

The Economic Impact of Innovative Therapies for Rare Diseases on Healthcare Providers and the Healthcare System in Germany – The Example of Spinal Muscular Atrophy

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Research

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Abstract

Background: Despite a constant number of prescriptions, the expenditures of the statutory health insurance funds for pharmaceuticals are rising sharply. This is due to high prices for orphan drugs and advanced therapy medicinal products (ATMPs). Despite attempts by policymakers to intervene, such as the 2011 *German Pharmaceutical Market Restructuring Act* (Arzneimittelmarktneuordnungsgesetz, AMNOG), the use of these therapies poses numerous challenges for the healthcare system, especially insurance companies and healthcare providers.

Results: Using data from the University Hospital Heidelberg, we found that the division of pediatric neurology is experiencing a disproportionate increase in drug costs, caused by two drugs for the treatment of spinal muscular atrophy (SMA), Nusinersen and Onasemnogen Aporvec. A survey of 41 German SMA treatment centers revealed a lack of human and infrastructural resources to manage therapy and follow-up care, which currently is insufficiently reimbursed. Disease-independent registers that comply with the rules of the European Union for medication surveillance and which are not tied to the pharmaceutical industry are necessary.

Conclusion: Innovative forms of therapy require a critical discussion and regulation of application, aftercare and reimbursement as well as (inter)national industry independent registry work. Based on the model of evidence-based dynamic pricing by the *Techniker Krankenkasse*, we propose a concept which offers an internationally scalable solution to combat these challenges.

Background

The pharmaceutical market has seen rising expenditure on prescription drugs over the past years although the number of prescriptions has remained constant.(1, 2) This is mainly due to high prices and increased availability of patented drugs, including orphan drugs (OD) and advanced therapy medicinal products (ATMPs), a group which includes gene therapies, somatic cell therapies and tissue engineered products.(3) In 2019, expenses for drugs in the statutory health insurance system in Germany for the first time exceeded € 45 billion, and while OD accounted for only 0.05 % of all prescribed daily doses, they caused 10 % of the total expenditure.(1) The share of orphan drugs in the worldwide total drug market is expected to increase to 18 % by 2024, making it the most dynamic segment of innovation development in the field of pharmaceuticals.(4)

First regulations were implemented by the European Union in the 1990s to provide targeted incentives for the development of drugs for rare diseases.(5, 6) The resulting increment in approved orphan drugs has raised the discussion of the mechanisms of research funding, pricing of drugs and means of reimbursement.(2, 6-8) Since then, national legislators are trying to find ways to better regulate drug prices at the national level. In Germany, the postmarket comparative benefit assessment stipulated in the 2011 *German Pharmaceutical Market Restructuring Act* (Arzneimittelmarktneuordnungsgesetz, or AMNOG) represents the linchpin of the Federal Joint Committee (the German main regulatory institution

for legally binding decisions in healthcare) for price negotiations of the statutory health insurance companies with pharmaceutical firms.(9) However, during the first 12 months after approval of the drug, prices are freely chosen by the pharmaceutical manufacturers. Only afterwards price negotiation between the pharmaceutical company and the umbrella association of insurers is possible. Nevertheless, several years after its introduction it can be stated that the AMNOG has improved the ratio of negotiated prices and the clinical benefit of evaluated compounds.(10)

The evaluation of an ODs efficacy and safety is proven in the context of the centralized approval for the European Economic Area.(5) However, an evaluation of the therapy's benefit is missing at the time of approval and a valid statement on the benefit-risk assessment can, therefore, often not be made by the European Medicines Agency (EMA) at this early stage.(11) In this context, Onasemnogene Apeparvovec, a gene therapy product for the treatment of spinal muscular atrophy (SMA), is a very prominent example. Lately it received a conditional approval based on the results of a Phase 1/2A study with only 15 SMA-patients compared to historical control cases and preliminary non-published data of an international phase-3-study with 55 SMA-children.(12, 13) With costs of € 1.945 million per single application, Onasemnogen Apeparvovec is the world's most expensive drug to date. However, the high costs associated with such innovative therapies require standards in research and risk assessment of such orphan drugs that are at least equivalent to those of non-orphan drugs.

