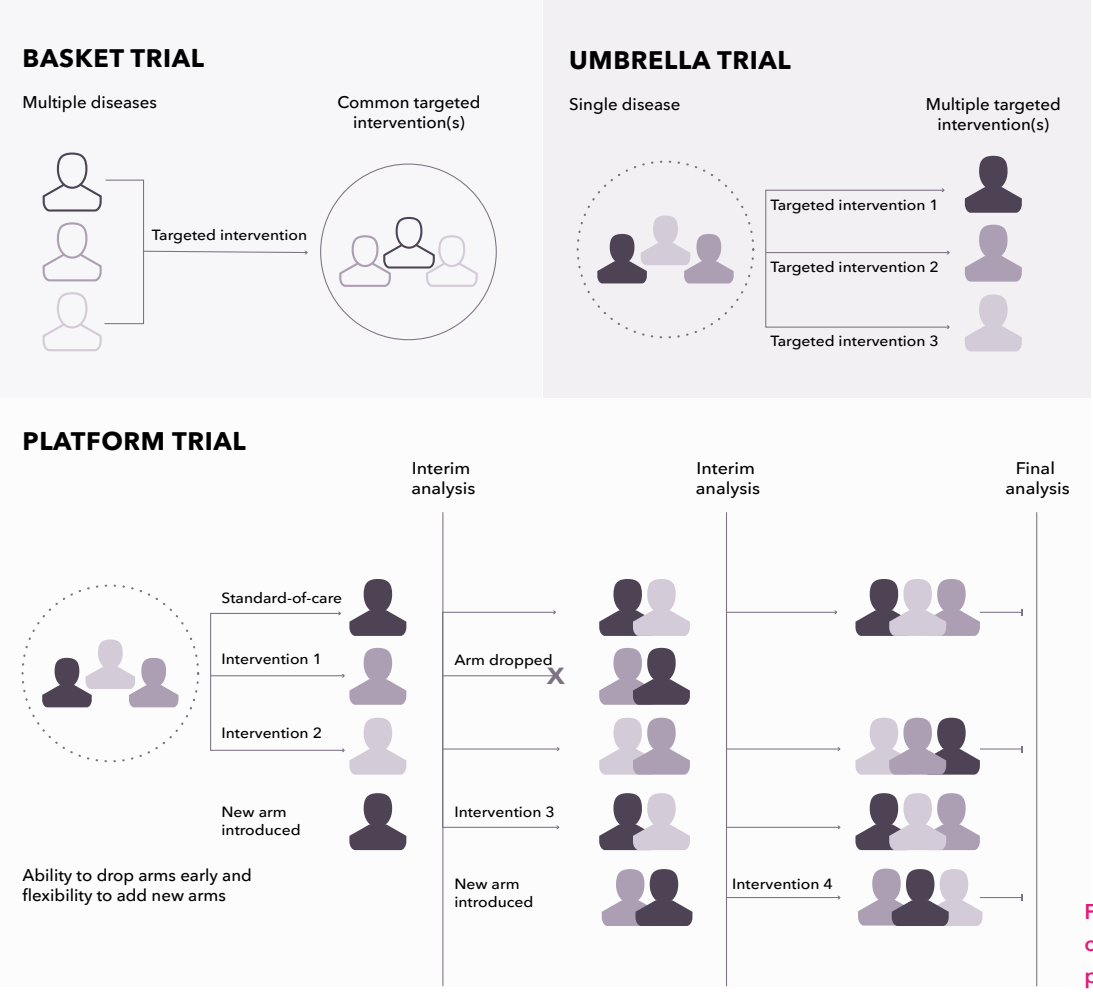

Figure 1: Graphical representation of basket trials, umbrella trials, and platform trials

They have not filed for patents, but rather are covering the sharing of data by establishing it as 'prior art.' This means that the shared data cannot be used by third parties for filing patents, yet encourages disclosure.

Create a Culture of Site Collaboration

Another key contributor to the success of clinical trials are the investigators at sites. Pediatric institutions tend to prefer investigator-led research where they can have more input on study design rather than industry-sponsored as they are likely to have less involvement, especially in the early stages of trial development.[43] This, together with additional challenges of insufficient training and expertise in conducting pediatric trials for drug approval, inadequate clinical trial infrastructure and site resources, and scarce funding sources,[44] make it difficult for sponsors to recruit sites for pediatric studies. Another way to think of site collaboration is site engagement. Having engaged investigators could help boost overall success rate.[45] An important way for sponsors to cultivate site relationships and engagement covering trials in multiple therapeutic areas is to collaborate and consult with investigators early on in the process on key components like feasibility evaluation, study design, and protocol development. Getting sites and investigators invested will help them to take ownership of sponsor-led studies,[46] likely leading to better site recruitment. There are many other attributes of successfully run clinical trials that continue to be pertinent especially in rare disease spaces. The table below was created to provide a comparison of the key responsibilities of the industry and non-industry partner relationship in Company Sponsored Research, Collaborative

Research, and Investigator Initiated Research that helps to align these and other key considerations when sites and sponsors work collaboratively on clinical trials (Table 1).

