CONSTITUTION OF VALUES AND SUBJECTS IN PERSONALIZED MEDICINE: THE CASE OF SPINAL MUSCULAR ATROPHY DISEASE

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Contents

ABSTRACT

Novel therapies are often welcomed by patients especially who have been waiting for a treatment on their rare condition. Yet, these therapies that are developed and marketed with the logic of personalized medicine may imply certain evidence limitations for public authorities related to safety and efficacy, in addition to their high price tags. Hence, they are often associated with challenges for the regulatory decisions on reimbursement and patients` access to them. This tension implicates potential differences in the valuation of therapies by patients, patient organizations and regulatory authorities at different levels. To understand the construction of markets and effects of personalized medicine on the relationship between the actors, this study follows the circulation of two gene-based therapies targeting Spinal Muscular Atrophy (SMA) disease from its marketing approval in Europe to its appraisal and use in a specific national jurisdiction, Turkey. Drawing on the valuation studies and STS work about agency of individuals in relation to genetic technologies and authorities, I study *valuation practices* alongside the *subject constitutions*. I show how regulatory frameworks at the national and European level, marketing strategies of corporations and *valuation practices* of medical and public authorities and families of patients have been performative in enacting and shaping *values* as well as *subjectivities*. I argue that *valuation practices* have ordering effects among these actors, which are closely related to the discussion of agency and subjectivity of individuals.

1. Introduction

As Eurobarometer survey of 2021 about public expectations from science and technologies indicated, there has been a growing public interest in new medical discoveries since the last survey of 2010 (European Commission, 2021). When asked where science and innovation could make the most difference, European citizens frequently mentioned health and medical care, alongside the problem of climate change. Indeed, hoping for advances in the protection and enhancement of human health has been a legitimate and common public expectation from science, as Bower (2005) pointed out: It was the hope for "the realization of one of man's ancient dreams—the conquest of disease through the use of successful drugs" (p.184). This expectation from science and technological developments is particularly salient for patients who usually suffer from life threatening rare diseases and have difficulties in finding the right diagnosis and a treatment for their condition. However, to what extent these high expectations are addressed with respect to access to these health technologies is open to discussion.

Advances in life sciences such as the development of DNA technologies in 1970s and the initiation of the Human Genome Project in the United States (US) in 1990 have heightened expectations for innovations in health. This has spurred various developments, including significant expansion of public funding in medical research, a growing pharmaceutical industry with a commitment for successful transition from laboratory to clinic (Mittra, 2016, p.85) and the increasing promise of genomics for the personalized diagnostic or therapeutic tools that are tailored to individual genetic profiles (Sunder Rajan, 2011, p.198). In this work, I study the two novel gene-based therapies, emerged as the returns of these investments and promises of personalized medicine, Spinraza (Nusinersen) and Zolgensma that target the same genetic and rare disease, Spinal Muscular Atrophy (SMA). SMA is a serious inherited neuromuscular disease characterized by progressive muscle weakness, which represents the major genetic cause of infant deaths. Since the discovery of its underlying genetic defect as the SMN gene, therapies that target the disease have undergone rapid improvements. There are now three treatments approved firstly in the US, then in the EU. Spinraza (Nusinersen) which was developed by the US-based biotechnology company Biogen/Ionis Pharmaceuticals, was authorized in the EU by EMA in 2017 as the first disease modifying therapy in SMA disease. Zolgensma, developed by the US-based AveXis, which then was sold to Swiss pharmaceutical company Novartis, received marketing authorization from EMA in 2020, on the condition that the company would submit the results of further studies within a certain time frame.

These advanced therapies embody a transformation in how pharmaceuticals discovered, developed and marketed especially since the late 1990s. Particularly, a so-called *productivity crisis* in the industry with the conventional drug development system based on simple and small molecule drugs, led to the adoption of more complex technologies and strategies by multinational companies to identify new compounds and potential users (Mittra, 2016, p. 28). In response to this alleged crisis, *personalized medicine* -also called *stratified medicine*- has been championed by the industry, national and transnational public authorities as the future of health innovation, against the challenges of conventional drug development such high failure rates of new drugs and increasing costs of development and marketing (Mittra, 2016; Prainsack, 2017b).

However, capitalizing on the investments of research and development of these novel technologies has also entailed the need for new regulatory pathways for marketing approval and evaluation by responsible authorities. In line with this need, regulations specific to orphan medicines (medicines that target rare diseases) and advanced technology products such as genetic medicines have been adopted in the US and the EU. Since these products often aim to address an unmet medical need implicating the urgency for early access, new regulatory pathways have provided innovative mechanisms such as *conditional marketing authorization* that implicated the approval of medicines based on “less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk” (EMA, n.d.).

Alongside the new regulatory pathways, advanced technologies and the approach of personalized medicine have strengthened the value of patients` involvement in health innovation at various levels. Patients` data and bio-materials have become more relevant to better understand diseases mechanisms and facilitate the development of diagnostic and therapeutic technologies especially for small populations as in rare diseases. Patient-reported outcomes have increasingly been utilized in clinical trials for adjustment between drug effects and target population. Besides, patients` experiences with the therapies have gained significance as having the potential to be used in monitoring the safety and clinical effectiveness of these therapies for regulatory decision-making.

Despite the proclaimed patient-centred approach in health innovation, these novel technologies usually come with extremely high prices and they are economically out of reach for the majority of their target population, unless there are covered by the public or private payers. Besides, since they are marketed through special regulatory pathways and approved based on relatively smaller clinical trials and adjusted control methods, clinical data remains limited at the time of their market approval compared to conventional therapies. The trend of high-cost medicines with uncertainties on their safety and efficacy

put pressures on the public authorities in deciding which technologies to reimburse in their health systems; while patients were usually pressing for access to these treatments.

Through regulating the pharmaceutical use, public authorities ideally aim to create a desirable collective order for patients as well as for the rest of the society. By doing so, they imagine the disease and patients in certain ways and shape society`s interaction with the techno-scientific object, the pharmaceuticals, and their access to these technologies. On the other hand, patients and patient organizations mobilize their rhetorical and financial resources in shaping these policies for the optimal access conditions, which brings the disease also into the public view. This implies political spaces where regulatory choices are negotiated among various actors, particularly between patient representatives and different public authorities. These negotiations showcase the contestations about the values of these technologies based on the knowledges about disease and effects of technologies. In addition to legal and institutional structures, they are performative in the establishment of the values regarding new technologies. It is pertinent to dig into the valuation of pharmaceuticals because this not only affects the markets and patients` access to these technologies, but also reveals how risks and benefits of these technologies are distributed among patients, society and other actors.

In this regard, by focusing on the first two therapies that target SMA disease, namely Spinraza and Zolgensma, I question *how values of gene-based technologies are discussed and enacted by different groups, namely patients` families, regulatory and medical authorities?* Besides, considering the problems of access despite the growing recognition of patient perspectives for generating the promises of health research, I question the role and agency of patients and patient organizations in the valuation of those technologies and how valuation affects their experience with the disease and therapies. For the purpose of this research focus, I follow the *circulation of pharmaceuticals* (Lakoff, 2008) beginning from their marketing approval by the European Medicines Agency (EMA) to their adoption by national authorities and clinical use. Drawing on the documents and interviews that could indicate different valuations and concerns related to the therapies, I focus on the European context, then the case of Turkey, where the SMA disease has received extensive public attention and media coverage with the activism of patient organizations since the development and marketing of the first therapy Spinraza and families` crowdfunding campaigns for access to Zolgensma. I argue that scientific knowledge, regulatory and political matters and values about the novel therapies are *co-produced* in the *circulation of pharmaceuticals*, from their development and marketing to the adoption into the health systems and clinical use (Jasanoff, 2004, 2011; Lakoff, 2008). Focusing on this research question, I aim to

highlight how valuation practices reconfigure markets and patients` experiences in relation to disease, these technologies and public authorities. Against this backdrop, I trace these sub-questions: *Which actors (human and non-human) take part in the construction of the values of these treatments? What kind of arguments do they use (scientific, political, moral, economic etc.) in the valuation practices? Who decides who can access to which treatment?*

In the next chapter (chapter 2), I review the literature from Science and Technology Studies (STS), which are relevant to the research question particularly governance of science and technologies; the role and agency of public and patients in this governance and valuation and regulation of personalized medicine and genetic technologies. In the 3rd chapter, I discuss what kind of concepts and focuses guide my theoretical framework that leads me in the analysis of subject and value constitutions. In the 4th chapter, I present the forms of qualitative data, the approach for looking into the data and limitations and ethical matters related to the research. In chapter 5, I touch upon the discussions on the definition and classification of the disease, regulatory framework in the EU that shape the knowledges and values, and contested concerns and values of the actors related to the therapies. In chapter 6, I lay social, political and institutional/legal aspects that are relevant to the governance of these therapies in Turkey, and pinpoint the values and valuation practices of different actors. By focusing on the negotiations particularly between patient families/ organizations and the regulatory authorities in the valuation of two therapies, I flesh out the ordering effects of valuation practices and how patients` access to those therapies is shaped. In chapter 7, I analyse and discuss what these two empirical chapters show with regard the *enactment of values* in pharmaceuticals, as well as *constitution of subjectivities*. In chapter 8, I conclude with my remarks on how studying agency and subjectivity alongside the value generation could be linked to one of the main concerns of STS, which is public participation in governing science and technologies.

2. Literature Review

2.1. Governance of Science and Technologies

The discussion that is laid in the introduction prompts the following questions that have highly occupied the scholars of STS: *Who decides or who should decide on the policies about science and technology that affect our everyday life* (Jasanoff, 2004, p.33). Regulatory decision making is heavily dependent on scientific knowledge especially in the industrialized nations, in which regulatory institutions organize and control markets and technologies by performing various functions, such as setting standards, ordering tests and trials, interpreting them and giving authorizations and patents (Irwin et.al., 1997). The

use of expertise for policy decisions in areas of high uncertainty is the characteristic of todays` governance practices. Particularly in the hardship of maintaining the balance between smooth functioning of the market economy and protection of health, safety and environment; cooperation between scientists and policy makers is inevitable.

Policy decisions that are based on science have been conventionally regarded unproblematic as long as science and politics are separated. In the post war times, political and administrative elites have contended that science and politics exist in separate spheres of facts and values and scientific input to policy problems should be developed independently of political influences (Jasanoff, 2003, p.225). However, especially with the contentious issues such as GMO debate and technological disasters of the 20th century such as Bhopal and Chernobyl, credibility of expert advice has been questioned (Irwin et.al., 1997, p. 19; Wynne, 2002). Irwin (1997) has plainly indicated that various interests are involved in the policy making such as political and commercial considerations, and concerns about health and environment, which are interwoven with the scientific activities (p.25). This prompts asking how these interests can be compromised if scientific experts also disagree about the facts.

Questions that arise at the science-policy interface have been defined by Weinberg, (1972) with the term *trans-science,* implying the need for non-scientific mechanisms in case of any conflict and open discussions with the public involvement. With regard to the question of which issues could be regarded as scientific or trans-scientific, Weinberg has indicated scientists as the responsible actors, since they are the only ones who know what science `is` (1972, p.220). Sheila Jasanoff (1987) on the other hand, has emphasized that what should be counted as scientific and what as a political problem, and who has a right or duty to have a say are constantly being negotiated. `Science` and `policy` are used as labels for cognitive authority in order to achieve certain goals, hence efforts to draw a boundary are politically charged (p.199). Facts are regarded as authoritative not because they can be objectively confirmed, but because they are established via these negotiation procedures and this is how things are ordered in a particular way at the expense of other alternatives (Jasanoff, 1987). Jasanoff (2004) has indicated that scientific knowledge and social and political order are *co-produced*, and criticized the separation of facts, objectivity and policy from values, subjectivity and politics.

When the disasters and contentious techno-scientific policies have incited the public mistrust in the proper use of scientific advice by the governments; it has highlighted the need of better engagement with citizens in science and technology governance (Irwin, 2001, Jasanoff, 2005). Initially political authorities have pointed at the knowledge deficits

and scientific illiteracy of citizens as the main sources of controversies and hostilities towards scientific and technological developments (Pfotenhauer, Juhl & Aarden, 2018; Ziman, 1991).Yet, later it has been accepted that *deficit model* as a way to look into these controversies have failed (Pfotenhauer et.al., 2018). In his influential study on ´misunderstood misunderstandings` Wynne (1992) has contended that it was not the "inability or unwillingness to understand 'correct' messages about risks" that led lay people responded to the expert advice (p.281). Rather they logically judged the risks and related information according to their interest, interactions and social relationships (p.281). This is relevant to think off considering the patients` responses vis-à-vis governments` policies on the reimbursement of therapies in the SMA case.

In an effort to restore public trust, national governments and organizations oriented towards public engagement and dialogue practices. In parallel, the phenomenon of public participation in science and technologies received scholarly attention, especially from STS. In response to the flaws of *deficit model of public understanding of science*; prominent STS scholars Jasanoff (2003), Irwin (2001) and Wynne (2002) have called for *upstream*, socially inclusive, open-ended public involvement in governing science and technologies. *Public engagement from above* has been criticized through various arguments: It often disregards local, flexible and inter-generational knowledge and experience (Wynne, 1992); questions are restrictedly framed in terms of risk related concerns (Wynne, 2002); or citizens are involved at the very late stages of the development (Wilsdon & Willis, 2004; Jasanoff, 2003). Jasanoff (2003) has highlighted that although the public engagement efforts through formal participatory channels are valuable, they do not guarantee "the representative and democratic governance of science", unless they uphold the *technologies of humility* approach to governance, which allows public to challenge the purposes and benefits of concerned technologies (p.237). It brings this question into the mind: *How can be patients` involvement in the development and governance of SMA treatments reviewed considering this debate about public participation?*

2.2. Patients Engagement with Medical Research and Technologies

Medical sciences and technologies are among densely researched areas to understand public participation in the collective knowledge making practices. According to Collins and Pinch (2005), it is more difficult to write about medicine than other topics on science and technology, as "medicine is much more personal and immediately consequential" (p.204). It is not easy to arrive at a judgement about what is for the benefit of public or patient in the already recognized dilemmas related to health such as choice of medical intervention versus a dignified death, vaccination or not, or alternative medicine

versus western medicine for cancer treatment. The literature has covered various case studies and provided valuable conceptual discussions about the publics` and patients` engagements with health sciences and technologies. Mittra (2016) has highlighted that the value of patients` involvement has been increasingly recognized at various stages of health innovation of ecosystem. The rhetoric such as *active patients* (Barbot, 2006) and *patients as partners* have been mobilized by the industry, patient organizations and policy communities, which underlines a shift in the patients` position from passive recipients to active participants in the development of science and technologies (Mittra, 2016).