This process of a sharp increase in medication expenditure was previously observed with the approval of Nusinersen, another drug for the treatment of SMA. Regardless of their therapeutic potential, ODs and ATMPs generate major challenges for national healthcare systems, healthcare providers and insurance companies as many issues regarding their use, associated (organizational and personnel) costs as well as the reimbursement of follow-up care remain to be addressed.

In order to provide a solution for the dilemma between rising drug expenditures and the evidence gap regarding the efficacy and safety of innovative therapies, we have developed a model in collaboration with the *Techniker Krankenkasse*, Germany's largest health insurance company, which attempts to help regulate price-finding as well as the financing of patient registries and follow-up care independently of the disease.

Results

From 2010 to 2019, inpatient departments of the Heidelberg University Hospital incurred average annual costs of € 45.1 million (SD = ±7.6 million) for drugs and pharmaceutical products. In 2019, the highest costs ever of € 60.5 million were recorded. Figure 1 shows the annual expenditure on drugs in the five departments that generate the largest annual costs for pharmaceuticals at Heidelberg University Hospital.

Since 2016, the strongest increase in drug expenditure took place in the Center for Child and Adolescent Medicine with annual progressions of up to 84 percent. In 2019, € 14.46 million were spent on pharmaceuticals in the field of pediatrics. Compared to 2010, this represents an increase in expenditure by a factor of 5.3, essentially generated by the Department of Pediatric Neurology (74 %) (Figure 1).

A detailed investigation of the Department of Pediatric Neurology identified in particular two drugs for the treatment of SMA as the main cost drivers: Nusinersen and Onasemnogene Apeparvovec. In 2019, 92 doses of Nusinersen were applied at the Centre for Children and Adolescent Medicine Heidelberg with a total expenditure of € 8.44 million. The average drug cost of a single application was € 91,739.13. In the same year, a first patient was treated with Onasemnogene Apeparvovec, the net drug cost amounted to € 1.945 million.⁽¹⁴⁾ The conditional marketing authorization of Onasemnogene Apeparvovec by the EMA was granted in May 2020. However, already in the first half of 2020, three more patients were treated with Onasemnogene Apeparvovec with total drug expenditures of € 5.835 million plus import VAT, more patients will follow in the course of the year.

The incidence of SMA is estimated at 1:7,500 for Germany. It represents the most common genetic cause of infant and childhood mortality.^(15, 16) Most patients suffer from subtype 1 (Werdnig-Hoffmann) and are diagnosed in infancy. In our survey 1,097 patients were included. Of these patients, 646 (59 %) were younger than 18 years of age at the time of the survey. Based on our survey, in Germany, 92 patients are expected to qualify for start of treatment with Onasemnogen Apeparvovec during the next 12 months, confronting payors with total drug costs of € 178.94 million (corresponding to € 212.94 million gross). According to the survey results, the number of patients with Nusinersen therapy will decrease from 867 during the last 12 months to 761 in the coming 12 months (Supplementary Table 1).

All 41 respondents state that the application of innovative SMA therapies in standard care create new challenges, 28 (68.3%) expect challenges half medical and half non-medical in character. A total of 82.9 % (n = 34) of those responsible for the organization in their centers report an additional workload of more than 5 hours per week. New tasks will primarily arise in the areas of case management, pre- and post-clinical care, and administration of reimbursement or invoicing. The need for additional human resources (even more so than infrastructural or financial resources) is thus perceived as the biggest challenge in the overall process of applying innovative therapies (Figure 2).

Those responsible for the SMA treatment centers see the need for standardization of processes. While both, the indication process as well as the pharmacy process were reported to be well regulated, there is a strong need for improvement and more precise standardization of follow-up care, by 39 (95.1 %) respondents. At the time of investigation only 25 (61 %) of the centers reported to have standard operating procedures (SOPs) related to SMA treatment. While reporting an increase of workload, 80.5 % (n = 33) of the respondents do not consider the reimbursement for the healthcare providers of innovative therapies to be appropriate. With regard to follow-up care, 87.8 % (n = 36) even stated that compensation was insufficient, and 95.2 % (n = 39) saw the reason for this in the existing outpatient remuneration systems. When respondents were given the opportunity to prioritize different areas of optimization, the compensation for aftercare was ranked highest.