Sponsors can be aware of these characteristics and have systems in place to help support even the most complex pediatric trials. Improved collaboration is a start and sponsors will discover what collaboration techniques work best for which trials and at what sort of sites. All this involves close involvement, communication, and understanding of the entire process, especially from trial design and informed consent. The goal of developing these relationships isn't just for one individual trial. Good sponsor-site relationships also go a long way for consideration of sites and patient recruitment for future trials.

Key Responsibilities	Company Sponsored Research	Collaborative Research	Investigator Initiated Research
Initiator of study proposal	Industry/Company	Industry or Non-industry partner/ investigator	Non-industry investigator, *must not be solicited by industry partner*
Regulatory responsibility/sponsor	Industry/Company	Non-industry investigator	Non-industry investigator
Study objectives	Industry/Company	Both parties	Non-industry investigator, but may be aligned with Industry Objectives
Study design	Industry/Company	Non-industry partner, driving the design and input from both parties	Non-industry investigator
Protocol design/development	Industry/Company	Non-industry partner, driving the development and input from both parties	Non-industry investigator
Study execution	Industry/Company	Non-industry partner, driving the execution but potential input from both parties	Non-industry investigator
Data ownership/sharing (including alignment with General Data Protection Regulation)	Industry/Company	As per agreement	Non-industry investigator
Data reporting (including registration and clinical study report disclosure and publications)	Industry/Company	As per agreement	Non-industry investigator
Ownership of intellectual property	Industry/Company	As per agreement	Non-industry investigator

Table 1: Key responsibilities of the industry and non-industry partner relationship in Company Sponsored Research, Collaborative Research, and Investigator Initiated Research[47]

Mitigating Pediatric Master Protocol Challenges for Sites

There is no denying that pediatric clinical research is challenging. Multiple causes underlying this increasing trial complexity include reliance on biomarkers, innovative biostatistical input, input from advocacy groups, regulatory requirements, appreciation of multiple unmet clinical needs in areas of study, and the improved understanding of clinical research itself.[48] In addition, disease pathology, pharmacokinetics, and response to treatment often differ with age, patient size, and/or maturation, meaning that multiple age groups must be studied. This leads to more complex—and expensive—clinical trials,[49] such as master protocols (Figure 1). The advantage of such trials is flexibility and efficiency, especially in the rare disease space where there are small patient numbers. Certain aspects of these complex trials can be difficult for investigators to manage, such as contract and budget negotiations, investigator meetings, site research personnel training, multiple required committee approvals including institutional review boards, multiple sample collections, intensive patient monitoring, complex drug administration, and multiple protocol amendments.[50] It's important for sponsors to collaborate with sites to reduce the burden of pediatric trials as much as possible. This should include recognition and consideration of site cost including staff time and minimizing and consolidating amendments when possible.

Sponsors should be thoughtful of the wide range of collaborative relationships that investigators have with other disciplines that are also helping to care for the pediatric patient/trial participant. For example, a pediatric solid tumor patient may need biopsies that need to be coordinated and prioritized per the trial with interventional radiology, and/or surgery. Sometimes even major academic centers may have difficulty meeting specific trial demands so no assumptions should be made.[51] It is important for sites themselves to be involved in the education of their immediate colleagues to help ensure the right test and timing is placed at high priority.

Pediatric Consortia Collaboration

One of the best examples of collaborating rather than competing in the history of clinical trials goes back to the roots of the Children's Oncology Group (COG). Instead of four different consortia (Children's Cancer Group, The Pediatric Oncology Group, the National Wilms' Tumor Study Group, and the Intergroup Rhabdomyosarcoma Study Group) each trying to separately improve pediatric cancer outcomes, these four organizations joined forces in 2000 to form COG. COG is the largest consortia offering pediatric trials across the globe and has been instrumental in improving overall survival rates for childhood cancer from 10% in the 1950s to almost 80% presently.[52]

The comparatively low incidence of cancer in children and resulting sample size constraints require a multi-center and multi-disciplinary approach to manage and oversee clinical trials in pediatric cancer, as for other rare diseases. International and multidisciplinary collaboration has emerged due to the small sample sizes with even further sub-classification based often on biology of the tumor and trial complexity. According to the COG website, 90% of all children under the age of 15 years with a newly diagnosed malignancy are seen at a COG institution and if a clinical trial is available, 60% of eligible children are enrolled.[53] Patient and trial resources are set up at consortia sites and it is through a collaborative approach that further trials with the same common aim of cures and improved outcomes can be tapped by working with consortia, though there may also be unique challenges similar to those outlined above regarding feasibility, study design, and protocol development. Stakeholder priorities and key roles will need to be discussed and clearly designated. In the upcoming era of more FDA requirements, such as the emphasis on precision medicine in pediatric oncology and the RACE for Children Act in an already rare field, it is expected we will need to go to different and new sites to meet our enrollment expectations as well. Collaboration will need to be fostered in order to develop new relationships and effective new sites. Other networks such as pediatric site or trial networks may also offer sites that are experienced, knowledgeable, and place a high priority on pediatric trials. Networks of sites may provide efficiency gains through shared procedures and processes, and standardized

regulatory grade data collection.[54] Such collaboration can also extend to streamlining start-up of network sites through the selection of a central Institutional Review Board (cIRB) in the US.[55] This was the approach taken by the Institute for Advanced Clinical Trials for Children (I-ACT for Children) who selected Advarra to provide cIRB services for its 44 pediatric research sites.