One influential study about patient participation has been presented by Steven Epstein about AIDS activism in the late 80s (Epstein, 1996; 2000). He explored how AIDS activists became *lay-experts* with the experiential knowledge about their disease and gained credibility through advocacy groups as the organized voice of patients. Accordingly, they challenged the inadequacy of biomedical and public health interventions in the epidemic and lack of available effective therapies. They demanded accelerated evaluation of their medicines by the FDA and alternative access mechanisms such as parallel clinical trials for those who could not enrol in the trials. For Epstein, AIDS activism was distinctive, since they questioned the methodologies and processes of biomedical research, which has not been achieved in other cases such as by self-help groups or feminist health movements (Epstein, 1996, p.13). However, also relevant to the discussions about SMA therapies, he has called attention to the risk of undue acceleration in the approval of drugs with the *urgency* narrative and increasing hype around new drugs (Epstein, 2000). As shown by Epstein, AIDS activists had a significant impact in challenging the regulations, being the “key players in pushing for the approval of AIDS drugs at an earlier stage in the drug development pipeline” (Epstein, 1996, p.339).

A similar probe about the nuances of patient participation has been held by Prainsack (2017a), in her work about public involvement in scientific development, defined as the *citizen science initiatives* with reference to Irwin (1995). Prainsack (2017a) has studied the case of online personal genomics testing service 23andMe and explored the potential of *grassrootedness* or *social-robustness* “(i.e. corresponding with dominant social, political, ecological, and commonly shared values”) of *citizen science* projects, attending to how much influence participants have over the aim, design, and utilisation of results (p.150). Accordingly, the initiative incorporated strong participatory elements, such as implementing participants` suggestions for agenda setting in research and providing participants` access to and control over their data. However, the company was publicly criticized by acting like a for-profit actor when sharing and exploiting research findings: They did not acknowledged the contribution of participants in published academic papers;

they did not share any financial profit with those who had provided the data and they limited research by enforcing intellectual property rights on tests and applications they developed (Prainsack, 2017a, p.156). This discussion points at the significance of delving into the peculiarity of each case, to understanding the emancipatory potential of the patients' involvement with biomedical sciences and technologies.

2.3. Gene-Based Health Technologies and Personalized Medicine

The investment in life sciences and the medical research and development were marked with a significant focus in 1990s: Sequencing the human genome with an international effort incorporated in the Human Genome Project (HGP) of 1990-2003. The reading of the complete human genome in 2003 as a result of those efforts generated an enthusiasm towards achieving comprehensive knowledge about health and diseases and the optimism for the development of new therapies. The genomic research, as mainly focused on the functions of genes and identification of genetic variants that could lead to diseases, would facilitate the development of tailored diagnostic and therapeutic technologies for individual patients or patient groups. A notion of *bio-economy* has become visible in the public and policy discourses, that is based on the idea of benefiting from the combination of individual`s data and biomaterial for the potential of protection of health, curing diseases and creation of jobs (Martin, 2018, p.80; Sunder Rajan, 2011). *Personalized medicine* (or *stratified medicine*) which implies identification of patient sub-populations according to their responses to the drug (efficacy) and adverse reactions (safety) has emerged to deliver those promises (Mittra & Tait, 2012, p.711; Mittra, 2016, p.145). This phenomenon has also received attention from social science researchers, studied through various concepts and theoretical frameworks, some of which will be held here in relation to the research question. I will review the literature that touches upon the transformations in the *bio-economy*; firstly the ones which have a focus on the rights and responsibilities of individuals in relation to these technologies and their governance; and secondly, the literature which emphasizes development and regulation of therapies.

2.3.1. Subjectivity and Agency of the Individual in Gene-based Technologies

One important segment of the literature for the purposes of this study is about relationship of individuals with these technologies. A great deal of scholars in STS has studied public agency in relation to biomedical knowledge and technologies. These works represent an opposition to "the idea that citizens are merely passive objects of the state's top- down regulation of life, or biopower" (Jasanoff, 2011, p.20). Significant for the development of diagnostic and therapeutic technologies in SMA disease, the case of French Muscular Dystrophy Association (AFM) has been investigated by Callon and

Rabeharisoa in various articles (Callon & Rabeharisoa, 2008; Rabeharisoa & Callon, 2002; Rabeharisoa, 2003). Rabeharisoa (2003) has asserted that the groups which gathered around SMA disease against the lack of knowledge and research interest on their disease, managed to present their experience with the disease in a formalized way that could attract the attention of researchers and clinicians (Rabeharisoa, 2003, p.2132). According to Rabeharisoa (2003), this dialogue between parents and specialists contributed to the collection of patients` DNA, discovery of different disease forms and eventually the identification of the gene associated with the disease. In another article about Muscular Dystrophy Disease and AFM, Callon and Rabeharisoa (2008) highlighted that at a time when the disease was seen like `errors of nature`, patients gathered as an *emergent concerned group* with shared *matters of concern*. Their agency has been materialized by the construction and mobilization of a genetic identity, and given rise to new technologies which has reconfigured the trajectories of the life with the disease (Callon & Rabeharisoa, 2008). Their research prompted interrogating how the life with the disease has been shaped after the development of genetic technologies about SMA disease.

Inspired by the Foucault`s concept of *bio-power* (Foucault, 1987), Rose and Novas (2005) and Rose (2007) have focused on the changing facets of the relationship between individual and public and private authorities with the developments in biomedicine. Rose & Novas (2005) has indicated that the *biological citizen* is *made up* in the contemporary political economy in this concomitant relationship between individuals and authorities. On the one hand, it is related to novel ways of governing citizens through strategies for *making up* the biological citizen. This points to how authorities interpret individuals by dividing and unifying them under certain categories about health and illness such as blind, deaf, chronically sick or disabled; which also shape how they receive treatment (p.445). On the other hand, *biological citizenship* does not only imply the making up the citizenship from above, but also incorporates the ways in which individuals define their identities and act upon them as someone such as who carries the risk of breast cancer, depression or a kind of genetic disease (Rose & Novas, 2005, p.446). This form of citizenship is intermingled with a notion of responsibility about the self against the health risks and need for action with the hope of treatment or prevention related to individual`s condition.

Rose & Novas (2005) have also framed the concept of *political economy of hope* to capture the form of actions to be taken by the individuals through cultivating scientific knowledge about their conditions and the political activism that is usually gathered around patient organizations. In parallel to the responsibility for the self for shaping the future; *biological citizenship* generates new forms of *biosociality* to act upon the new objects of

contestations created by the contemporary biomedicine (Rose & Novas, 2005, p.442). For instance, *biological citizenship* implicates "forms of activism such as campaigning for better treatment, ending stigma, gaining access to services", which can also utilize the digital communication technologies to organize as communities (Rose & Novas, 2005, p.442). Those notions of activism and responsibility, they argue, "have now become not only desirable but virtually obligatory (…) [for] the active biological citizen (…)" (p.451). This understanding speaks to the families` responsibility and activism for access to treatments in the SMA case.

In her edited book *Bio-constitutionalism in the Genetic Age*, Jasanoff (2011) and her co-authors have emphasized that while genetic discourses and technologies offer individuals a chance to shape their future and collective identities with the emergent knowledge and technologies, this does not happen independently of the institutional structures. Here they frame the concept of *bio-consitutionalism* to stress firstly "constitutional implications of epochal changes in science and technology" and secondly the "sites and processes in which individuals work out their bio-political relationships with the institutions that regulate them" (p.10). The concerns that the concept deals with could be illustrated deftly with the following questions; which could point at the different responses in different legal regimes:

> What rights should humans have vis- à- vis new biological techniques that impinge on their lives; where should human agency (…) begin and end; when are humans entitled, as citizens, to participate in governing new forms of life (…). (Jasanoff, 2011, p.15).

Sunder Rajan (2011) as one of the co-authors of the book, has focused on the individual`s subjectivity that "emerges through genomics and its political economic context in different locales" (p.195). In contrast to the studies that emphasize the "self-reinvention" of the subject vis-à-vis new biomedical knowledge and technologies, as he argues, he has engaged with the *subject-constitution* in its relationship with capital and state in different regions of the world (Sunder Rajan, 2011, p.195). He has used the term *constitution* with reference to both the institutional and legal codes; and the *co-production* of the scientific facts and technological system with the legal, corporate and governmental institutional practices.

In this study Sunder Rajan (2011) has explored "how the neoliberal state configures the possibilities for the subjects" differently in India and the United States (p.196). In in the US case, he has investigated a biotechnology company called Genomic Health that was specialized in consumer genomics. Accordingly, the company endorsed a business model

that was based on shaping individuals` future health through genetic based consumables such as diagnostic tests or other preventive or therapeutic options, according to each of their unique personal genome. As he indicated, patients were positioned by the company as "always already consumers- in- waiting" for receiving the genetic information and technologies, who had the freedom and capacity to choice rationally and responsibly among the available options (Sunder Rajan, 2011, p.200). Here, individuals were subjected to the rationality of consumption and imagined as *sovereign consumers* and "the source[s] of potential market value" through their choices in the genomic marketplace (Sunder Rajan, 2011, p.202).

In the Indian case this imagination was different. As it was easier and less costly to recruit patients in India, Western biotech companies outsourced some of the services related to clinical trials to an institutional structure composed of a for-profit research organization, hospital and a private company that was focused on pharmacogenomics. This infrastructure in India was engaged in conducting clinical trials as its business model and positioned more as "an experimental site rather than a therapeutic one" (Sunder Rajan, 2011, p.204). Since there was a high level of unemployment among the previous workers of some disintegrated industries, people tended to be recruited in the clinical trials in exchange of compensation (p.204). Sunder Rajan (2011) indicated that the sovereign agents were the stakeholders of the institutional structure that were conducting the research, as well as the state by determining the conditions of conducting international clinical trials (p.205).

Contrary to the *sovereign subjects* configured as potential consumers in the US case, the individuals in the Parel/India case were casted as *experimental subjects* to Western corporate interests. In the words of Sunder Rajan: "Instead of being consumers, they are *consumables* —their bodies made targets of experimental therapeutic intervention so that other bodies in other locations can benefit from drugs as sovereign consumers" (p.205). Based on those empirical cases, he argued that his focus on the subjectivity referred both the *subjection* which implies that individuals are subjected to power; and *subjectivation* which emphasizes their agency and autonomy vis-à-vis power. However, he also underlined that both cases reflected individuals as not entirely free agents, as "both types of subjectivity are always already available to be appropriated by capital" (Sunder Rajan, 2011, p.209).

2.3.2. Development and Regulation of Personalized Medicine

With regard to the relationship between law and technology, Jasanoff (2011) argues that there is a popular understanding where "the law is depicted as trying to bridge gaps

and lags created by advances in science and technology" (p.11). She criticizes such a view and underlines that all technological developments "play out on terrain already occupied by law" (Jasanoff, 2011, p.6). This implies that the circulation of new medical technologies takes effect with already established regulatory frameworks as well as new regulatory efforts at different levels. In parallel with Jasanoff, various STS scholars working on the governance of medical technologies have highlighted the contingent relationship between knowledge making and regulatory mechanisms at various levels. Works concerned with the role of these mechanisms in this relationship view regulatory structures as constitutive of scientific knowledge production (Cambrosio et al., 2006; Hedgecoe, 2005; Green, Carusi & Hoeyer, 2022; Lakoff, 2008; Wadmann & Hauge, 2021).

Most of these works have pointed to the re-organization in research and development (R&D) of medical technologies and transformations in the regulatory structures especially after 1990s and 2000s (Lakoff, 2008; Martin, 2018; Mittra, 2016; Sunder Rajan, 2011). What they have jointly highlighted as a trigger of such change has been the phenomenon of *productivity crisis* in pharmaceutical industry which has shaped new discourses and institutional structures for generating the benefits of scientific advances. The *productivity crisis* implied that the medicines based on small-molecule targets and their patent protection had already been exploited and there has been high failure rates in the clinical trials related to safety and efficacy of medicines (Mittra, 2016, p.36). Consequently, decrease in the number of novel medicines, alongside the rise in R&D costs prompted new approaches to the development and regulation of pharmaceuticals (Martin, 2018, p.83; Mittra, 2016). As a response to these challenges, understanding of *personalized medicine* has coupled with the development of genetic diagnostics that facilitate more efficient screening of populations for genetic markers to correlate with drug responses. The idea of tailoring medicines according to individual characteristics of patients has been embraced by industry and political leaders around the world, particularly for delivering the promises of investments in research by developing path-breaking therapies (Green et.al., 2022; Mittra, 2016, p.145, Prainsack, 2017b, p.1).