All respondents indicated that structured documentation and analysis of the outcomes of innovative therapies should be carried out in international registries, 94.4% (n = 39) also support that this should be done independently of the pharmaceutical industry. There was also broad consensus concerning

financing of clinical trial registers, where 80.5 % (n = 33) of the respondents were in favor of a fund to be administered in trust by the Federal Joint Committee, into which the pharmaceutical company would have to pay an amount based on the price of the drug after approval. Only a small proportion of those surveyed saw responsibility for structured documentation with the insurance companies (12.2 %, n = 5) or with the health-care providers (7.3 %, n = 3). Since international recommendations for the implementation of registry work are missing so far, a modified model of quality management and price-finding based on the *dynamic evidence price* will be presented in the discussion.

Discussion

The present analysis using the example of Heidelberg University Hospital reveals a considerable annual increase in drug expenditure over the last few years, which is largely attributable to orphan drugs and ATMPs, predominantly in the field of pediatric and adolescent neurology. An increasing number of gene therapy products, which will soon reach market maturity, are not yet matched by adequate standards of organization and structured pre- and post-treatment pathways for patients and caregivers.

In view of rising prices and rapidly increasing application of innovative therapies, the current billing models expose treatment centers to a potential but threatening liquidity problem. In general, the medication is ordered through the hospital's in-house pharmacy. In a first step, the costs for the drug are, therefore, pre-financed by the treatment center. Only after the therapy has been completed the costs of drugs can be claimed against the responsible insurance company. This corresponds to the granting of an interest-free loan to a pharmaceutical company by the public authorities. What initially was manageable for a large academic center with a low number of cases will become more difficult or even impossible in the coming years. Alternative billing models, which allow linear direct billing are being discussed. For Zynteglo[®], a gene therapy drug for the therapy of Beta-Thalassemia, direct billing between pharmaceutical companies and the insurance company in a pay-for-performance model is being considered, but this is a case-by-case arrangement between the insurance company and the manufacturer and cannot be automatically transferred to other preparations and areas of application. (17) Models spanning diseases and medications are therefore urgently needed. (18) The survey of 41 SMA treatment centers revealed that the implementation of innovative forms of therapy lacks personnel resources for case management and administrative processes in particular. Transparent linear direct billing between the payer and the pharmaceutical company would make it possible to allocate processes that are not directly related to the patient to the primarily responsible actors, thus relieving the burden on service providers.

Costs for organizational, personnel and infrastructural resources that arise for the service provider through the application of innovative forms of therapy must be refinanced. A fund to be financed by the pharmaceutical companies and administered in trust by the Federal Joint Committee could be used for centers that fulfill quality requirements (e.g., defined by the Federal Joint Committee) for the implementation of innovative therapies. A structured medical treatment pathway developed by the professional associations and the treatment centers on behalf of the Federal Joint Committee at the time

of approval (comparable to the recommendations for action for SMA gene therapy published by the treatment centers at the time of approval, see (19)) would be a milestone for quality assurance. The thorough documentation of therapy process would have to be refinanced on the basis of corresponding cost models by the cost units or via the above-mentioned trust fund (Figure 3). (14).

Due to the low prevalence of rare diseases, ODs cannot be tested extensively for efficacy and safety in clinical trials.(20) Nevertheless, patients are entitled to comparable standards in research, approval and testing. Registers collecting agreed minimum of data to monitor diagnostic and therapeutic processes in combination with valid patient outcomes are therefore necessary.(21) The European legislator has formulated clear requirements for the marketing of drugs in Regulation (EC) 726/2004; Regulation (EC) 141/2000 provides a similar framework for orphan drugs.(5, 22) The implementation of patient registries of orphan medicinal products available in Europe is an integral part of this regulation. The establishment and operation of such a patient register by scientific consortia of academic centers independent of industry should be aimed at in order to avoid data fragmentation and duplication at national and European levels, to adapt the data model of the Registry to the requirements of a patient-centered disease registry instead of a drug-centered therapy registry and to ensure the interoperability of the registry through compliance with the FAIR principles (F = findable, A = accessible, I = interoperable, R = reusable). (23, 24) For SMA, the SMARtCARE Registry fulfills parts of these requirements.(25) For the future, a cross-entity, modularly expandable registry that complies with European registry standards is reasonable and necessary to avoid a multitude of disease-specific individual registries. We propose a modified model of the *dynamic evidence price* of the *Techniker Krankenkasse*, extended by an obligatory, fiduciary and industry independent register for the application centers (Figure 3).(26)