Another NIH-funded research network is the Rare Diseases Clinical Research Network (RDCRN) which is made up of 23 active consortia each focused on a group of rare disorders. Approximately 25 million people in the US are affected by one or more of an estimated 7,000 rare diseases or conditions. Collaboration of these specialized networks can begin to connect the dots by sharing information. A requirement of the RDCRN is for each consortium to include patient advocacy groups (PAG) as research partners. The RDCRN investigators, affiliated PAGs and patient leaders, NIH Office of Rare Diseases Research, National Center for Advancing Translational Sciences, and collaborating institutes' program staff at NIH and other key stakeholders all agree that the substantial partnership and involvement of patients from the start has been a major factor in the success of the network and helped the consortia conduct important research in a large number of rare diseases.

Patient Collaboration

Patients are an important stakeholder in drug development and are key to the success or failure of a clinical trial. Without patient participation there would be no clinical trials. Patients are the experts in their disease symptoms; they can give insight into the impact of their disease on daily living and which symptoms matter most to them. However, patients are not always the first to be considered when clinical trials are being designed, be that due to regulatory requirements for certain indications or due to sponsors having set ideas on how they intend to conduct their development program. The importance of the patient voice at all stages of drug development is being recognized more and more. Regulators and Health Technology Assessment (HTA) authorities give high value to the patient perspective which can in turn help a drug successfully reach the market. Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) understand the importance of patient input and that patients can help inform the regulatory agencies in their decision making throughout the drug development process. The agencies hold quarterly meetings to share best practices for patient engagement during the regulatory lifecycle of a drug.

At the clinical trial stage this can include input to improve the relevance of patient reported outcomes (PROs), selecting appropriate endpoints for both the indication and the patient population that are also acceptable to the regulators, improving the clinical trial experience for patients and caregivers, and optimizing recruitment and retention strategies. All of these can potentially reduce development costs through the mitigation of aspects that often lead to the need for protocol amendments or worse, trial failure.[56] This is particularly important for pediatric studies where many struggle to succeed due to patient recruitment, adherence, and retention issues. The fact that most EU Pediatric Investigational Plans (PIPs) require modification after the initial agreement,[57] some several times, could be seen as a reflection of such challenges.

So where can the patient voice make the biggest impact and how do we harness this? Patients and PAGs are keen to provide their input, and platforms are available to them to have their voices heard. Patients and PAGs often utilize their online communities to discuss and share their thoughts, but they also require more formal platforms to have their voice incorporated into the drug development process. Various resources and guidance are available to stakeholders on how best to engage with patients and PAGs. The European Federation of Pharmaceutical Industries and Associations (EFPIA) Patient Think Tank provides the platform for sharing knowledge and ideas between patient groups and the pharmaceutical industry to enable patient perspectives to be an integral part of clinical research. The guidance document[58] prepared by EFPIA highlights the principles for successful engagement with patients. This includes ensuring clarity of the purpose of the engagement, transparency regarding the aims of the engagement, including any financial compensation, and respect, all of which help build trust with the patients and PAGs.

Patient input into other regulatory guidance documents is also important. At the invitation of the FDA, the Parent Project Muscular Dystrophy (PPMD) spearheaded an effort to develop the first patient advocacy-led FDA draft guidance[60] for a rare

disease to help accelerate the development and review of potential Duchenne Muscular Dystrophy (DMD). This was done in collaboration with the FDA and the various stakeholders involved in development of new treatments to ensure the final guidance was both evidence-based and responsive to the needs of the DMD patient community. This not only resulted in the guidance (draft in 2015 and finalized guidance in 2018) being issued, but also a much stronger relationship between the FDA, sponsors, and the DMD community.

The role of patient reported outcomes is becoming increasingly important in clinical research to inform decisions during the drug development lifecycle. PROs help stakeholders understand the impact of treatment on the patient's functioning and can help differentiate treatments or treatment regimens with similar survival benefits. However, PROs used in clinical trials often fail to provide robust patient relevant data[61] which can result in the PRO labelling not being received. This failure can be due to inappropriate choice of PRO measure, poor reporting of PROs, and high rates of missing PRO data.