According to the literature on *personalised medicine* (Green et.al., 2022; Mittra, 2016; Prainsack, 2017b; Wadmann & Hague, 2021), this vision is based on stratification of patients for ensuring that they are using the right drug, that is potentially safe and effective according to their genotypic and phenotypic (physically observable) characteristics. For Sunder Rajan (2011), this has represented a transformation in the diagnosis and treatment of diseases, what he has defined as the *genetic approach* which could be summarized as the following process: The identification of a disease with a

genetic component and the involved gene(s); then using the gene as a drug as in the case of genetic therapies or understanding the biology of the disease to develop therapies that could target the molecular mechanisms of the disease; then “tailoring prescriptions and drug regimens to individuals based on their likely, genetically determined, response to these drugs”, which known as *pharmacogenomics* (Sunder Rajan, 2011, p.199). Especially the technological platform of *pharmacogenomics* has been incorporated into clinical trials to test the safety and efficacy of new medicines (Sunder Rajan, 2011, p.202).

Among the work that has interrogated stratified approaches to diagnosis and treatment of diseases, both Lakoff (2008) and Green et.al. (2022) have focused on coding and classifying diseases as the regulatory mechanisms that shape scientific knowledge about diseases and technologies. Lakoff (2008) has indicated that classifying and coding diseases has been a tool in addressing a large span of technical and administrative requirements for the circulation of pharmaceuticals. This has involved the need for defining a target population to for clinical trials to test and demonstrate the safety and efficacy, as well as for benefiting from the insurance. Accordingly, in order to circulate in a regulated system, a pharmaceutical needs to work on a specific disease that is classified in a standardized way (p.746). However, as Lakoff indicates, it is not easy task “to stabilize the relation between diagnosed patient and targeted intervention” (p.748). He then put the following question under spotlight: “How might recent developments in the life sciences address this problem of identifying ideal treatment responders?” (2008, p.752).

He argued that developments in the life sciences such as gene-based diagnostic tests and the vision of *personalised medicine* have shifted the way of matching the right treatments to patients towards the identification of ideal responders to the treatments. For Lakoff (2008), companies have showed interest to this vision and related technologies particularly for marketing medicines more quickly. They have casted the difficulty of showing the safety and efficacy of products through clinical trials as a distinctive reason of slow and expensive drug development, which has been linked to heterogeneity of patient populations. *Pharmacogenetics* has allowed them to “stratify trials based on patients who are most likely to benefit from therapy” (Lakoff, 2008, p.754). As he illustrates with the psychiatric disorders: “[D]iagnostic questions would appear no longer as—´is it bipolar disorder or schizophrenia?´ but as—´is it a lithium or an olanzapine response profile?´”(Lakoff, 2008, p.755). Lakoff has defined this phenomenon as *finding right patients for the drug* which reconfigured the knowledge about illness, the effects of medication and as well as patient identity (2008). This evoked the following questions that are closely related with the focus of this study: What would be the implications of this transformation

underlined by Lakoff (2008) and Sunder Rajan (2011), for the regulatory frameworks of medicines regarding to marketing approval and adoption in the health systems?

Green et.al. (2022) has explored the vision of personalized medicine in the production of regulatory evidence, that has been promoted as a way to address the strict prioritization of standardization and statistical evidence in evidence-based medicine (p.2). As they have highlighted, “through finer-grained stratification of diseases and patient groups, personalized medicine promises to overcome the limitations of classical phase III trials that agencies like the (…) FDA and EMA traditionally have seen as the gold standard of evidence” (p.4). They pointed to “a shift in the regulatory regime of evidence standards, where evidence is supposed to result from new treatments rather than being the basis for them” (Green et.al., 2022, p.6). They have stressed that the political enthusiasm for using real-world data (after authorization of treatments) as evidence for speeding up the implementation of new treatments should be treated with caution, since it positions each individual case as an experiment that can generate evidence (Green et.al., 2022, p.7).

In a similar vein, Nik-Khah (2018) has approached to the new regulatory regime quite critically and defined it as the neoliberal view on the regulations. He has argued that neoliberalism, as its most distinctive characteristics, adopts the idea that market has certain epistemic virtues, which has the best capacity for processing and conveying the information. In this vein, neoliberal understanding of pharmaceutical regulation champions post-market surveillance instead of large-scale randomized clinical trials (Nik-Khah, 2018, p.59). Using real-world data as evidence for treatments after market approval phase is particularly upheld by neoliberal institutes, think-tanks and companies, as a better way of producing evidence than randomized clinical trials. With this vision, liberals promote reducing the scope of the clinical trials or “partial approval” of pharmaceuticals, which allow companies to market their products with “incomplete” data and overcome “time-consuming and expensive pre-market product testing” (2018, p.94). Here the rhetoric of *personalized medicine* is used by neoliberal circles, as it denotes the “possibility of constructing markets to better generate knowledge”; which accords with their imagination on patients as agents of knowledge discovery (Nik-Khah, 2018, p.59). These discussions prompt interrogating the SMA case through the lens of co-constitution of scientific practice with regulations. Specifically, this literature evokes questioning the conflicts emerged out of regulatory challenges that personalized medicine brings and their implications for the patient populations in the SMA case.

2.4. Values and Valuation in Life Sciences

Recent studies of sociology and STS that are grappled with the questions of value in bio-economy stress that values of the bio-technology market and its commodities are not inherent in themselves; they are rather constructed through a series of *valuation practices* (Birch, 2017; Dussuage, Helgesson & Lee, 2015; Helgesson & Muniesa, 2013; Mittra, 2016; Wadmann & Hague, 2021). In their article about *valuation studies* as an emerging field, Helgesson and Muniesa (2013) have argued that value is “the outcome of the organized social work (…) and the result of a wide range of activities (from production and combination to circulation and assessment) that aim at making things valuable” (p.6). They have accentuated the multiplicity of values and have indicated that the worth of the things can be manifold, can conflict, overlap or combine each other (Helgesson & Muniesa, 2013, p.7).

From the scholars that work on life sciences and technologies with this emerging perspective on value, Birch (2017) has explored the political-economic processes of valuation in the bio-economy, with a focus on bio-technology firms, their assets and financial knowledges related to them. According to Birch, despite their failure of generating new products and services; the increasing financial value of the life sciences market showcases the uncertainty in values and how future promises constitute the values in present (p.461). In this vein, he takes *valuation practices* as “an active, ongoing, and performative *management* of value" (Birch, 2017, p.462). Different than Birch`s focus on finance and economy, Dussauge et.al. (2015) have had a critical stance on “giv[ing] analytical precedence to one set of values” (p.16) and have suggested “narrowing the gap between social and cultural values and economic value (…) [and] study them in connection” (p.9). According to this understanding;

> [w]hen the distinction between values (…) is dissolved, we cannot use one concept to explain the arrangement of the other. Economic value can no longer be seen as a determinant of social and cultural values. Conversely, social and cultural values can no longer be seen as determinants of economic value (p.8).

They have focused on *making up values* which let them observe the power struggles for making boundaries among values as well as making certain values dominant over others (Dussauge et.al., 2015, p.16). Drawing on the work of Latour on *matters of concerns* (2004) and de la Bellacasa on *matters of care* (2011), they reflect that “value practices are crucial practices by which people and things make stakes, matters of concern, or matters of care—or displace them” (p.9).Yet, they have brought an additional dimension to these works, framing their analytical focus with reference to these concepts:

> [R]ather than just counting concerns or attending to those who care, we wish also to call for attention to the making of concerns; the production—in practice—of what comes to count as valuable, desirable, or otherwise worth caring for". (Dussauge et.al., 2015, p.10)

Their approach represents an invitation for approaching all concerns in the valuation processes with *care* without confining to the mere critique of power (de la Bellacasa, 2011, p.97). While concerns can differ widely, so do the valuations of these concerns such as differences in the "valuations of life, knowledge, and money" (p.11). They have evoked certain relevant questions: Whose assessments will be valid? How are matters of concerns performed "through economic valuation practices?"; "technical, classificatory and institutional systems"; and "use of scientific theories" (p.12).

Similarly, Wadmann & Hauge (2021) have indicated that manufacturers, regulators, clinicians and patients may value health technologies differently, with different *registers* that correspond to particular concerns, such as effectiveness, safety and fairness. Drawing on Heuts & Mol (2013), they defined *registers of valuation* as "the reference scale employed to assess the worth of a given object" (Wadmann & Hauge, 2021, p.631). They have also pointed at the calculative strategies mobilized by regulators, manufacturers, patients, and clinicians, what they called *strategies of stratification*, which involve using typologies to divide or assemble patient populations (p.646). In the valuation of Spinraza by EMA and in Denmark by different stakeholders, these registers and strategies were used as a way to limit or broaden the treatment indication, which have shaped the market, patient populations and patients` access to the treatment.

3. Theoretical Framework

In this study, I focus on the first two approved pharmaceuticals that target SMA disease as a techno-scientific object, and social and political order that surround them. In specific, I interrogate how the definition and classification of the disease have been configured with the development and regulation of the SMA therapies; and how hopes and expectations of relevant actors and negotiations between them shape -and being shaped by- these therapies and their market. In this attempt, firstly, I am inspired by the work Andrew Lakoff (2008) and his focus questions, especially by the emphasis on "the role of regulatory norms and technical standards" in channelling the access to medicines (p.742). The questions he has posed in this regard are in great harmony with the questions that trigger and guide this research: "Into which bodies should drugs go? Who should be able to prescribe them, and on what grounds? How can we know what they "do" to these bodies? How much should they cost, and who should pay for them?" (Lakoff, 2008, p.742). Since they are the concerns of the regulatory science which are related to

problems of patients` access to these techno-scientific objects, these questions prompt interrogating the politics of technical matters in pharmaceutical circulation. As Lakoff has indicated, “struggles over inclusion and exclusion [of patients] arise around conflicting demands of health and profit, as mediated by government policy (…)” (2008, p.742). Echoing Lakoff (2008), my main emphasis is on the scientific and political controversies that are surrounding the access environment in Europe and Turkey.

Secondly, inspired by Jasanoff (2011) and Sunder Rajan (2011), I take the development and marketing of first treatments of SMA disease as the *constitutional* moments that have implications related to the individuals` rights and responsibilities. These moments are crucial for the discussion on the *subjectivity* (Sunder Rajan, 2011) and individual and collective actions derived from the *biological citizenship* (Rose & Novas, 2005). As the theoretical and analytical framework, I benefit from three strands of *subjectivity* defined by Sunder Rajan (2011) in order to discuss the constitution of biomedical subjectivity in different but “globally interconnected regimes of knowledge and economics” (p.209).

- First strand is related to the **self-understandings** of people on their subjectivity. It concerns “how people who are subjected to new biomedical technologies (…) might think about their enrolment and experience” (Sunder Rajan, 2011, p.207). These understandings are shaped by various social and cultural factors. As Sunder Rajan argues, the focus here is closer to the anthropological studies about subjectivity such as Novas & Rose (2005).
- Second strand engages with the **institutional aspects of subject-constitution**, in which subjectivity materializes through the construction of law, bio-medicine, bioethics, capital and related values. These institutions generate categories and classifications about people and their health, which also affect the understandings of their own subjectivity. However, he highlights that individuals can learn and negotiate their subject positions, although it can be unequally or unevenly compared to the institutions (p.207).
- The third strand concerns **epistemological aspects of the subject constitution**, which involve construction of statistical categories through genetic knowledge or methodologies of the clinical trials or bioinformatics to forecast the market. They present the epistemic basis for the imagination of patients either as a consumer in a marketplace or as an experimental subject (p.207).

Similar to the interest of Sunder Rajan on subject constitution in different regions of the world, I will focus on how the subject is “constructed in a relationship to the state as well as capital” particularly in Turkey. Yet, I argue that the constitutive elements of these

subjectivities go beyond the legal, political and techno-scientific structures of a nation state.

As indicated by Lakoff (2008), pharmaceuticals take effect in heterogonous networks involving "government regulations, biomedical expertise, commercial interest, and patient experience" as well as the substances they include (p.741). Therefore, the effects of pharmaceuticals are not embedded in themselves, but they are shaped in the relationship between these actors. Since a pharmaceutical is "meant to heal" as part of a system of related diagnosis and treatment, its value is linked to its effects (Lakoff, 2008, p.742). In parallel to what Lakoff has argued with regard to pharmaceutical effects, as well as the works that regard *valuation* as a social practice (Dussuage et.al., 2015; Helgesson & Muniesa, 2013; Wadmann & Hague, 2021), I take *value* as an outcome of a set of practices referred to as *valuation*, rather than being an intrinsic quality of these therapies or the mere reflection of subjective elements such as hopes and expectations.

Drawing on this understanding about valuation, I trace *valuation practices* in the circulation of SMA therapies, including their marketing, regulation and use, which may reflect certain dissonances among actors (Dussauge et.al., 2015, p.1). Accordingly, different actors and their practices shape the values of the SMA therapies, including industry through their development and marketing strategies; different regulatory authorities by developing innovative regulatory frameworks, their authorization and assessments for pricing and reimbursement; and patients by making their concerns and shaping the market through their advocacy and preferences. Following Dussauge et.al. (2015), I will be concerned with "the composition of values and the making of boundaries between them" (p.16). Hence, I will explore the *valuation practices* for enacting the values of Spinraza and Zolgensma; with a focus on *registers of valuation*, *stratification* of disease populations in line with the understanding of personalized medicine (Wadmann & Hague, 2021) and *subject constitutions* (Sunder Rajan, 2011).

Studies that help me open up the SMA case are in concordance with what *co-productionist* understanding particularly posits: The symmetrical attention "to the social dimensions of cognitive commitments and understandings, [and] (…) the epistemic and material correlates of social formations" (Jasanoff, 2004, p.3). Therefore, this study builds on the STS work on *co-production* of science and society, especially on novel biomedical technologies. The focus of Lakoff`s work has been both on "how are technoscientific objects stabilized?" and "how are users configured?" (p.741). He has dealt with how patients as subjects are imagined and positioned in "a socio-technical system for circulating pharmaceuticals (p.743). Sunder Rajan (2011) has engaged with the elaboration of "joint institutional and epistemological construction of biomedical

subjectivity" (p.208), which requires a symmetrical emphasis on the subjects and objects. Similarly, studies that focus on *valuation practices* in medicine have explored the scientific and political entanglements of value making; and argue that *valuation practices* are not separate to the knowledge making practices (Dussauge et.al., 2015, Wadmann & Hague, 2021). In a similar vein, I aim to follow the "methodological prescription" of *co-production* by looking at the *"*amalgamation of representations and discourses and institutions and identities", not only discourses or representations (Pickersgill & Jasanoff, 2018, p.329).