In the proposed model, the Federal Joint Committee would delegate the coordination of registry work to specialized treatment centers, usually academic institutions. The documentation obligation of the pharmaceutical manufacturer would be taken care of in such an approach, while the data sovereignty would not remain in industry-dependent registries, but in the hands of the regulatory authorities at the level of the European Union. A royalty payment for the use of data from such registers would be conceivable.

The determination of a maximum drug price based on European average prices and methods of health technology assessment is an integral part of the dynamic evidence price model and has the potential to counteract a cost explosion and impeding liquidity problems of health care providers and insurance companies.(26) The dynamic adjustment of the medication costs is based on the evidence created by the registry work regarding the efficacy and safety of the drugs. This will ultimately ensure long-term availability of high-quality patient care with innovative therapies and secure the profitability of health care providers.

Conclusions

The application example of SMA is suitable as a blueprint for the rapidly increasing number of ATMPs and innovative orphan drugs expected in the coming years. First experiences show that existing structures are not sufficiently prepared for the associated economic challenges. However, health care systems, the insurance payers and the health care providers must be prepared for such (cost-)relevant treatments by creating appropriate structures and regulations. Last but not least, the responsibilities of the pharmaceutical company, especially with regard to high-priced drugs, must be more clearly defined and proper quality assurance guidelines must be formulated within the framework of national and European legislation. The model of the modified dynamic evidence price presented here offers a possibility to address the rising costs of innovative drugs and can serve as a blueprint for the development of national guidelines and laws in other (European) countries.

Methods

Data sources

Total quantities and expenditures for prescriptions and ready-to-use drugs of the University Pharmacy of the Heidelberg University Hospital were analyzed for the time period of 2009 – 2019. Data from the Center for Pediatric and Adolescent Medicine were assigned to individual departments and the main driving forces behind pharmaceutical expenditures were identified. Using a structured questionnaire survey distributed to all German SMA treatment centers, the following dimensions were investigated: 1) workload before and after the introduction of innovative forms of therapies, 2) standardization of procedures, and 3) availability of registries. Questionnaire items were designed as 5 point Likert scales, implemented into the Limesurvey tool as an anonymous survey and then sent via e-mail to the participating centers of the SMARtCARE registry (25) (URL <https://www.smartcare.de/>, n = 49) and the list of "Neuromuscular Centers" of the German Society for Muscular Diseases (DGM). A total of 41 questionnaires were completed, covering 1,097 SMA patients (see Supplementary Table 1) corresponding approximately to the SMA prevalence of 1:100,000 expected for Germany.(27)

Limitations

The National Center for Tumor Diseases (NCT) is located at Heidelberg University Hospital, where patients receive highly specific and individualized oncological therapy. These treatments generate extremely high costs totaling € 36.46 million per year (corresponding to 37.6 % of total expenditure on drugs at the University Hospital Heidelberg). Due to the lack of comparability to other sites, NCT data were excluded from the analysis. The true cost of medicines in Germany is partly subject to individually negotiated discount rates between the health care provider and the health insurance company, which are highly confidential. In our assessment we only consider the costs directly caused by drugs. Costs for the implementation of the therapy, such as personnel costs and costs for the maintenance of the infrastructure could not be considered due to their complexity. Our cost analysis can therefore only provide an approximation of the true costs, but it nevertheless expresses a clearly discernible trend in the application of innovative therapies.