From a pediatric perspective, development of suitable PROs is an ongoing task and has additional challenges, including the need to consider developmental differences and age-based criteria specific to the indication. These can be included as primary, secondary, or exploratory endpoints. However, for the PRO to be considered acceptable for regulatory decision making, it is necessary to demonstrate content validity and acceptable psychometric properties in the target age range, both of which require direct input from the target population. Patients, in particular pediatric patients and PAGs, should be seen as co-creators.[62]

Children and adolescents can be an invaluable resource in pediatric PRO development, providing real-life experience input. They have the knowledge of their disease, the symptoms, and the impact on their wider lives. They can also help identify aspects missing from PROs and those that are not relevant for the intended population to help ensure completion of the PROs is not burdensome. These patients can be effective content experts, ensuring PROs are meaningful to the target age group and target patients, including both the relevance of the content and suitability of the format to ensure engagement of the patient. This may include input on specific words or language used by children and adolescents to describe their treatment or illness. They also enable the necessary cognitive interviews to determine the validity of the content for the intended patient age group. Such cognitive interviewing was used during the development of the PedsQL Diabetes Module where several terms were identified as incomprehensible to some children and the version was updated to include more age appropriate language.[63]

In oncology in particular, the quality of PROs in all patient populations is suboptimal and needs to be improved to ensure they add value to the decision making process.[64] PRO use in pediatric oncology is still uncommon and the lack of PROs can mean that pediatric patients are under reporting how they are feeling as they do not have a standardized reporting process. Having suitable pediatric specific PROs for oncology would allow for the child's voice to be heard and help improve care.[65]

The FDA Oncology Centre of Excellence Patient Focused Drug Development (PFDD) program focuses on patient outcomes research in cancer patients. This was recognized with an announcement on June 23, 2020 of the launch of a new pilot program called Project Patient Voice. This pilot program will include a public website where sponsors can make data available from PROs in oncology trials.

Cancer patient experiences and the impact of treatment side effects on quality of life can help identify methods to provide additional methods for agencies to assess the effect of cancer therapies on patients alongside survival and tumor information. It should be noted that the FDA and the EMA use different evidentiary standards for PROs in oncology. The FDA has granted very few oncology PRO labels, whilst the EMA is more prepared to grant PRO labelling based on health-related quality of life PROs in addition to other PRO measures. The most common reason to reject the PRO data was that no statistical or clinical difference was seen, followed by excessive missing data. The FDA often cites poor study design and lack of validity of the PROs.[66]

Endpoints are another key area where the patient voice is important. Listening to and understanding what patients think is critical to relevant and meaningful outcomes of a trial. Novel endpoints, particularly for rare diseases, are encouraged by regulators but it is necessary to show they can measure clinically meaningful effects. Regulators continue to advise that patients and PAGs are engaged early in discussions on

selection and development of efficacy endpoints. The FDA PFDD initiative includes a pilot grant program to support development of a core set of publicly available Clinical Outcome Assessments (COAs) and related endpoints for specific indications. To date, three awards have been made, including for Clinical Outcome Assessments for Acute Pain Therapeutics in Infants and Young Children (COA APTIC)[67] which aims to identify meaningful outcomes for acute pain clinical trials in pediatrics through patient and caregiver engagement.

Duchene Muscular Dystrophy (DMD) provides yet another example of how patient advocacy can help develop and drive through the acceptance of a new endpoint for trials. Various DMD PAGs collaborated with and supported the company responsible for developing ActiMyo,[68] a device that measures stride velocity. The European Medicines Agency (EMA) has qualified Stride Velocity 95th centile as a secondary endpoint in DMD trials, making it the first digital endpoint qualified by the EMA. The FDA opinion is still pending.

Patients and the Regulators

Patients have been involved in a number of activities within the EMA since 1996. Article 78(2) of Regulation (EC) No 726/2004 allowed for such interaction on a legal basis, with the inclusion of young people added with Regulation (EC) No 1901/2006. The EMA has a framework[69] for patient interaction. This includes a network of patients and organizations, a forum for exchange of information (EMA Patients' and Consumers' Working Party), and a pool of patients acting as experts in their disease and its treatment. These patients are sometimes included in scientific advice (SA) procedures, with one in five SA procedures including patients in 2018.[70] In 90% of cases, the patient input was considered to have added value to the SA. In one in four cases, recommendations were made by the SA working party to modify the development plan to reflect the patient advice.

Guidance[71] has also been developed for interaction with young patients. The EMA sees that "involving young patients/consumers/carers at this level will also increase their understanding and trust in healthcare."[72] In relation to clinical trial design, features such as endpoints, acceptability of placebo use, study duration, visit frequency, and tests required are seen as areas where young patient input can be useful to the decision making process for the Pediatric Committee (PDCO). Patient representatives are members of the PDCO to provide such input.

The FDA's PFDD[73] initiative was started back in 2012. It "aims to more systematically obtain the patient perspective on specific diseases and their treatments" and to encourage sponsors to incorporate the patient voice in drug development. In order to comply with the 21st Century Cures Act,[74] the FDA is developing a series of PFDD guidance documents.[75] The first was finalized in June 2020 for drug development stakeholders to assist with the collection and use of patient input in drug development and its importance for regulatory decision making. However, the guidances are just that—they are not binding on the regulators.

To help gather patient input, the FDA set up public PFDD meetings to engage patients and gather their views on the impact of their condition on daily life, their most significant symptoms, and their treatments. Over 25 disease-specific, FDA-led PFDD meetings were held gathering feedback on how patients want to be engaged with and their perspectives on meaningful benefits of treatment. In addition, the FDA encouraged and facilitated patient organization-led meetings.