Consequently, these analytical and conceptual frameworks have configured this research towards this question: *How the values of SMA therapies are enacted along with their governance and different modes of constructing individual subjectivity?* Hence, this study represents an attempt to "bring together two streams of STS, one related to the construction of markets and the other to democratic ordering in relation to technology" (Laurent, 2022, p.22). I argue that following the valuation practices in the circulation of pharmaceuticals and the construction of subjectivities will highlight how different regulatory authorities, pharmaceutical companies and patients shape the "flow of medication into some bodies and not others" (Lakoff, 2008, p.742). They has led me to attend to the complex valuation processes first at the European level and then in Turkey to see the relationship between the values and valuations in different geographies. I study the case in a specific national jurisdiction to better zoom in the co-constitution of biomedical subjectivity, the values of these technologies and their ordering effects on individuals.

4. Data and Methods

The study has been based on a combination of qualitative research materials which primarily include interviews, written documents and videos. The dataset consist of the following:

- Written documents: Articles on the disease and treatments written by the medical community especially by the experts on neurological disorders; assessment reports of EMA for Spinraza and Zolgensma; publicly available assessment reports of national public authorities; reports, studies and articles published by patient organizations in Europe and in Turkey; other online materials that announce constitutional moments and that reflect stakeholder views on the treatments.
- Interviews with the stakeholders in Turkey: Six semi-structured interviews which lasted approximately an hour→ Three with representatives of different responsible public authorities; three with patient representatives: two interviews with

representatives of two different patient organizations, one interview with a patient mother who is not involved in a patient organization

- Online events and video recordings: One event related to access to SMA therapies which gathered representatives from industry, EU institutions and patient organizations; one video recording published by a media channel which reflected the view of patients and patient representatives
- Observations from the fieldwork in Turkey: Protests and gatherings of patient representatives; news of media outlets and social media channels

I have conducted three face-to-face and three online interviews; audio-recorded and transcribed them. I have treated the data from online events and videos similar to interviews and transcribed them accordingly. I have also collected photos of significant moments as part my fieldwork in Turkey, to better understand the situation -without the intention of using them in the analysis with ethical concerns- such as photos from the protests of patient families and representatives in front of the Ministry of Health with their demands about treatments; photos of SMA patients usually with respiratory support, flowing on the billboards in local transportation in Ankara and also on Twitter for the collection of the required money for Zolgensma treatment.

There are also some methodological and ethical concerns and limitations of the study. Although I have read interview and event transcriptions in parallel to written documents such as regulations and policy reports in order to validate my understanding on complex technical and legal matters, the citations from the interview respondents have not been reviewed and approved by themselves due to the time limitations. Besides, as price and reimbursement negotiations between national authorities and pharmaceutical companies are conducted confidentially without a published documentation in Turkey, I could not reach out to the views of pharmaceutical companies in these negotiations. This has turned to a decision to limit my focus mostly to the interaction among the patient families, patient organizations and regulatory authorities.

I initially classified all documents according to actors involving regulatory authorities, patient organizations, medical experts and clinicians. However, first analysis has indicated that these actors could embody different identities or could collectively produce materials and actions. This has particularly been manifested in a White Paper on the assessment of policy and access environment in Europe for SMA patients (Charles River Associates, 2021), co-developed by the European level patient organization SMA Europe and Biogen, the manufacturer of Spinraza, with the support of a consultancy company, Charles River Associates (CRA). Therefore, they were re-classified in a way that could better reflect the *situations*. As Adele Clark has highlighted, the focus of research should be “on generating

understandings of the relationalities among all the elements empirically found in the situation of interest through mapping them in various ways" (Clarke, 2019, p.15). She has termed this understanding as *situational analysis* which has implied a shift of focus in the grounded theory, from human action to collective action; realization of the *situation* as the main unit of analysis and taking into account the human, non-human, discursive, and other elements of the situation (Clarke, 2005; 2019). Inspired by this approach, I have taken patients´ access to treatments of SMA disease as the *situation* and utilized from the situational maps "for articulating the elements in the situation and examining relations among them" (Clarke, 2005, p.86). Yet, I have used these maps not as the results of the analysis, but as tools to think systematically throughout the research that have guided the analysis.

5. Institutional and Epistemological Aspects Surrounding the Disease and Values of the Therapies

5.1. Spinal Muscular Atrophy: Definition and Classification of the Disease

Spinal Muscular Atrophy (SMA) is a known as a group of rare disorders characterized by the degeneration of spinal neurons and progressive muscle weakness. It affects the muscles close to shoulders, hips and back that are necessary for crawling, walking, sitting and head control. In more severe types of SMA, muscles involved in swallowing and breathing can be affected. Respiratory muscle failure constitutes the major reason of mortality of the patients with the severe form of the disease (Kariyawasam et.al, 2018). Although regarded as a rare disease with an estimated incidence of approximately 1 in 10,000 live births globally, SMA is known as the major genetic cause of infant deaths (Arnold, Kassar & Kissel, 2015; Chen, 2020, p. 1).

The disease was first described in the 1890s by Werdnig and Hoffman. It was a century later, in 1995, that the genetic cause of SMA was mapped and the survival motor neurons (SMN) were identified as the SMA determining genes (Lefebre et.al, 1995). SMA is associated with the low levels of the Survival Motor Neuron (SMN) protein resulting from having two faulty copies of SMN1 gene (Chen, 2020; Kariyawasam et.al, 2018). SMN2, which is known as the "back-up gene", also produces this protein, yet it is a shortened and less stable version that cannot compensate the protein production (Spinal Muscular Atrophy UK, 2022). 95% of the SMA cases are caused by the absence of both copies of SMN1 gene on chromosome 5 (Arnold et.al., 2015; SMA New Born Screening Alliance, 2021, p.4). This common form is known as *5q SMA* referring to its genetic cause (Spinal Muscular Atrophy UK, 2022).

With the identification of the genetic cause and development of diagnostic technologies, DNA testing has become the main practice of diagnosing SMA, after the evaluation of medical history and physical examination of an infant. The diagnosis is confirmed by considering the situation of SMN1 and SMN2 genes (Spinal Muscular Atrophy UK, 2022). Prior to the availability of genetic testing, electromyography and muscle biopsy were the tools used in the diagnosis of SMA, which are now regarded as invasive and non-efficient by the medical community compared to genetic testing (Arnold et.al., 2015). After the discovery of the SMN1 gene, it has become possible to diagnose previously unrecognized cases with atypical presentation based on the absence of the gene (Dubowitz, 2009, p.73).

Traditionally, SMA has been classified under three categories according to the clinical observation of the patient`s motor functions and age of symptom onset (Kirschner et.al., 2020; Verhaart et.al., 2017). Yet, additional subtypes including 0 and IV can also be used (Arnold et.al., 2015). As the most severe and common type of SMA representing 45% to 60% of the cases (EMA, 2020c), SMA Type I is characterised by symptom onset in the first months of infants and such as weakness in muscles that usually starts before 6 months. Patients may have problems with swallowing and head control. Many need non-invasive ventilation (a machine provides air pressure through a face mask) or invasive ventilation (tubes going through the mouth for temporary use or through a hole in the neck for long-term use, which is known as tracheostomy) (Sajac, 2021). Although depending on the respiratory functions and the proactive management of the disease through new therapies, life expectancy is less than two years for the majority of patients (Chen, 2020, p.3).

SMA Type II is marked by the age of symptom onset between the age of 7-18 months (SMA UK, 2022). Patients mostly reach the ability to sit independently, which can be lost in their later life. Few patients can stand and walk without an aid. They are described by the clinicians as `sitters` (Spinal Muscular Atrophy UK, 2022). In SMA Type III, symptoms usually occur after 18 months, or in late childhood or early adulthood. Patients can survive into adulthood. Although initially patients can stand and walk, they can be bound to wheelchair in the later stages due to the progressive muscle weakness. In the extended version of the classification, Type 0 and IV could also be used. Although it is rarely seen, Type 0 is associated with the characteristics such as respiratory distress, poor feeding and intrauterine movement usually with the onset of prior to birth. Most of the patients can only survive up to 1 month and only few live up to 6 months (Chen, 2020). Type IV is known as the mildest form; patients have average life spans but have some symptoms such as weakness of lower extremities (legs and feet), mostly with an onset

between the ages of 20 to mid-30s (Chen, 2020, p. 3). Only a limited share of the patients loses the ability to move or walk independently (p. 4).

Having defined that, the classification of the disease types is a contested issue among the medical community due to certain reasons (Dubowitz, 2009). While lack of SMN gene is accepted as the genetic basis of the majority of the cases, the phenotypic characteristics may differ among patients even those who are categorized in the same disease type (Kirschner et.al., 2020). Besides, since the disease represents a continuum, which implies continuous degeneration of muscles, severity of the patients` condition may change over time (Chen, 2020). As a progressive disease, SMA can represent phases from pre-symptomatic, to rapid disease progression and then slow progression in the later plateau. There is a high consensus among the medical community on that "clinical status of an individual patient does not only depend on the type of SMA but also on the stage of the disease" (Kirschner et.al., 2020, p.39). Besides, experts indicate that there are significant overlaps in the clinical conditions of patients who are diagnosed with different disease types. For instance, the condition of patients with SMA Type II in their later stage can be more severe than the condition of patients with SMA I in their early stages (Kirschner et.al., 2020, p.39).

The number of the SMN2 gene, which has been involved in the diagnosis with the development of diagnostic technologies, is also a matter of discussion. In the `International Conference on the Standards of Care for SMA` (2007), experts have argued that "although a higher copy number of SMN2 is correlated with milder phenotype, phenotypes can vary substantially (…); [therefore] predicting clinical phenotype using SMN2 copy number can be risky and is not currently recommended" (Wang et.al., 2007, p.1033). However, this consensus has been updated in 2017 after further evidence about the natural history of SMA types and the approval of the first therapy in 2016. In their article on the revisited standards of care, Mercuri et.al. (2018) have used SMN2 copies in the classification of SMA types, and indicated that "number of SMN2 copies is an important factor influencing the severity of the SMA phenotype" (p.105). Correlation of symptom onset and severity of the disease with SMN2 copy number have also been adopted in the authorization reports of EMA:

Table 1: Classification of the disease used by EMA

Type	Age at Symptom Onset		Maximum Motor Function	Life Expectancy	*SMN2* Copy No.
0	Fetal		Nil	Days – Weeks	1
1	< 6 months	1A: Birth – 2 weeks 1B: < 3 months 1C: > 3 months	Never sits	< 2 years	1, **2**, 3
2	6 – 18 months		Never walks	20 – 40 years	2, **3**, 4
3	1.5 – 10 years	3A: < 3 years 3B: > 3 years	Walks, regression	Normal	3, **4**, 5
4	> 35 years		Slow decline	Normal	4, 5

(Source: European Medicines Agency, 2020c, p.12)

As I discuss in the next chapters, the number of SMN2 copies has been a significant tool used in the regulation of the treatments, both in the authorization of treatments by EMA and in the reimbursement decisions of the national authorities.

5.2. Institutional and Regulatory Framework in the EU

The EU has had an established legislative framework since 1965; which regulates the whole life-cycle of medicines, from their clinical research to post-marketing surveillance. This framework has been evolved in parallel to scientific, technologic and social developments. In 1995, European Medicines Agency (EMA) was established as the responsible institution for scientific evaluation of quality, safety and efficacy of medicines within the EU. According to the regulatory framework, there are two mechanisms for marketing medicines: Centralised or national (EMA, 2016). In the centralized authorization, pharmaceutical companies submit a single authorisation application to EMA and based on the EMA`s recommendation, the European Commission (EC) grants marketing authorization of medicines which becomes valid throughout the EU (EMA, 2016). This centralized mechanism is valid for medicines which contain a new active substance to treat conditions such as HIV or AIDS, cancer, diabetes; medicines for rare diseases (orphan medicines); and advanced-therapy medicines. It allows companies to market their `innovative medicines` throughout the EU on the basis of a single marketing authorisation (EMA, 2016).

Over time, EU has developed and revised its regulatory structure especially by publishing different regulations for specific conditions including orphan medicines targeting rare diseases with prevalence of no more than 5 in 10,000 people affected by the disease (European Commission, 2008), paediatric medicines (medicines for children) and advanced therapy medicines that are based on genes, tissues or cells. Since they have been associated with complex and costly research and development processes or being economically unattractive with small market sizes, the EU developed tailored

regulatory pathways that could incentivise their manufacturers. For instance, companies which develop orphan medicines could secure R&D financing from the EU or national funding mechanisms; receive free scientific advice from EMA before the authorization and have longer market exclusivity for their products which means similar products with the same therapeutic indication could not be placed on the market within that period (European Commission, 2020, p.12). More importantly, these tailored regulatory frameworks would allow manufacturers to conduct clinical trials with smaller patient populations, such as in orphan medicines, since they affect smaller patient populations; or deviate from randomized clinical trials when it is not feasible or it does not provide high quality evidence. This implies that the limitations on patient recruitments could be taken into account in the marketing authorization decisions and they could resort to other trial control methods defined at the lower level of the hierarchy of evidence (EMA, 2006, p.4). These adaptive pathways would also apply to the advanced therapy medicinal products if they target a rare disease, an unmet medical need or/and paediatric patient populations, which is considered as a justification for "more flexible clinical designs and methodologies" (Iglesias-Lopez et.al., 2021, p.606).