Abbreviations

AMNOG: Arzneimittelmarktneuordnungsgesetz / German Pharmaceutical Market Restructuring Act, ATMP: Advanced therapy medicinal products, EMA: European Medicines Agency, DGM: German Society for Muscular Diseases, NCT: National Center for Tumor Diseases, OD: Orphan drugs, SMA: Spinal muscular atrophy, SOP: Standard operating procedure, VAT: Value added tax

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Competing interests

H.B., K.G., D.S., T.H.-T., P.B., U.K., S.K., S.N., G.S., T.S., J.B., G.F.H., I.A. do not declare to have any conflict of interest as defined in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the ICMJE. A.Z. declares to have received fees for consulting services related to the subject of the publication from the companies Biogen, Avexis, Roche and PTC. A.Z. declares to have received fees from Biogen to a third-party account for conducting clinical trials related to the subject of the publication. A.Z. declares to have received funds from Biogen into a third-party account for a research project it initiated related to the subject of the publication.

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Authors' contributions

Conceptualization, H.B., A.Z.; methodology, H.B., K.G., D.S., T.H.-T., P.B.; validation, H.B., P.B., K.G., D.S., S.K.; formal analysis, H.B., A.Z.; writing—original draft preparation, H.B.; writing—review and editing, K.G., D.S., T.H.-T., P.B., U.K., S.K., S.N., G.S., T.S., J.B., G.F.H., I.A., A.Z.; visualization, H.B.; supervision, A.Z.; all authors have read and agreed to the published version of the manuscript.

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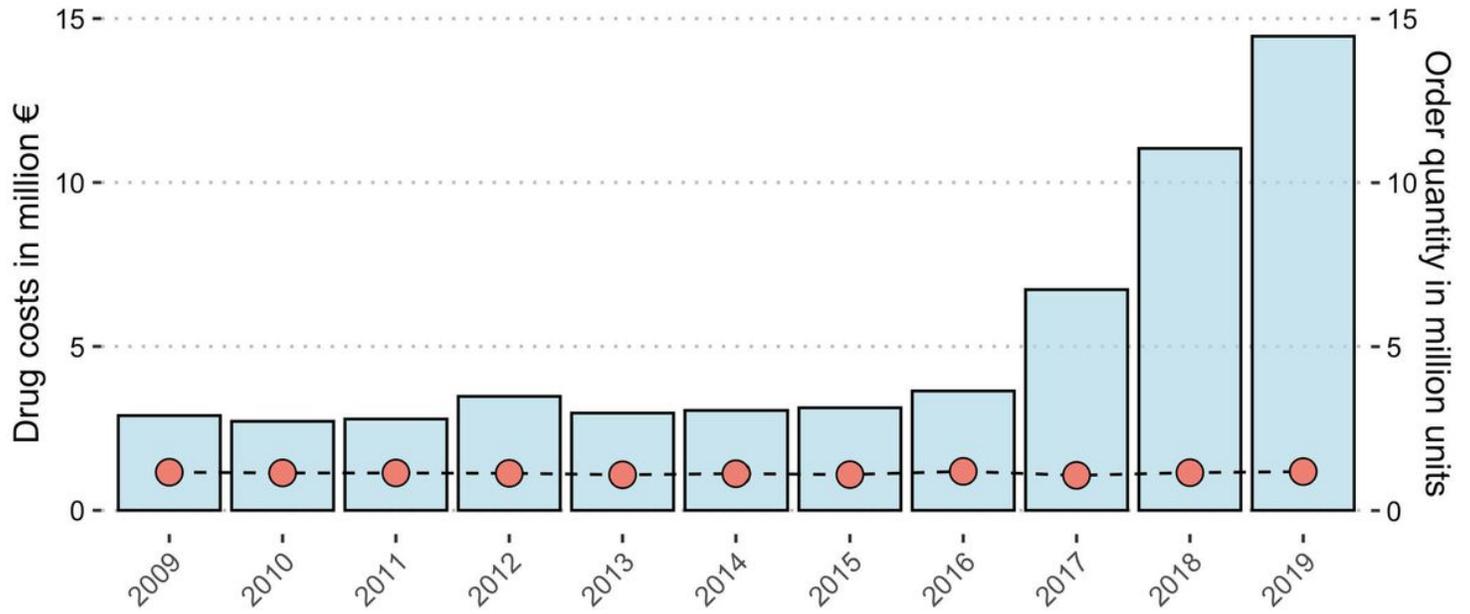
Tables

Table 1: Annual costs for drugs (in € million) and the percentage change compared to the previous year for the five most cost-intensive centers at Heidelberg University Hospital.