While significant progress has been made to incorporate the patient voice into global drug development, agency collaboration that addresses regulators' views on the acceptability of endpoints, data collection methods, and trial designs which are driven by the patient voice will be critical in making this goal a reality. In Part Two of this series, we'll discuss how global agencies can align to better support global pediatric drug development.

Conclusion

Dr. Klaus Rose, who has more than twenty years in research and development and championed pediatric drug development, stated, "Children do not need more studies; they require reasonable ones."[76] How very true! With small patient populations, more trials are not necessarily better. What is needed is the right trial brought to the right patient at the right time. Discussions about clinical trial prioritization are not unheard of in any therapeutic area and are even more prevalent in pediatric clinical research where the global demand for patients often exceeds the enrollment requirement for all planned trials. Success requires consideration of the needs and perspectives of multiple stakeholders, not the least of which are the patients. Perhaps, ironically, the most recently recognized stakeholders to contribute to clinical research, patients, and PAGs are well placed to continue collaboration with industry and regulators. Patients have a better understanding of what can and can't be changed based on regulatory requirements, but the regulatory agencies must continue to be challenged to adapt and ensure that the patient perspective is implemented in the drug development process. The value that the patient voice has in this process has already been demonstrated with such advocacy efforts as described above.

Global collaboration to seek alignment between agencies and all stakeholders involved in research is key for successful drug development, particularly in pediatrics. The development of medicines for the pediatric population is both challenging and imperative. Hence, we are witnessing increased collaboration among all parties, which could also serve as inspiration for the development of drugs for adults.

Sponsors benefit most from the profits of drug development efforts, but should bear in mind that this is best done if they serve the patients, listen and work with the sites, and follow the guidance and requirements of regulators. Doing so collaboratively and in innovative ways rather than the more prescriptive and competitive *status quo* can release synergies through untapped depth of expertise within and between academic sites, shared data, and ultimately unexpected profits, and further may be the only way to avoid a profit plunge as patent cliffs loom.

From the site perspective, clinical research is a part of their practice and must be coordinated with day-to-day activities. Protocols should be aligned with standard of care where possible. This is facilitated by early engagement of sites and investigators, with investigators ideally having input and ownership of the trial *with the sponsor*. This includes collaborations and integrations with consortia and site networks, whose collective expertise and resources may be leveraged if consulted early and can help mitigate challenges downstream.

How can collaboration be encouraged overall? We've provided examples throughout this paper, but one way is to incentivize collaboration. This may help to ensure that all interests are considered including pharmaceutical companies, academic institutions, hospitals, and regulatory agencies. If not, alignment issues regarding intellectual property, publication policy, conflict of interest, antitrust, or rewards could be compromised.[77] While this was implied for pediatric oncology trials, it could be considered outside of this domain. Any restrictions can slow the development of new drugs that could lead to the discovery of potential therapeutic benefit for patients.

Consider the model that Stand Up to Cancer (SU2C) created which entices innovation and collaboration of these sort of disciplines. This model is made up of a variety of organizations, including those directly in the drug field, advocacy, and even professional clubs and major companies that help to fund research. Here, collaboration is key. "Almost everybody is really good at working in a defined team," Jessica Dudley, MD, Chief Clinical Officer at Press Ganey said. "The majority are able to say, this is my team. And we can work well as a team. The challenge was that in a hospital or clinical setting, you can't just be on one team, because there's so much integration that happens."[78]

Similarly, industry needs to band together to be successful. The SU2C provides the "Dream Team' to grant to multi-institutional groups of scientists who are working together rather than competing, as well as "Innovative Research" grants to cancer research projects which are high-risk but also high-impact. The funds are managed by the American Association for Cancer Research (AACR) while grant management and allocation is controlled by a committee of clinical investigators, physicians, and other experts in the field.[79]

We all have goals, and some that are seemingly in competition are best arrived at working collaboratively.

Together, we can find the cures.