A novel mechanism that targets early access for certain cases including rare diseases or public health threats like COVID 19, is the *conditional marketing authorisation,* which is particularly significant for this study, as it has been used by EMA in the authorization of Zolgensma. According to EMA, it is a tool for the fast-track approval of a medicine that fulfils an unmet medical need, which implies a condition for which there is no proper treatment or the new treatment will provide a major *therapeutic advantage* (EMA, n.d.). According to EMA, this procedure allows approval of a medicine on the basis of less comprehensive data than normally required, if the available data indicate that benefits outweigh the risks and the company commits to provide further data after the authorization (EMA, n.d.). EMA stresses that "conditional marketing authorisation can help speed up patient access to new medicines" (EMA, n.d.). Therefore, besides the manufacturers of the pharmaceuticals, these special mechanisms have also been upheld by patient representatives with their potential of encouraging the development of innovative therapies and accelerating patients` access.

While rare disease and advanced therapy medicines are marketed across the EU through the mutual recognition of the EMA`s central approval, decisions related to price of medicines and reimbursement (covering them under insurance or not) are among the Member States` responsibilities. EMA`s responsibility in marketing authorization is restricted with the assessment of safety and efficacy; however, Member States can consider various parameters in their assessment for the price/ reimbursement decisions in

addition to these concerns, such as relative effectiveness of the new medicines in comparison to existing ones, seriousness of the disease and their impact to healthcare budgets. Considering the increasing prices of health technologies and national budget constraints, national authorities aim to ensure the sustainability of their health budgets. Therefore, they assess a new health technology not only with regard to the safety and efficacy, but also in terms of their cost-effectiveness compared to its alternatives. This implies the responsibility on the side of industry to provide further data to each national authority for their decisions on pricing and reimbursement (Mittra, 2016, p.156; Wadmann & Hauge, 2021, p.629).

In this regulatory framework, each country individually negotiates with the manufacturers and decides on the price and reimbursement of medicines, which is often driven by a systematic assessment of the concerned technologies that is called health technology assessment (HTA). Especially in 1990s new national or regional agencies for HTA were established in Europe, for providing assessments to decision-making bodies for their coverage decision, such as the German Institute for Quality and Efficiency in Health Care (IQWiG), the French National Authority for Health (HAS) and Austrian Institute for Health Technology Assessment (AIHTA) (Garrido et.al., 2008). Decisions of regulatory authorities on prices and reimbursement of medicines have begun to benefit from these assessments which could include clinical, economic and ethical matters according to the specificities of each country. Yet, they could also be dependent on the negotiations between the pharmaceutical companies and national authorities, and initial prices set by the manufacturers could be higher than the price agreed with the national authorities for the reimbursement, which have been usually kept confidential by the countries (Atikeler, Leufkens & Goettsch, 2020, p.590; European Parliament, 2010, p.36).

This regulatory structure implies inconsistencies among Member States in terms of prices of medicines and decisions related to their reimbursement, especially on the high cost orphan medicines. Besides, it points to potential differences about valuation of medicines by EMA and national authorities, as SMA case will reveal. For the industry, these differences create unpredictability in terms of anticipating whether their investments will be covered by the reimbursements. For the regulators, development and marketing of these medicines at substantially higher prices increase the financial burden of drug procurement and imply allocation of less money for other healthcare expenses and medicines for other diseases (Blonda et.al., 2021; Kerpel-Fronius et.al., 2020). For patients on the other hand, this can be an issue of life and death as in diseases like SMA.

5.3. Valuation of SMA Therapies

5.3.1. Contestations on the Values over Risks and Benefits

EMA`s evaluation that constitutes the basis of the authorization of medicines by the European Commission implies not only the positive scientific opinion on the safety and efficacy of a medicines, but also the delineation of the population that is expected to use this medicine. Authorization of medicines on a broad or limited patient population shapes regulatory decisions of national authorities related to use and reimbursement of medicines, and thereby patients` access. It also represents a crucial part of the knowledge production and value formation on medicines.

Spinraza (nusinersen), as the first medicine that targets 5q SMA was designated as an orphan medicinal product in 2012 by EMA. Biogen applied to EMA for marketing authorisation of Spinraza in 2016, through the centralised procedure required for the orphan medicines. In 2017, EMA granted its positive opinion for the authorization to be valid across the EU. According to the summary document about the authorization, Spinraza includes a genetic material which "enables the SMN2 gene to produce full length protein (…) thereby relieving the symptoms of the disease" (EMA, 2017b, p.2). It is administered through an injection into the spine in the lower back (intrathecal injection). According to the EMA`s report, 51% of the 173 babies with Type I, II or III showed improvement including head control, sitting, standing and walking, and developed a later need of breathing support compared to the babies who received placebo (EMA, 2017b, p.2). The Agency reflected that another study by the company has manifested progress in the movement of the 57% of less severe patients with a later stage diagnosis (p.2). Based on these data presented by the company, EMA highlighted that the medicine has shown significant efficacy for a broad range of phenotypes in both pre-symptomatic and symptomatic SMA patients with infantile or later onset (EMA, 2017a, p. 83).

However, the Agency also recognized some uncertainties and limitations of the data provided by Biogen. Accordingly, there was no data related to dose adjustments according to patients` increased body height or other relevant parameters; and also no safety profile for patients whose diseases can be categorized as Type 0 or Type IV (EMA, 2017a, p.104). EMA stressed that despite not all patients have responded the treatment, its benefits outweigh the risks associated with the intrathecal administration (p.115). Besides, although clinical data were not available for patients with mild and adult onset, the efficacy shown in other prevalent forms were regarded as sufficient by referring that "these patients are part of the continuum in phenotypes of one genetically defined but clinically heterogeneous disease" (p.115). Therefore, EMA adopted a positive opinion on

the marketing authorization for Spinraza, with a general indication of all SMA patients sharing the genetic basis of the disease, from type I to IV.

Zolgensma (onasemnogene abeparvovec) on the other hand is a gene replacement therapy that targets the SMN1 gene with a virus, which aims to deliver a functional copy of the SMN1 gene to the motor neurons (Hoy, 2019, p.1255). It is therefore classified as an advanced-therapy medicine. It was also designated as an orphan medicine in 2015 by EMA. EMA published its decision for authorization of Zolgensma in 2020. According to the EMA`s report, the main study used in the assessment of efficacy was a single-arm study (without a placebo arm) with symptomatic SMA patients with 2 SMN2 copies, who were below the age of 6 months (EMA, 2020c, p.65). Additionally, preliminary data were used from the ongoing studies on patients with 2 SMN2 copies and in pre-symptomatic patients with 2 or 3 SMN2 copies (EMA, 2020c, p.97). According to EMA`s assessment of the clinical studies, a one-time infusion of the therapy could reduce the need for a permanent ventilator, improved survival in these patients and helped them reach development of certain milestones such as sitting unaided for some time, which could not normally be achieved by the untreated babies with severe disease (EMA, 2020a, p.2). Related to the safety, the side effects such as raised liver enzymes were regarded as “manageable”, since steroid treatment could solve this side effect (EMA, 2020a, p.2).

On the other hand, EMA indicated that there were uncertainties and limitations about favourable and unfavourable effects (EMA, 2020c). For instance, in addition to the lack of studies on patients with 1 SMN copy among the provided study results, only pre-symptomatic patients with 3 SMN2 copies were studied, with a limited follow-up time (EMA, 2020c, p.138). Regarding to the unfavourable effects, EMA indicated that the safety data was based on a small trial and the risk of carcinogenicity in the long term was among the unknowns (p.140). Particularly, the single arm study made it difficult to understand whether an adverse event was caused by Zolgensma and the needed corticosteroid use to suppress the immune system or by SMA I (p.140). Furthermore, there were some uncertainties with regard to consistency of the batches used in different studies and the determination of the optimal dose (p.138). With regard to that, EMA stressed that “the dose finding for Zolgensma was not optimal, leading to uncertainties about the optimal effective and tolerable dose” (p.146); since, the decided dose was based on nonclinical studies and studies with animal models (p.65). Therefore, Zolgensma could only be used for SMA type I infants weighing between 2.6 kg to 21 kg, as adjusted dose were determined up to that weight (EMA, 2020c, p.48).

Based on this evaluation, EMA decided that benefits were greater than its risks and authorized Zolgensma on the condition of provision of additional data by the company from the ongoing studies and from the observational registries to monitor patients using the treatment (EMA, 2020a, p.2). Contrary to the broad indication of Spinraza covering all 5q SMA patients; authorization of Zolgensma has included the treatment of patients with *5q SMA* who either has*;*

→*a clinical diagnosis SMA Type 1* or

→*up to 3 copies of the SMN2 gene* (EMA, 2020b, p.1).

When it comes to the views of medical authorities, a group of European neuromuscular experts were published an ad-hoc consensus statement for the appropriate selection of patients that could benefit from Zolgensma. They indicated that theoretically a large number of patients would be eligible for the treatment with Zolgensma according to EMA`s authorization; however, this broad label was beyond the age and weight limits that have been studied in the clinical trials and its effectiveness and safety in all patients who meet the criteria (Kirschner et.al., 2020, p.40). They particularly highlighted that trials of Zolgensma only covered patients up to six months with a weight below 8.4 kg and there was not enough evidence on safety and efficacy of Zolgensma in older or heavier patients (Kirschner et.al., 2020, p.39). Although additional data on patients up to 2 years and weighing up to 13.5 kg were made public later, they were not based on the systematic data collection. Regarding to that, they emphasized the unknown risk of applying higher dose of treatment required for heavier patients, compared to the dose studied in the clinical trials (Kirschner et.al., 2020, p.40). Therefore, they underlined that patients above the weight of 13.5 should only be treated with Zolgensma in certain circumstances, and should rather be directed to other disease modifying therapies (p.40).

One therapy over the other?

The discussions on risks and benefits have sometimes pointed at a comparison between the therapies in the valuation practices. For instance, EMA highlighted the unmet medical need and *compared added value* of Zolgensma vis-à-vis Spinraza. Accordingly;

> [a]lthough it is clear patients benefit from nusinersen treatment, indirect comparison with the results of nusinersen indicate that the effects on survival, (…) and motor milestone achievement of Zolgensma supersede the effects of nusinersen in the SMA type 1 population. In addition, the single treatment of Zolgensma is an advantage for the patients compared to the need for repeated treatment with nusinersen. (EMA, 2020c, p.146)

According to the indications of use defined by EMA, Spinraza is applied through an injection into the spine of the patient, which was regarded as a more interventionist and risky method, compared to intravenous (IV) infusion of Zolegsnma (EMA, 2020c, p.147). Besides, as EMA indicated, it should be applied as consecutive doses, the first dose as soon as possible after the diagnosis, "followed by 3 more doses after 2, 4, and 9 weeks and then one dose every 4 months thereafter", as long as the patient benefits from it (EMA, 2017b, p.2). On the other hand, Zolgensma aims to deliver a working copy of SMN1 gene into patient`s cell through a single infusion (EMA, 2020b, p.1). These comparative benefits were also presented by Novartis as the benchmark of Zolgensma`s price. Since Spinraza necessitates injections every four months, but Zolgensma is introduced as a therapy with life-long effect through a once-only application, its price is justified by Novartis in comparison to Spinraza. The president of AveXis declared that "the view that Zolgensma is the most expensive therapy in the world is, frankly, wrong (…); [t]he fact that we compress the cost into one treatment makes it look expensive" (Green, 2019, para.5).

On the other hand, Kirschner et.al. (2020) discussed the limits of Zolgensma`s clinical trials in contrast to Spinraza. With reference to broader EMA`s approval, compared to available data with patients up 6 months and 8.4 kg, they indicated the following point:

> This discrepancy poses major challenges to patients, clinicians and payers associated with the question who should be treated under which circumstances, also in view of the fact that an effective and safe treatment, nusinersen, is already widely available in this patient population. (Kirschner et.al., 2020, p.39)

After pointing at the safety concerns of using Zolgensma in patients with higher body weights, they compared it with the level of evidence about safety and efficacy of Spinraza for the use in older (and heavier) patients:

> Nusinersen is an approved drug which (…) has been studied in a double-blind placebo controlled trial in later-onset types of SMA. Several recent manuscripts also address the efficacy and safety of nusinersen in the real world setting, broadly confirming the observation from the original phase 3 studies, and extending the age range of patients in whom the role of this drug has been explored (Kirschner et.al., 2020, p.40).

The comparison between the therapies has also been used in the assessments of national authorities with the concept of *added therapeutic value*, which implies measuring the therapeutic advantages of new health technologies compared to the alternatives

(European Parliament, 2014). With aim of assessing the added value of new SMA therapies compared to the first manufactured Spinraza, IQWiG, the German responsible authority for HTA, touched upon the issue of comparability. According to the head of the institution Thomas Kaiser, the comparisons over the clinical trials of Zolgensma and Nusinersen were not interpretable, because their study populations were not identical (IQWiG, 2021). As he indicated, patients in the trial of Spinraza were in a worse condition than patients participated in the trial of Zolgensma; and patients treated with Zolgensma were younger at the time of the therapy compared to patients in the Spinraza`s studies (IQWiG, 2021). As there was no comparative study conducted by the manufacturer in contrast to Spinraza, it was not "easy for physicians and parents to choose the suitable therapy for these very young patients" (IQWIG, 2021). Therefore, the institution has concluded that there is no proven added benefit of Zolgensma for any of the SMA types, comparative to existing therapies.