Year	Child and Adolescent Medicine		Internal Medicine		Surgery		Anesthesiology		Neurology	
	Costs (Mio. €)	%	Costs (Mio. €)	%	Costs (Mio. €)	%	Costs (Mio. €)	%	Costs (Mio. €)	%
2010	2,72	-6,04	19,51	-2,91	6,77	16,89	4,53	3,9	2,24	-15,37
2011	2,79	2,6	15,25	-21,8	5,76	-14,82	4,88	7,6	3,02	34,84
2012	3,48	24,77	16,3	6,9	5,85	1,55	4,57	-6,24	2,86	-5,27
2013	2,97	-14,6	18,49	13,39	4,6	-21,35	4,14	-9,54	3,04	6,25
2014	3,05	2,69	17,82	-3,63	4,33	-5,92	4,33	4,66	3,28	7,83
2015	3,13	2,66	17,94	0,72	4,15	-4,12	5,11	17,99	4,08	24,5
2016	3,64	16,36	20,35	13,41	4,23	1,92	4,35	-14,84	3,74	-8,32
2017	6,73	84,94	23,61	15,99	3,96	-6,54	3,46	-20,54	3,48	-7,08
2018	11,04	63,96	23,18	-1,79	4,27	7,9	3,42	-0,98	8,85	154,51
2019	14,46	31,01	23,14	-0,17	4,52	5,83	4,44	29,59	7,76	-12,35

Figures

A Comparison of drug costs and order quantity at the Center for Children and Adolescent Medicine Heidelberg