References

1. US Food & Drug Administration. (2019). CFR - Code of Federal Regulations Title 21. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.3#:~:text=Sponsor%20means%20a%20person%20who,private%20organization%2C%20or%20other%20organization.
2. Ehrhardt, S., Appel, L.J., Meinert, C.L. (2015). Trends in National Institutes of Health Funding for Clinical Trials Registered in ClinicalTrials.gov. JAMA, 314:. 2566-2567.
3. Shah, K., 2011. Trends in food and drug administration inspection: A warning for the industry! Perspect.Clin.Res., 2: 81-82.
4. Parrish, M. (2019). Pharma's Damaged Reputation. Pharma Manuf. Available at https://www.pharmamanufacturing.com/articles/2019/pharmas-damaged-reputation/.
5. Betz, M. (2018). The New Nonprofit Pharmaceutical World: What's Up with That? Non-Profit Quarterly, 12 September.
6. DiMasi, J.A., Grabowski, H.G., Hansen, R.W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. J.Health Econ., 47: 20-33.
7. Wouters, O. J. P., Martin McKee, M. & Jeroen Luyten, P., 2020. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA, 323: 844-853.
8. Yildirim, O., Gottwald, M., Schueler, P., et al. (2016). Opportunities and challenges for drug development: public-private partnerships, adaptive designs and big data. Front.Pharmacol., 7: 1-13.
9. Mikulic, M. (2019). Branded vs. generic U.S. drug prescriptions dispensed 2005-2018 Statistica. Available at: https://www.statista.com/statistics/205042/proportion-of-brand-to-generic-prescriptions-dispensed/.
10. DiGrande, S. (2018). Second Patent Cliff Lies Ahead for Pharma With $251 Billion in Sales at Risk by 2024. Available at: https://www.centerforbiosimilars.com/news/second-patent-cliff-lies-ahead-for-pharma-with-251-billion-in-sales-at-risk-by-2024.
11. Linker, A., Yang, A., Roper, N., et al. (2017). Impact of industry collaboration on randomized controlled trials in oncology. Eur.J.Cancer, 72: 71-77.
12. Grainger, D. (2015). Why Too Many Clinical Trials Fail -- And A Simple Solution That Could Increase Returns On Pharma R&D. Available at: https://www.forbes.com/sites/davidgrainger/2015/01/29/why-too-many-clinical-trials-fail-and-a-simple-solution-that-could-increase-returns-on-pharma-rd/#15aec05adb8b.
13. Fogel, D.B. 2018. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp.Clin.Trials Commun., 11: 156-164.
14. Paul, S.M., Mytelka, D.S., Dunwiddie, C.T., et al. (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews: Drug Discovery, 9: 203-214.
15. Yildirim, O., Gottwald, M., Schueler, P., et al. (2016). Opportunities and challenges for drug development: public-private partnerships, adaptive designs and big data. Fronti.Pharmacol., 7: 1-13.

16. Silva, P.J., Schaibley, V.M., Ramos, K.S. (2018). Academic medical centers as innovation ecosystems to address population –omics challenges in precision medicine. J.Translat.Med., 16: 1-12.

17. Yildirim, O., Gottwald, M., Schueler, P., et al. (2016). Opportunities and challenges for drug development: public-private partnerships, adaptive designs and big data. Fronti.Pharmacol., 7: 1-13.

18. de Vrueh, R.L.A., Commelin, D.J.A. (2017). Reflections on the Future of Pharmaceutical Public-Private Partnerships: From Input to Impact. Pharm. Res., 34: 1985-1999.

19. Yildirim, O., Gottwald, M., Schueler, P., et al. (2016). Opportunities and challenges for drug development: public-private partnerships, adaptive designs and big data. Fronti.Pharmacol., 7: 1-13.

20. Laverty, L., Meilien, P. (2019). The Innovative Medicines Initiative −10 Years of Public-Private Collaboration. Frontiers in Medicine Translational Medicine. Available at https://www.frontiersin.org/articles/10.3389/fmed.2019.00275/full.

21. US Food & Drug Administration. (2018). Critical Path Initiative. Available at: https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative.

22. The Structural Genomics Consortium. (2020) Available at https://www.thesgc.org/.

23. Wapner, J., 2014. *The Philadelphia Chromosome: A Genetic Mystery, a Lethal Cancer, and the Improbable Invention of a Lifesaving Treatment*. s.l.:Open Road Integrated Media.

24. Capdeville, R., Buchdunger, E., Zimmermann, J, et al. (2002). Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. Nat.Rev.Drug Discov. 1: 493-502; Pray, L. A. (2008). Gleevec: the Breakthrough in Cancer Treatment. Nature Education, 1:37.

25. Grinfeld, J.; Nangalia, J.; Baxter, E. J.; et al. (2018). Classification and Personalized Prognosis in Myeloproliferative Neoplasms. NEJM, 379: 1416-1430; Jorgensen, J.T. (2019). Twenty Years with Personalized Medicine: Past, Present, and Future of Individualized Pharmacotherapy. The Oncologist, 24: e432-e440.

26. Silva, P.J., Schaibley, V.M., Ramos, K.S. (2018). Academic medical centers as innovation ecosystems to address population –omics challenges in precision medicine. J.Translat.Med., 16: 1-12.

27. Deloitte, 2020. Ten years on: Measuring the return from pharmaceutical innovation 2019, s.l.: Deloitte LLP; Stegmeier, F., Warmuth, M., Sellers, W.R., et al. (2010). Targeted Cancer Therapies in the Twenty-First Century: Lessons From Imatinib. Clin.Pharmacol.Ther., 67: 543-52.

28. Grossman, R.L., Heath, A., Murphy, M., et al. (2016). A Case for Data Commons Toward Data Science as a Service. Comput.Sci.Eng, 18 10-20.

29. Silva, P.J., Schaibley, V.M., Ramos, K.S. (2018). Academic medical centers as innovation ecosystems to address population –omics challenges in precision medicine. J.Translat.Med., 16: 1-12.