The Earlier is the Better: Value Associated with the Early Access

Discourses of stakeholders have jointly pointed to the value of both therapies when they are administered as early as possible, even before the patients` motor neurons are already damaged and muscle weakness begins. Some experts in neurology framed the importance of the timing of intervention with this analogy: "Time is motor neuron" for SMA disease (Govoni et.al., 2018, p.6307). Similarly, experts in the consensus statement indicated that both treatments reveal better outcomes when they are applied to pre-symptomatic patients (before their symptoms begin). They stressed that the videos of SMA type 1 patients walking and climbing after the treatment with Zolgensma belong to pre-symptomatic patients, and this might represent an exceptional case for symptomatic patients (Kirschner et.al., 2020, p.40). Likewise in Spinraza, as they highlighted, higher motor functions of the patient at the time of initiation of the treatment imply higher chances of benefit for the patient.

Experts` consensus on the value of early treatment has also been shared by the industry and patient organizations. According to Nicole Gusset, who is the president of SMA Europe as well as a mother of a SMA Type II patient; since SMA is a progressive disease and every infection can be life threatening for the child, the families are in a "constant challenge to deal with" (Euractiv, 2021). In one of the articles published by the representatives of SMA organizations in Europe, the importance of early access to medicines for the maximal therapeutic benefit was stressed, yet with a caution indicating that older patients might still benefit from the treatments as shown by real world data and recent clinical trials (Gusset et.al., 2021a, p.426).

The narratives that attach the values of treatments to early access have also been employed by the industry, which have been manifested in their investments and practices. As early diagnosis is vital for early treatment, SMA has been added to the routine new-born screening (NBS) programmes in some countries including Belgium, Germany, the Netherlands, Poland and Turkey (CRA, 2021, p.25). According to the head of public policy & government affairs of Biogen, "newborn screening alone is not sufficient; (…) every SMA diagnosis should be translated into an emergency to treat" (Tempra, 2022). In relation to that, manufacturers of SMA treatments have pushed for new-born screening programmes and invested in the screening studies ("Biogen Canada investment in newborn screening", 2020; Zimmerman, 2017). For instance, in Wallonia & Brussels regions of Belgium, Novartis, Biogen and Roche together sponsored the pilot screening program (SMA New Born Screening Alliance, 2021).

5.3.2. How to Assess Advanced Therapies? Sharing the Risks and Benefits

As discussed in the European Commission`s Strategy document for pharmaceuticals, there has been a "growing uncertainty as to their real-life effectiveness and related overall costs" of these novel technologies which "puts the budgetary sustainability of health systems at risk, and reduces the possibilities for patients to have access to these medicines" (European Commission, 2020, p.8). Between the pressures of high prices of novel therapies and patients demands, national authorities try to adjust their institutional and regulatory systems for their assessments. For instance, they can use flexible cost effectiveness thresholds according to certain criteria such as prevalence, severity of the disease or its social value; they can cooperate with other countries in the assessment and price negotiations to have more pressure on the companies; or link reimbursement decisions to the real-world data about risks and benefits of therapies on patients.

For instance, according to its regulations, Germany conducts cost-benefit assessment of the orphan medicines if the annual cost exceeds 50 million euros. Since Spinraza`s turnover exceeded that amount, responsible authority conducted an assessment and Federal Joint Committee (G-BA) published the assessment report. According to the report, there was data insufficiency about the added benefit of Spinraza for SMA Type III and IV patients (Federal Joint Committee, 2021, p.22). Yet, based on other determinants such as mortality and morbidity related to the disease, the medicine remained reimbursed for all SMA types (Blonde et.al., 2022, p.24). Netherlands assesses all health technologies according to variable thresholds, depending on the disease severity (Blonda et.al, 2022, p.4). However, in the assessment of Spinraza, Netherland`s authority evaluated that the medicine was not cost effective and initially declared a

negative opinion for reimbursement unless price was decreased by 85% percent (Blonda et.al., 2022, p.23). As part of the Beneluxa collaboration, Belgium and the Netherlands initiated a joint technology assessment and price/ reimbursement negotiations with Biogen for Spinraza (Beneluxa, 2018). They received a discount from the manufacturer; made the therapy available a year after its authorization by EMA and linked the reimbursement to the performance of the medicine (Blonda et.al., 2022, p.23).

Similarly, the assessment bodies in Belgium, Ireland and the Netherlands jointly carried out the clinical and cost effectiveness assessment of Zolgensma through the same initiative. According to the assessment, the National Healthcare Institute of the Netherlands advised its responsible Ministry to reimburse Zolgensma under two conditions: Firstly, there should be a 50 % reduction in the price. The institution pointed to that, since the long-lasting effect of Zolgensma has not been proven, only with the proposed price reduction, the risk could be regarded as divided between the state and the manufacturer. Secondly, there must be a performance-dependent payment agreement with the manufacturer, in which the payment depends on how the therapy really works (National Healthcare Institute, 2021). HTA authority in Ireland came up with a similar recommendation for reimbursement of Zolgensma: It recommended not considering the therapy for reimbursement unless cost effectiveness relative to existing treatments is improved (National Centre for Pharmacoeconomics Ireland, 2021). Finally, towards the end of 2021, Belgium, Ireland, and the Netherlands arrived at a reimbursement agreement with Novartis following confidential price negotiations (Beneluxa, 2021).

In the process of muddling through uncertainties associated with advanced therapies, there has been an emerging discourse highlighting the need for sharing the risks and benefits between the companies and national authorities, such as through *outcome based reimbursement* strategies (Kerpel-Fronius, 2020, p.6; Mittra, 2016, Jørgensen & Kefalas, 2021). For instance, the head of the Austrian Institute for Health Technology Assessment (AIHTA) reflected that *outcome based managed entry agreements* as a way of "sharing the risk fairly between the public sector and the manufacturing companies" (AIHTA, 2021). She suggested that agreements between industry and public sector that are based on the studies for attaining patient reported outcomes from patient registries could facilitate financing high cost medicines under clearly defined conditions (AIHTA, 2021). According to the Austrian HTA authority, within the scope of such agreements, it should be made clear that "what benefit is expected from the therapy (…) [and] at what point the therapy is discontinued" (AIHTA, 2021). Since there is usually limited data on the benefit of the orphan medicines, payers have to make their reimbursement decisions under uncertainties and public pressure. She

highlighted that that`s why Austrian authority tries to be cautious and “only pay when children reach a certain `milestone´” (AIHTA, 2021).

Reimbursement based on the patient outcomes implies the necessity of gathering real world data that could constitute the basis of reimbursement decisions. However, this may imply that reimbursement is hinged on the demonstration of added value for each patient, as in the case of Netherlands, where Spinraza is reimbursed to patients with SMA Type I to III, “only when an added value in these patients is demonstrated” (Blonda et.al., 2022, p.23). This brings concerns such as which outcomes are selected, how they are measured and interpreted. Thus, another point of discussion on the valuation of medicines is which outcome measures could be regarded as ´added value´ or `progress`.

5.3.3. Progress for Whom? Reaching Certain `Milestones`

There are various assessment frameworks adopted by national authorities, be it using flexible clinical or economic data requirements, or not considering cost effectiveness for orphan medicines and taking into account prevalence, severity of the disease or its social value (Blonda et.al, 2022; CRA, 2021). That’s why, what they consider as the ´value´ in their assessments can be considerably different. Valuation of medicines could also manifest differences among industry, regulatory authorities, clinicians and families in many respects. It can differ in terms of who to involve in the decisions and who the values will address. For instance, according to the umbrella patient organization SMA Europe, national authorities should formally incorporate patient experts and clinical specialists in their decisions about reimbursement and consider “the value that medicines bring to both their caregivers and society as a whole” (CRA, 2021, p.12). According to the organization, national authorities should provide reimbursed access in line with the labels approved by EMA, and leave decisions about which treatment(s) to apply to the physicians in collaboration with the patients and based on their clinical needs (CRA, 2021, p.13).

Another point is what should be the clinical value achieved by the treatments. In the EMA`s report, it is discussed that while experts often regard motor milestone improvement as a progress when evaluating the efficacy of the treatment; patient representatives attribute importance to respiratory improvements and other effects such as in swallowing (EMA, 2020c, p.130). For the head of SMA Europe Nicole Gusset, the values of SMA medicines are defined by motor skills as the primary outcome in the clinical trials; however people are much more than motor skills (Gusset et.al., 2021a). From the SMA Europe`s perspective, patients living with SMA consider `stabilization as a progress` (Gusset et.al., 2021a, p.420). Furthermore, even small improvements in motor

functions mean a lot for the quality of patients` lives, which should be considered when defining responders and non-responders to a treatment" (Gusset et.al., 2021a, 427).

Experts in the ad-hoc consensus statement indicate that "gene replacement therapy and other disease modifying treatments might stabilize the disease but not necessarily reduce disability or improve quality of life" in severe conditions (Kirschner et al., 2020, p.40). As a response to their consensus statement, SMA Europe published an article in a reputable journal about paediatric neurology and stated their concerns as to potential negative implications of the experts` statement on the life of patients: "We fear that this statement leaves little room for the necessary joint decision in such cases; that it could be misinterpreted by less acquainted clinicians; and that it can bias families' perspectives and perturb their decision-making process" (Gusset et.al., 2021b, p.105). How do all those discussions in the practices of value making reverberate in a national setting in terms of the ways in which actors experience the disease and enact the value of therapies. What kind of governing effect do they have on individuals? Next chapter grapples with these questions, with reference to the countries` social and political system and economic conditions.

6. SMA Case in Turkey

6.1. Socio-Political Situation, Relevant Actors and Institutional Structure

State and society relationship in Turkey can be portrayed with reference to different terms, which notably the single party rule since 1946, first free elections in 1950 and interventions by two military coups in 1960 and 1980, privatization and liberalization after 1980s and rule of Justice and Development Party (AKP) since 2002. Although, the Constitution defines the Turkish Republic as a ´democratic and social´ state, the understanding of democracy in Turkey has reflected some flaws especially with regard to the involvement of civil society in the policy making, almost in each term, albeit at different levels. When AKP came to power, it rested its ideological stance against the authoritarian practice of state led modernism, tutelary role of military over the regime and alienation of the state from the society. AKP government was upholding a liberal democratic, pro-EU and pro-West agenda at the onset of its rule (Esen & Gümüscü, 2016). It realized several social and democratic reforms during this process and engaged in a relatively free debate on the Kurdish, Alevi and non-Muslim minority. Through this democratization trend and close ties with the West, Turkey started the membership negotiations with the EU in 2005. Besides, AKP consolidated the conservative population which were culturally and politically alienated from the state (Aydin-Duzgit & Keyman, 2013). As a result, it has

gradually extended its power base and attained almost 50 percent of the votes in the 2011 elections.

However, in the second decade of the century, it has reflected a more authoritarian stance with “the erosion of the institutional checks on the executive power, the weakening of the distinctions between state and party, government restrictions of civic freedoms and the skewing of the electoral playing field in favour of the incumbent party” (Somer, 2016, p.482). After the June 2015 elections, when AKP lost its majority in the Parliament, peace process with the Kurdish movement was brought to an end. Since a coalition government could not be formed until the deadline, the elections were repeated in November 2015, which provided the AKP the majority to form one party government again. The coup attempt of 15 June 2016 added to the escalating tension in the country and government resorted to the state of emergency for two years, during which numerous civil society organizations were closed, gatherings were prohibited and organizers were arrested (European Commission, 2018). In this emergency rule, parliamentary system is replaced by the ´executive presidential system´ through a referendum in 2017, which has further eroded the checks and balances on the executive. Besides, the “degree of political and societal polarisation along the axis of the Islamist-secularist divide as well as that of Turkish-Kurdish nationalism” has been increased (Aydin-Duzgit & Keyman, 2013, p.4).

Despite the increasing authoritarian characteristic of the regime, the civil society in Turkey has shown a growth in terms of number of organizations and type of engagement in the AKP rule. However, this expansion does not imply a more pluralist interest representation and reflect the conflicting interests of the party in “appropriating and containing civil society” (Yabancı, 2019, p.285). AKP managed to establish a stable and growing economy especially through the coalitional ties with pro-government businesses. While the business has benefited from the government for the capital accumulation, the government has in turn utilized from them in various ways including through their donations to pro-AKP foundations and provision of goods to the urban poor (Esen & Gümüscü, 2021). This way, the party used civil society organizations and charities in distributing public recourses selectively to the low-income groups who lend electoral support to the government so that it could stay in power and attain “´democratic legitimacy´ to the system despite its increasingly undemocratic character” (Esen & Gümüscü, 2021, p.1080).

While like-minded civil society groups and the ones which have fulfilled the gap left by the state in terms of service provision have flourished, civil society that voice open criticism to the political authority has been repressed and civil society participation in policy making have deteriorated (Yabancı, 2019). Certain groups especially which have

engaged with politically sensitive issues such as minority issues, particularly Kurdish rights, human rights monitoring and defence came under pressure and selectively repressed, and many rights-based organisations were closed (European Commission, 2018, p.4; Yabancı, 2019). Within the environment of selective repression and arbitrary containment, civil society has adapted and expanded by "engaging with politically less-sensitive issues, such as environmental issues, the rights of disabled, children, Roma, LGBT and animals" (Yabancı, 2019, p.293). Therefore, groups like SMA organizations that "advocate the rights of their smaller constituencies without risking to be labelled 'politically motivated'" could become active in defending their concerns (Yabancı, 2019, p.294).

6.1.2. SMA Patient Organizations as Concerned Groups

Despite the fact that rare diseases occur frequently in Turkey due to high rate of consanguineous marriages and different ethnic structures, rare diseases and orphan medicine have not occupied the agenda as much as other health problems in Turkey until recently. In parallel to rising trend of the number and engagement of NGOs, associations related to rare diseases have been increased with the aim of access diagnosis and treatment. Public authorities have also gradually recognized their role in raising public awareness on rare diseases and ensuring communication with patients and their relatives (Turkish Parliament, 2020). This role has become more visible particularly with the SMA focused NGOs.