B

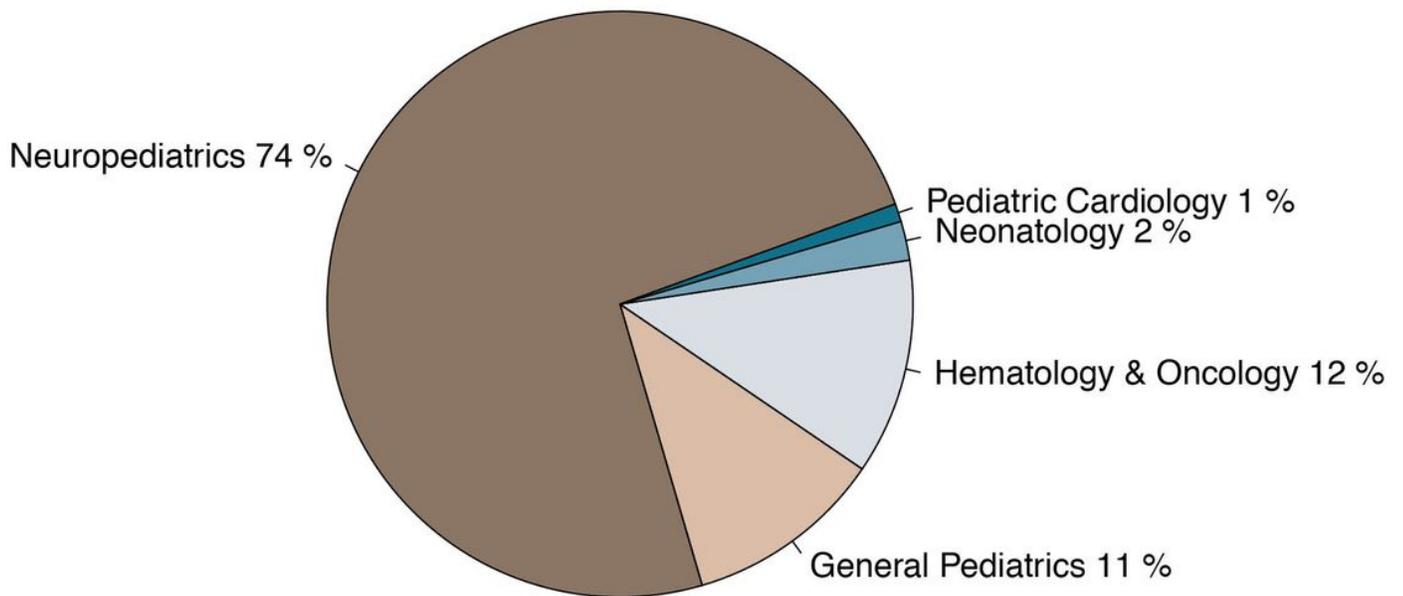


Figure 1

Total drug costs at the Center for Child and Adolescent Medicine Heidelberg from 2009 – 2019. A) Drug costs (bars) and order quantities (dots and lines) at the Center for Child and Adolescent Medicine Heidelberg. B) Distribution of drug costs across the departments of the Center for Child and Adolescent in 2019.

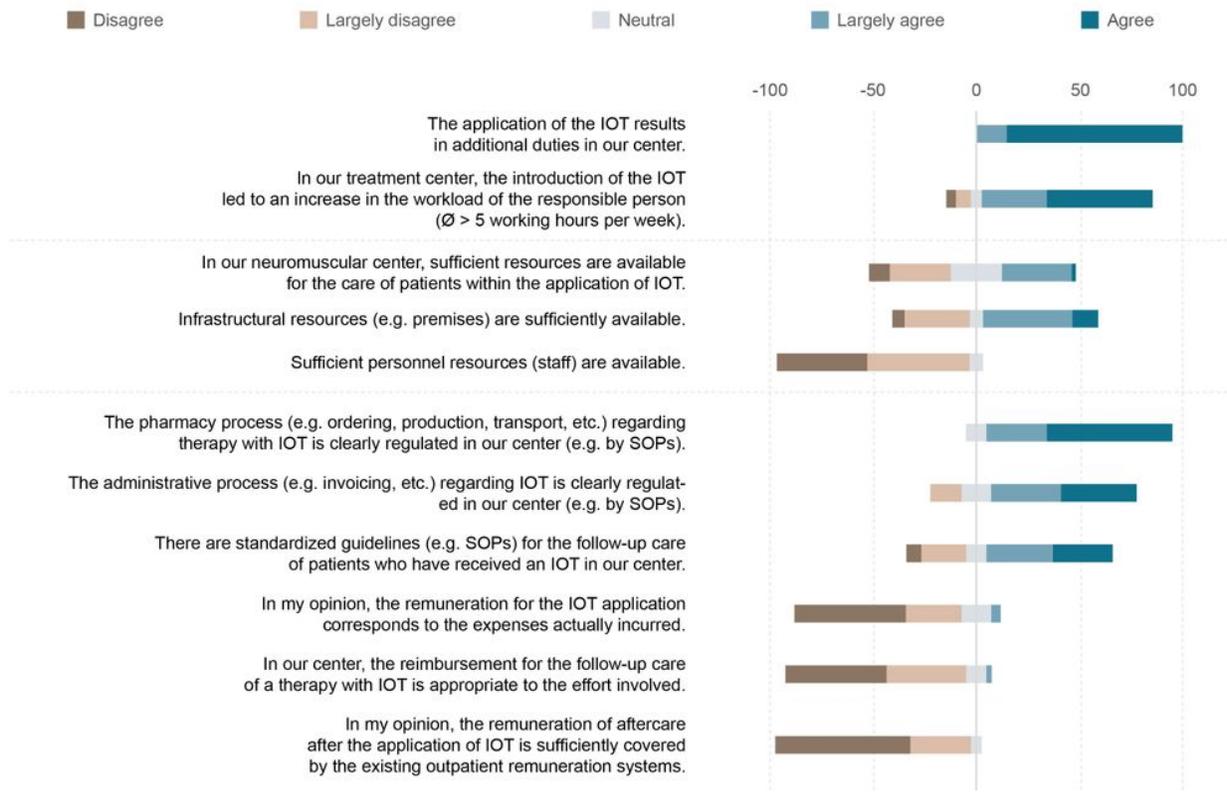


Figure 2

Newly emerged tasks and challenges in the application of innovative forms of therapy. Abbreviations: IOT = Innovative Orphan (or ATMP) - Therapeutics, SOP = Standard Operating Procedure Development of total drug costs at the Center for Child and Adolescent Medicine Heidelberg in the years 2009 – 2019.