30. Maertens, O., McCurrach, M.e., Braun, B.S., et al. (2017). Collaborative model for accelerating the discovery and translation of cancer therapies. Cancer Res., 77: 5706-5711; Stevens, H., Van Overwalle, G., Van Looy, B., et al. (2013). Perspectives and Opportunities for Precompetitive Public-Private Partnerships in the Biomedical Sector. Biotech.Law Rep., 32: 131-139.

31. Pammolli, F., Righetto, L., Abrignani, S., et al. (2020). The endless frontier? The recent increase of R&D productivity in pharmaceuticals. J.Translat.Med., 18: 1-14.

32. Groebner, S.N., Worst, B.C., Weischenfeldt, J. et al. (2018). The landscape of genomic alterations across childhood cancers. Nature, 555: 321-327.

33. Pediatric Preclinical Testing Consortium: www.ncipptc.org.

34. ITCC P4 platform: www.itccp4.eu.

35. US Food & Drug Administration. Master Protocols: Efficient Clinical Trial Design Strategies To Expedite Development of Oncology Drugs and Biologics. Draft Guidance for Industry. September 2018. Available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm .

36. https://dictionary.reverso.net/english-definition/coordinate+efforts).

37. Barone, A., Casey, D., McKee, A., et al. (2019). Cancer drugs approved for use in children: Impact of legislative initiatives and future opportunities. Ped.Blood Cancer, 66: e27809

38. National Cancer Institute. (2016). NCI-MATCH Trial (Molecular Analysis for Therapy Choice) Available at: https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.

39. Leukemia and Lymphoma Society. LLS Children's Initiative. Cures And Care For Children. Available at https://www.lls.org/childrens-initiative.

40. Lennox Children's Cancer Fund. (2020). Facts and Statistics. Available at http://www.lennoxccf.org.uk/facts-and-statistics.html#:~:text=The%20survival%20rate%20for%20children's,than%20doubled%20since%20the%201960s.&text=It%20is%20estimated%20that%20there,childhood%20cancer%20survivors%20in%20Britain.&text=Eight%20out%20of%20ten%20children,only%20one%20in%20ten%20survived.; CureSearch for Children's Cancer. (2020). 5-Year Survival Rate. Available at https://curesearch.org/5-Year-Survival-Rate.

41. American Cancer Society, (2020). Key Statistics for Childhood Cancers. Available at: https://www.cancer.org/cancer/cancer-in-children/key-statistics.html.

42. Adamson, M.P.C. (2015). Improving the Outcome for Children With Cancer: Development of Targeted New Agents. CA Cancer J.Clin., 65: 212-220.

43. Treem, W., Jose Redondo, M., and Sears, C. (2016) Pediatric clinical trials: Is collaboration between sites and sponsors the answer? Global Forum, August 2016, 8:4; 52-55.

44. Treem, W., Jose Redondo, M., Sears, C. (2016) Pediatric clinical trials: Is collaboration between sites and sponsors the answer? Global Forum, 8: 52-55.

45. Sarajian, K. (2017) Site engagement: the key to running a successful clinical trial. Applied Clinical Trials. August.

46. Treem, W., Jose Redondo, M., & Sears, C. (2016) Pediatric clinical trials: Is collaboration between sites and sponsors the answer? Global Forum, 8: 52-55.

47. Lloyd, M., Barbitsch, C., Voehl, H.M., et al. (2019). Practical consideration for collaborative research between the pharmaceutical industry and external investigators. Available at https://doi.org/10.728/peerj.preprints.27785v1.

48. LoRusso, P.M., Canetta, R., Wagner, J.A., et al. (2012). Accelerating cancer therapy development: The importance of combination strategies and collaboration. Summary of an institute of medicine workshop. American Association for Cancer Research, 18: 6101-6109.

49. Treem, W., Jose Redondo, M., and Sears, C. (2016). Pediatric clinical trials: Is collaboration between sites and sponsors the answer? Global Forum, August 2016, 8:4; 52-55.

50. Cecchini, M., Rubin, E.H. Blumenthal, G.M., et al. (2019). Challenges with Novel Clinical Trial Designs: Master Protocols. Clin.Canc.Res., 25:. 2049-2057.

51. LoRusso, P.M., Canetta, R., Wagner, J.A., et al. (2012). Accelerating cancer therapy development: The importance of combination strategies and collaboration. Summary of an institute of medicine workshop. American Association for Cancer Research, 18: 6101-6109.

52. O'Leary, M., Krailo M., et al. (2008). Progress in childhood cancer: 50 years of research collaboration, A report from the children's oncology group. Semin Oncol.; 35: 484-493.

53. Childrens Oncology Group. Available at https://childrensoncologygroup.org/index.php/62-about-us/about-us#:~:-text=The%20Children's%20Oncology%20Group%20research,survival%20rate%20of%2080%25%20today.

54. Treem, W., Jose Redondo, M., Sears, C. (2016). Pediatric clinical trials: Is collaboration between sites and sponsors the answer? Global Forum, 8: 52-55.