There are three associations established with the name of the disease, alongside some social-media groups which could help patients with the fundraising campaigns for Zolgensma. The SMA patient associations support families of patients who receive SMA diagnosis, through distinct ways such as preparation and distribution of brochures that define the disease and crucial aspects of care; provision of necessary medical devices that are not covered by the public insurance and advocacy for access to diagnosis and treatment. These organizations which were initiated by the families of SMA patients in 2014 emerged as the *concerned groups* with the heightened need of advocacy after the development of the first SMA therapy (Callon & Rabeharisoa, 2008). Since then, they have been through a high level engagement process with the political authorities for ensuring the access to the new therapies. They developed first-hand experience with the disease and treatments and presented their *experiential knowledge* in a formalized way, to make their concerns related to access (Rabeharisoa, 2003). After Spinraza has become available in the country, they strived for achieving reimbursement for patients from all disease types. With the development and approval of other therapies, Zolgensma and Evrysdi respectively by FDA and EMA, their cause has been reconfigured towards

obtaining access to all therapies in fair and equal conditions (Interview with patient association, 17 May 2022). Through their cause, they have "contribute[d] to shaping the relations between technoscience, politics, and economic markets" (Callon & Rabeharisoa, 2008, p.230). Yet their engagement with the political authorities also has also been shaped according the dynamics of the country.

As growing concerns of the rare disease patients have become more visible in the social media, as well as in street protests, a parliamentary research commission was established in 2019 to address concerns about rare diseases including SMA. It gathered various stakeholders through consecutive meetings, which were concluded with a comprehensive report published in 2020 (Turkish Grand National Assembly, 2020). The need for rare disease specific policies has been recognized by the public authorities and it led to new administrative structures. A specific department dedicated to rare diseases, autism and special mental health needs has been established in the MoH in 2020, which is responsible from the improvement of the infrastructure for screening, diagnosis and management of these conditions, leading to the preparation of the action plans and regular communication with the patient organization (Ministry of Health, 2020).

These activities have reflected a recent apprehension on the burden of rare diseases on society and significance of taking action by the public authorities to address patients` concerns. However, according to a representative of SMA organization, those efforts and their high level of engagement with the public authorities has not generated the necessary action to solve the problems that patients having been through (Interview with patient association, 17 May 2022). For instance, the representative contended that it was a considerable development to have a specific department for rare diseases; however, in practice, this department has not been authorized to regulate the approval and reimbursement of the medicine. Thus, it was not the decision maker that could address their concerns on access to medicines. He indicated that:

> They invite us regularly, listen and understand us; and allege that they direct our message to the relevant institutions; however nothing changes. It seems like they represent a buffer between us and the institutions who are responsible such as TMMDA and SSI. We used to directly engage with TMMDA before this department was established (Interview with patient association, 17 May 2022).

In addition, while they could use administrative channels for delivering their complaints, they have not had a formal representation in the decision making bodies, such as involvement in the SMA Scientific Board meetings (Interview with patient association, 17 May 2022).

6.1.3. Authorization and Reimbursement of Medicines

According to Turkish legislation, medicines centrally authorized by EMA are not automatically recognized in Turkey, thus the pharmaceutical companies who want their product to be authorized apply to the responsible authority in Turkey. `Turkish Medicines and Medical Devices Agency` (TMMDA), which is an agency of the Ministry of Health (MoH) is responsible for the authorization, pricing and surveillance of medicines. On the other hand, the Social Security Institution (SSI), which is affiliated to the Ministry of Labour and Social Security, is responsible for the reimbursement of all healthcare goods and services including pharmaceuticals. There are different administrative structures under the responsibility of MoH, TMMDA and SSI to undertake clinical, economic and social assessment of health technologies; yet they do not have independent administrative and financial statuses to assess these technologies and guide responsible bodies in their regulatory decisions about reimbursement. Besides, although there is a dedicated department for the health technology assessment in MoH, their assessments are not necessarily linked to decisions on pricing and reimbursement. Although different institutions are defined as responsible from authorization, pricing and reimbursement of medicines, there is an entangled governance structure based on interaction among these authorities.

In order to place a product on the market, pharmaceutical companies should obtain a marketing authorization from TMMDA and a fixed price (World Trade Organization, 2022, p.24). Companies with or without market authorizations apply to the TMMDA with their demands for pricing of their products. According to the regulations on pricing, MoH coordinates an Inter-ministerial commission including the representatives of Presidency, Ministry of Treasury and Finance and SSI to evaluate and decide on the pricing of medicines and a certain currency rate to be used in the pricing (Council of Ministers, 2017). Prices are determined with the reference pricing policy by taking into account five EU countries, which is then subjected to specific discount rates (Atikeler & Özcelikay, 2015; Ministry of Health, 2017). For certain group of products including the orphan medicines, these discounts are not applied (Ministry of Health, 2017). While this low pricing policy aims at controlling the costs of medicines covered in the reimbursement scheme, it has become a subject of controversy especially with the devaluation of Turkish Lira (TL) against foreign currency. News about shortages in crucial medicines due to this policy has occupied the local and international media, according to which companies do not supply medicines to the Turkish market, as prices are not covering their costs (“´Temporary' solution to medicine shortage”, 2022; Ewing, 2018).

The main legislative framework that regulates the reimbursement in Turkey is the Health Implementation Regulation (known as SUT in Turkey) which lays the principles and procedures of benefiting from the healthcare services, products and medicines. Companies that request inclusion of their products in the list of ´reimbursed products´ submit their application to the SSI. SSI convenes a medical and economic evaluation commission, which is composed of different ministries, academicians and pharmaceutical industry, and sends their decision related to the reimbursement to the Inter-ministerial Reimbursement Committee to finalize the decision (Social Security Institution, 2016). Finally, the diseases and medicines that target them are regulated in SUT, involving indications of use as conditions of reimbursement (Social Security Institution, 2016).

In principle, the products cannot be marketed in Turkey unless they get authorization from the Agency. However, similar to other countries, there are some channels that aim to provide early access to medicines with high medical need, such as *compassionate use programs* which imply free access to some patients provided by the company (Kockaya et.al., 2014). Apart from that, the products which are not yet authorized or not available in the Turkish market due to different reasons can be provided to the patients through an early access mechanism, which is defined as *named-patient imports* (Atikeler, Leufkens & Goethttsch, 2020, p.586). In this case, a physician who wants to prescribe an unauthorized or unavailable medicine in Turkey that targets an unmet medical need such as orphan medicines applies to TMMDA. The application for each patient is evaluated in consultation with a relevant scientific commission in TMMDA according to the patient`s disease (Kockaya et.al., 2021, p.3; TMMDA, 2021). If TMMDA grants permission, the medicine is imported by the SSI or Turkish Pharmaceutical Association, which is then reimbursed by the SSI according to the conditions defined in SUT (Social Security Institution, 2013; Turkish Grand National Assembly, 2020).

This system, which is particularly used for orphan medicines, provides the availability of medicines in the pre-authorization phase and implies certain advantages to pharmaceutical companies: As market authorization is a long process, they can market their products earlier; they are exempted from mandatory discounts and reference pricing of the normal market authorization route (Atikeler et.al., 2020, p.590). Named-patient imports system has become a significant alternative pathway particularly for orphan medicines by enabling earlier access to medicines for patients with severe diseases. This emerged as a way to "´by-pass´ the market authorization" resulting in increasing costs of advanced medicines in Turkey (Atikeler et.al., 2020, p.588). As a way to address this issue, public authorities in Turkey have recently brought a limit to the time spent in the market through named patient import route before the application for the marketing

authorization (Atikeler et.al., 2020, p.588; TMMDA, 2021). These kind of exceptional access systems are becoming the means of regular access pathways. While they provide possibility for early access, they might create challenges for patients, by requiring complex layers of responsibility for the approval of each use, as will be discussed in the case of Spinraza.

6.2. Construction and Enactment of Values in SMA Therapies

From three therapies approved by EMA, only Spinraza has been made available in Turkey, albeit with differences in access between SMA sub-populations. The treatment indications, which were based on the stratification of patients according to their SMN2 number and clinical situation, were subjected to negotiations especially between patient organizations and regulatory authorities. These indications, which delineated who could access to the treatment and under which conditions, have been extended over time. However, a formal assessment report evaluating safety, efficacy or economic concerns, as the basis of reimbursement decisions has not been published.

A scientific board dedicated to the SMA disease were established by the Ministry after FDA`s approval of Spinraza in 2016. It has been convened on an ad hoc basis in order to `scientifically` evaluate the clinical studies and developments related to the disease and therapies. Evaluations regarding to therapies including the multi-stakeholder workshop reports and prospective regulatory changes have usually been announced by the Minister of Health after SMA Scientific Board meetings via press conferences, his Twitter account and from the Ministry`s webpage. Those press conferences and the accompanying updates to the Regulation imply a change in the valuation of Spinraza over time. However, the value of Spinraza and its adoption as the main and only therapy (so far) have been formally highlighted by the Minister only with reference to the safety concerns on Zolgensma (Koca, 2020). This instance indicates that the valuation process of Spinraza that I discuss in the next chapter played a significant role in the composition of value for Zolgensma.

6.2.1. Shaping Access to Spinraza: Stratification and Distributed Decision Making

In July 2017, three months after EMA`s approval, Spinraza was added to the list of reimbursement in Turkey for the patients having genetic and clinical diagnosis of SMA Type, through a change in the *Health Implementation Regulation (SUT)* (Social Security Institution, 2017a). However, access was not easy and straightforward. In this first version, the Regulation stipulated a condition of having at least 2 copies of SMN2 gene and excluded patients with 1 copy from access. Besides, patients with invasive ventilation (tracheostomy) were also excluded, based on the Scientific Board`s evaluation which

argued that there was not enough evidence presented by the clinical trials for those patient (Interview with patient association, 17 May 2022). With the protests and pressures from the patient organizations and families, the Regulation has been changed in two months, to include patients with this kind of pulmonary support (Social Security Institution, 2017b). In February 2019, reimbursed access was extended to SMA Type II and III (Social Security Institution, 2019). According to the Parliamentary Report on rare diseases, the public authority decided to add SMA Type II and III based on its evaluations of the recent scientific studies (Turkish Grand National Assembly, 2020, p.74).

On the other hand, for patient organizations, it was a success story that could not be achieved by any civil society organization in Turkey (Interview with patient association, 17 May 2022). According to the representatives of the patient associations, this has been the outcome of their continuous efforts: They gained a comprehensive knowledge about the disease while trying to keep their children alive, worked for raising public awareness and conducted visits to responsible authorities in order to put pressure for access to all approved (by FDA and EMA) medicines for all patients (Interview with patient association, 16 May 2022; Interview with patient association, 17 May 2022). However, this process was especially challenging, since the responsibility was distributed among various public authorities. They had to learn the legal and administrative procedures of access, as well experienced their complexity throughout the process (Interview with patient association, 17 May 2022).

According to the patient representatives, despite they finally achieved access for all disease categories; they were still facing with difficulties in access due to the different layers of responsibility. Since Turkish Medicines and Medical Devices Agency (TMMDA) is responsible for the registration, marketing authorization, pricing and monitoring of medicines, it is entitled to evaluate the clinical condition of each patient and gives an approval for Spinraza to be imported and used in that patient. On the other hand, the Social Security Institution (SSI) is responsible for covering healthcare goods including the medicines (reimbursement) and regulating the conditions of reimbursement with *SUT.* Therefore, while the Agencies` responsibility is associated with the scientific and clinical aspects of the medicine, the Institutions` responsibility is associated with the economic matters. However, SUT which is under the responsibility of SSI, regulates the conditions of use and reimbursement in great detail, with references to clinical and genetic characteristics of the patient and patient outcomes attached to the use of medicines. While this aims at the standardization and supervision of access and costs, the conditions determined in SUT can imply restrictions or administrative and technical difficulties for patients in access to the medicine.

According to the articles of SUT on Spinraza, it could be prescribed and applied in a specialized healthcare institution which has a multidisciplinary team including a paediatric neurologist, nutritionist, physical therapy and rehabilitation specialist. Since Spinraza has to be applied once in every four months after the first four loading doses, the administrative procedure -blended in scientific evaluation- that patients have to go through wears them and their families out, as patient representatives indicated (Interview with patient association, 17 May 2022; SMA Walk With Me Association, 2022). As SUT and a patient representative indicated, the following process should be completed in practice, once for the first four loading doses and then every four months for each application (Interview with patient association, 17 May 2022; Social Security Institution, 2017a): Specialists at the healthcare institution should prescribe the medicine and send their request to the TMMDA with a report about the condition of the patient and outcomes of the medicine. In the Agency, an ad hoc Commission responsible for the use of certain medicines for individual patients evaluates the report and gives its approval (or not). Then the patient´s family applies to the SII so that the medicine could be imported (and costs are covered) by the Institution. However, the criteria for the evaluation of the specialists` reports by TMMDA were not published; thereby the reasons for the approval or rejection were not transparent. According to a representative of the public authority, they take into account up-to-date scientific publications, clinical trials as well as authorization decisions of FDA and EMA, in order to decide whether there is progress in the patient`s condition thanks to the medicine, thus whether patient should continue (or not) receiving the medicine (Interview with public authority, 18 May 2022).