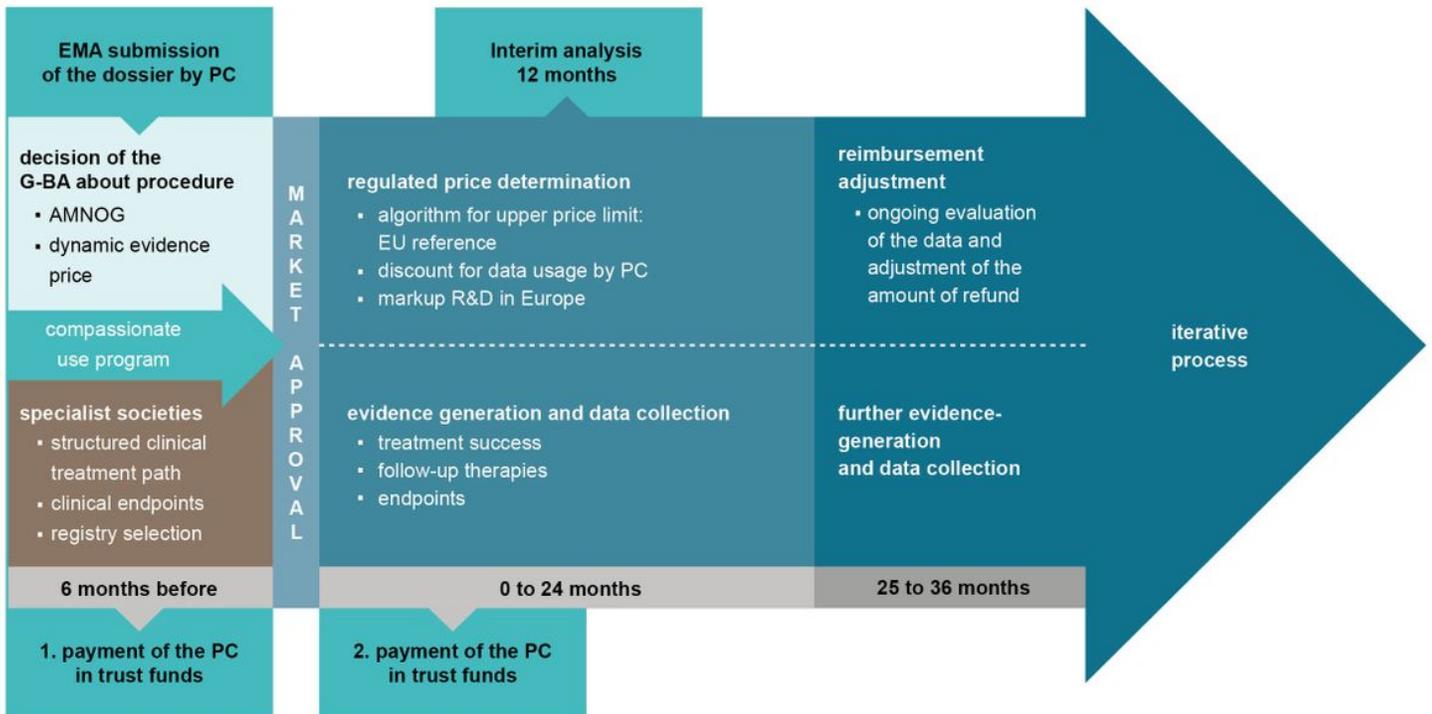


Figure 3

Modified dynamic evidence price. Abbreviations: AMNOG = German Drug Market Restructuring Act, EMA = European Medicines Agency, G-BA = Joint Federal Committee, PC = pharmaceutical company.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [OJRD20201009SupplementaryMaterial.docx](#)