55. Merkel, P.A., Manion, M., Gopal-Srivastava, R., et al. (2016). The partnership of patient advocacy groups and clinical investigators in the rare diseases clinical research network. Orphanet Journal Of Rare Diseases, 11: Art 66.

56. Levitan, B., Getz, K., Eisenstein, E., et al. (2018). Assessing the financial value of patient engagement: a quantitative approach from CTTI's patient groups and clinical trials project. Ther. Innov. Regul. Sci. 52, 220–229.

57. European Medicines Agency. 10-year Report to the European Commission. 15 August 2017. EMA/231225/2015. Available at https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/paediatrics_10_years_ema_technical_report.pdf.

58. EFPIA. Working Together With Patient Groups. September, 2017. Available at https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf.

59. Furlong, P., Bridges, J.F.P., Charnas, L., et al. (2015). How a patient advocacy group developed the first proposed draft guidance document for industry for submission to the U.S. Food and Drug Administration, Orphanet Journal of Rare Diseases 10: Article Number: 82. Published: June 24, 2015.

60. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry, February 2018. Available at https://www.fda.gov/media/92233/download.

61. Mercieca-Bebber, R., King, M.T., Calvert, M.J., et al. (2018). The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Related Outcome Measures, 9, 353-367.

62. Addario, B., Geissler, J., Horn, M.K., et al. (2019). Including the patient voice in the development and implementation of patient‐reported outcomes in cancer clinical trials, Health Expectations, 23, 41-51.

63. Varni, J.W., Curtis, B.H., Abetz, L.N. et al. (2013). Content validity of the PedsQL™ 3.2 Diabetes Module in newly diagnosed patients with Type 1 diabetes mellitus ages 8–45. Qual.Life Res., 22: 2169–2181.

64. Addario, B., Geissler, J., Horn, M.K., et al. (2020). Including the patient voice in the development and implementation of patient-reported outcomes in cancer clinical trials. Health Expect., 23: 41–51.

65. Leahy, A.B., Feudtner, C., Basch, E. (2018). Symptom Monitoring in Pediatric Oncology Using Patient-Reported Outcomes: Why, How, and Where Next. Patient-Patient Centered Outcomes Research, 11: 147-153.

66. Gnanasakthy, A., Barrett, A., Evans, E., et al. (2019). A Review of Patient-Reported Outcomes Labeling for Oncology Drugs Approved by the FDA and the EMA (2012-2016), Health Policy Analysis, 22, 203-209.

67. Duke Clinical Research Institute. The Clinical Outcome Assessments for Acute Pain Therapeutics in Infants and young Children (COA-APTIC) study. 2020. Available at https://dcri.org/coa-aptic/.

68. Sysnav Navigation Technologies. First digital endpoint released by EMA (European Medicine Agency) for clinical studies (Actimyo) 2020. Available at https://www.sysnav.fr/medical/actimyo/.

69. European Medicines Agency. Revised framework for interaction between the European Medicines Agency and patients and consumers and their organisations. 16 October 2014. EMA/637573/2014. Available at https://www.ema.europa.eu/en/documents/other/revised-framework-interaction-between-european-medicines-agency-patients-consumers-their_en-1.pdf.

70. European Medicines Agency. From laboratory to patient: the journey of a medicine assessed by EMA. EMA/103813/2018. Available at https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf.

71. European Medicines Agency. Principles on the involvement of young patients/consumers within EMA activities. 24 May 2017. EMA/494077/2016. Available at https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/principles-involvement-young-patients/consumers-within-ema-activities_en.pdf.

72. European Medicines Agency. Principles on the involvement of young patients/consumers within EMA activities. 24 May 2017. EMA/494077/2016. Available at https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/principles-involvement-young-patients/consumers-within-ema-activities_en.pdf.

73. US Food & Drugs Administration. CDER Patient-Focused Drug Development. Available at https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

74. US Congress. 21st Century Cures Act. H.R. 34, 114th Congress. 2016. Available at https://www.gpo.gov/fdsys/pkg/BILLS-114hr34enr/pdf/BILLS-114hr34enr.pdf.

75. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. June 2020. Available at https://www.fda.gov/media/139088/download; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Patient-Focused Drug Development: Methods to Identify What Is Important to Patients. Draft Guidance. October 2019. Available at https://www.fda.gov/media/131230/download.

76. Rose, K.. (2017). New drugs for rare disease in children. Clin.Ther., 39: 246-252.

77. LoRusso, P.M., Canetta, R., Wagner, J.A., et al. (2012). Accelerating cancer therapy development: The importance of combination strategies and collaboration. Summary of an institute of medicine workshop. American Association for Cancer Research, 18: 6101-6109.

78. Heath, S. (2020). How Coronavirus Sparked Industry Collaboration, Team-Based Care. Patient Engagement Hit. Xtelligent Healthcare Media. Available at https://patientengagementhit.com/features/how-coronavirus-sparked-industry-collaboration-team-based-care.

79. Stand up to Cancer (SU2C). Collaboration within and between teams. Available at https://standuptocancer.org/what-we-do/where-the-money-goes/.

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