As most interviews pointed, patients have been encountering with the hurdles especially after the first four loading doses in practice. First of all, the continuation of the each medicine after loading doses was subjected to neurological and functional motor scale tests (Hammersmith and CHOP INTEND tests) to be conducted by the multidisciplinary team at the healthcare institution, to be reported to the TMMDA for its approval. Specialists including physical therapists and neurologists have been responsible for the evaluation of the patient`s progress according to these tests and reporting the outcome of the medicine on the patient. SUT had stipulated improvements in the patient's respiration and motor functions in order to continue medication after the loading doses, such as staying without pulmonary support for a certain time and increase in points corresponding to motor functions according to CHOP-INTEND scale. It is mentioned in a TV program by a parent, who is also a representative of one patient organization, that these tests are quite traumatic for families and children:

> The patients are supposed to achieve certain milestones such as raising their hands up to a level and scored accordingly. We know that there are patients with interrupted access, since they could not get one or two points more in those tests. The decision on whether patients´ would take their medication should not be dependent on a missing score. Focus should be on the patients´ practical gains in life. For example, if a patient drinks water without the help of family members after the medication, it is definitely a progress. (…) Maybe they cannot raise their hand up to the level of their heads, but can scratch their head (…). (SMA Walk With Me Association, 2022)

The same parent added the following when talking about the hurdle of the process:

> You have to see different branches including pulmonary medicine, orthopaedics, cardiology and neurology as patients who already have difficulties in moving and even breathing in serious conditions. Babies with Type I stay alive with four-five machines. It is really difficult to organize the appointments to see these specialists for the control of pulmonary and motor abilities and get their approval on the same day. After their individual approval, you apply to the TMMDA; and if they approve as well, you then apply to the SII. If everything complies with the Regulation, SII accepts to import and cover the cost of the medicine. And you have to do this once in every four months. (SMA Walk With Me Association, 2022).

The patient representatives also reflected the importance of receiving regular physical therapy alongside the treatment with medicine. They highlighted that having better scores in the motor scale tests was also hinged on receiving regular physical therapy. However, as patients and parent advocates indicated, there was a lack of standardization in the assessment of certain physical movements as progress. Since therapists in the healthcare facilities change frequently, a movement which is regarded as a ´score´ by a physiotherapist might not be regarded as so by another (Interview with patient association, 17 May 2022). Therefore, the condition of progress measured through motor scale tests and the lack of standardization in these assessments stress the patient out like an exam, disrupt the predictability on the course of therapy or can lead to interruption of access (SMA Walk With Me Association, 2022).

Apart from that, as it was pointed by patient representatives, access to the medicine was also dependent on the availability of all necessary specialists at the healthcare institution. According to SUT, Ministry of Health was responsible for designating certain healthcare institutions as the ´application centres´ that could prescribe and apply Spinraza. According to a parent advocate, the number of application centres was raised

over time; however, it was not always possible to find the relevant specialists at the centres which made them ´out of order´ in practice. As reported by a patient mother: “If either the paediatric neurologist or pulmonary disease specialist do not exist in a healthcare institution – which can be a problem especially in the Eastern provinces–it cannot serve as an application centre, even though it was designated as one” (SMA Walk With Me Association, 2022).

In December 2021, SMA Expert Committee convened and Minister of Health announced that “some of the stringent criteria to become 'eligible for treatment' have been removed” (Ministry of Health, 2021a). Yet he also added that “it is extremely important to continue with standard controls for access to treatment” (Ministry of Health, 2021a). After the Minister`s announcement, SUT was changed in February 2022, which has *de jure* removed the condition related to Hammersmith and CHOP INTEND tests and included patients with 1 SMN2 gene to reimbursed access (Social Security Institution, 2022). This change has been widely welcomed by the patient families and by public. However, as mentioned by almost all interview respondents from patient groups and public authorities, hospitals were still conducting these tests since the TMMDA demanded them to monitor the clinical outcomes of the patients. It was for the evaluation of whether the medicine led to stabilization, progress or a decline in the pulmonary and motor functions; yet, this evaluation could also inform the decision for cutting-off the medication and reimbursement. A patient representative reflected his opinion about this ambivalence arose out of the difference between the Regulation and practice:

> The Regulation mentions neither CHOP INTEND nor Hammersmith tests, but it is still conducted by the hospitals. Before the change, SSI was the final layer of authority, which could deny the reimbursement despite the positive opinion of the TMMDA. With the new Regulation, SSI accepts the reimbursement if TMMDA approves the use of medication; therefore SSI is now positioned as the good cop and TMMDA as the bad cop. They declared that it was for monitoring purposes. The Regulation has changed, the make-up is fine, but access to medicine can now be blocked for trivial reasons. (Interview with patient association, 17 May 2022)

As a public authority representative pointed out, the regulatory revision implied more autonomy of TMMDA, since they were not anymore restricted with the conditions defined in SUT about patient`s improvement in certain milestones, and SSI would be bounded with TMMDA`s decision in its approval of reimbursement (Interview with public authority, 18 May 2022). These discussions in the valuation of Spinraza hint at the different layers of decision making authorities, as well as shifting responsibilities in the complex scientific and administrative infrastructure, which compel patient groups to redefine the channels to

convey their complaints, devise new ways to access to the optimal treatment and attach value to therapies accordingly.

6.2.2. Valuation of Zolgensma: Contested Values and Practices

On November 2020, the Ministry of Health (MoH) organized a workshop called "current treatments in SMA disease" with the participation of SMA Scientific Board and SMA patient associations, where they discussed the issue of access to Spinraza in Turkey and the latest scientific studies on the gene therapy Zolgensma. In their published meeting notes, MoH highlighted how SMA Scientific Board evaluated Zolgensma (Ministry of Health, 2020). Accordingly:

→The data on gene therapy that have been recently developed were immediately and meticulously examined by the SMA Scientific Board. In the last two months alone, the Board has met five times and analysed the data about the therapy.

→The evidence published on the scientific platforms about the efficacy of gene therapy Zolgensma is not yet sufficient and there is no evidence of its superiority to the current treatment. Some studies have reported serious side effects, including liver failure and bleeding tendency. In addition, immunosuppression is required for at least one month as part of the gene therapy application procedure, and this process can last up to 1 year, especially in some patients with higher weight. Suppression of the immune system and infections can pose a greater risk for SMA type-1 patients, who already have a very fragile structure.

The note particularly pointed at the availability of the trusted alternative treatment, Spinraza, in the country:

> Patients in Turkey already benefit from the treatment, whose efficacy and side effects are known. It is successfully applied in the country. The claims indicating that these patients have no treatment and would die if they do not receive gene therapy until the age of two do not reflect the truth. (Ministry of Health, 2020)

As a result, MoH indicated that "the application of gene therapy treatment in Turkey was not appropriate for that time being, on the grounds that the current data is insufficient in terms of risk-benefit ratio; and that a treatment with known efficacy is already being applied" (Ministry of Health, 2020).

In this process, patient families have organized fundraising campaigns to cover the expenses of the treatment that amounts to more than 2 million $. They have particularly used Twitter and Instagram, to gain the support of public, especially who could have more influence including singers, actors and actresses. Most of them have employed the

narrative of urgency for collecting the all amount before exceeding the limits of age and weight for the application of Zolgensma. The cries of patient families were all over public spaces: “It is the last 1 kg for not to miss the opportunity and I try to limit her weight” (“SMA patient ´Duru´ should not gain weight”, 2020). The campaigns of the families have highly occupied especially the conventional and social media channels, shaping the public perception about disease, therapies and government`s responsibility and attitude. This perception among public was also divided: Some people adopted a furious stance towards the government and its response to the issue. They argued that it should and indeed could allocate money for the treatment of these children and save the families from this precarious situation. Others highlighted that there were even difficulties in covering the costs of more common diseases such as diabetes; and the amount to be spent for Zolgensma for even one child could cover the expenses for many diseases. There were even discussions on collecting small amounts from all citizens to solve the issue, but then some asked ´why then citizens were paying their taxes´.

In January 2021, SMA Scientific Board was convened specifically for the assessment of Zolgensma. The Turkish Minister of Health Md. Fahrettin Koca who chaired the meeting, delivered a live press conference after the Board meeting. Referring to the Board`s assessment, he expressed that no additional evidence for the efficacy and safety of the treatment was found in the scientific publications since the workshop of 2020 and reiterated the safety related risks associated with the gene therapy. However, this time he also uttered a clear stance against families` campaigns for raising money to access to Zolgensma: “That it is not appropriate to organize campaigns for the application of gene therapy, for which there is not yet sufficient evidence in terms of efficacy and safety” (Koca, 2021; Ministry of Health, 2021b). He underlined that the public authorities did not consider costs: “It is not a question of [economic] resources. Our country is capable of treating its citizens under all circumstances. The state will continue to use every treatment free of charge that is proven to work for our children” (Koca, 2021). He also pointed at the pharmaceutical company for their marketing strategy, and associated it with a political plot against the country over the patients:

> As a nation, one of our most sensitive issues is our children. The treatment of diseases is carried out by following the path shown by science, not by displaying false heroism on social media. The main issue here is to advocate for global pharmaceutical companies by crossing the boundaries of morality and making our state look incapable. We will not be a part of this campaign that tries to make our state look incapable. (…) We will not allow our children to be used as guinea pigs under the pressure of pharmaceutical companies. (Koca, 2021)

As a response to the question of *who determined that which patients could get which treatment*, patient representatives indicated that they were usually patient families themselves who decided to head towards Zolgensma. The patient mother who could complete the campaign and had her child received Zolgensma abroad talked about who were involved in the process and how they opted for Zolgensma:

> Our physician was even hesitant about the outcomes and long term effects of Spinraza; that`s why I did not want to consult him on my decision for Zolgensma. Since the conditions to access to Spinraza after the first four doses were quite tedious, we wanted it to finish with one application (Interview with patient mother, 27 May 2022).

With that expression, she stressed how valuation of medical and regulatory authorities for one therapy shaped the value of the other therapy and also her families` actions.

In addition to the emotional burden of this "life-determining decision" (Gusset et.al., 2021b, p.105), the campaign process required a two sided effort from the families: Firstly, it demanded networking, internet literacy and constant online existence in the social media channels to raise the money, sum of which were increasing in the meantime in terms of local currency, with the depreciation of Turkish Lira against Euro and Dollar. According to the patient mother, since she had to reach as many people as possible through making contacts with business people, celebrities, as well as going live on Instagram and broadcasting videos every day to tell her cause; she could not even pay enough attention to her child`s abilities in this process (Interview with patient mother, 27 May 2022). Second aspect was the protection of their child's health status (muscles and respiratory functions) when trying to raise the amount for Zolgensma. Since loss of motor neurons were irreversible; patient families did not want to lose time and tried to get Spinraza and regular physical therapy. According to the patient representatives, despite their awareness about the lack of clinical trials showing the effects of consecutive use of therapies; they had to choose this way, since a campaign could last a year or more (Interview with patient organization, 17 May 2022; Interview with patient mother, 27 May 2022).

As the patient mother indicated, hospitals in different countries would reject the administration of Zolgensma for children who exceeded the certain age and weight limit; and this was another trigger for them to strive for raising the money and applying to the hospitals as soon as possible (Interview with patient mother, 27 May 2022). The interviewers mentioned that there were families who even limited their children's food intake so that they did not lose their chance for Zolgensma by gaining weight (Interview

with a patient organization, 17 May 2022; Interview with patient mother, 27 May 2022). The patient mother reflected her experience about this issue: “I used to get furious about those mothers, but I had to do the same thing for my child (…) (Interview with a patient mother, 27 May 2022).

As the same patient mother told, some families including hers received help from volunteer organizations in getting the offer for the treatment from the hospitals which administer Zolgensma in USA, Dubai, Hungary or Germany. They applied to hospitals which they learnt through other patient families from social media channels. Considering individual genetic and clinical condition of patients such as their status of respiratory support, their age and weight, hospitals accepted or declined the application. The mother uttered that some of the hospitals they applied rejected their application by stating the reason that their child exceeded the proper age for applying Zolgensma (Interview with patient mother, 27 May 2022).

On the other hand, SMA patient associations approach the campaigns cautiously. Firstly, they have raised their reservations about the therapy by evoking the safety and efficacy related concerns. As one interviewee from the patient association mentioned, it was quite normal to have hopes for a new therapy as a patient family. Yet, he reflected a balanced opinion on the value of the therapy:

> Our people love miracles; but we know that it has been studied on a small patient population. Besides, it has to be applied very early to be effective. Most of the European countries reimburse the application of Zolgensma on patients younger than 6 months of age. Yet we see campaigns here for children even older than 2-3 years. On the other hand, it is really advantageous for the early diagnosed children, as it is a one dose treatment. (Interview with patient association, 17 May 2022)

The same balanced attitude was captured in the interview with another association. Accordingly, “it could be beneficial if the child had the opportunity in the early stage of the disease. Yet, they already lose time in the campaign process and the therapy cannot reverse the loss” (Interview with patient association, 16 May 2022).

Another point of discussion related to the safety and efficacy of the therapies was the combination of two therapies. According to all interviewees, it has become a common procedure for patients to use Spinraza in the country, before and even after their application of Zolgensma abroad. As patient mother and associations stressed, families receive a recommendation letter from their physicians who implement Zolgensma abroad, with which they apply to TMMDA to use Spinraza in their return. The letter indicates that

“it is beneficial for the children to continue their treatment with Spinraza” (Interview with patient mother, 27 May 2022).

According to the announcement published by MoH after the SMA Scientific Board Meeting of 2021, the Board pointed to that “there is no information in the scientific literature on the safety of getting one therapy after another; therefore serious side effects may occur, and necessary measures should be taken by the public authorities in this regard” (Ministry of Health, 2021b). As MoH was opposed to the combination use by referring to the safety concerns; the applications of the families to use Spinraza after Zolgensma were rejected. However, in each case families applied to the Court to reverse MoH`s decisions and thereby attained the right to access to Spinraza with the Court`s decision that referred to ´right to live´. Talking about the process of before and after Zolgensma treatment, the patient mother reflected her opinion on the combination use:

> I applied for Spinraza when we returned to the country after Zolgensma treatment. I already knew that they would reject my application and I should follow the court procedure; because I thought that it was my child`s natural right to continue treatment with Spinraza (Interview with patient mother, 27 May 2022)

The representative of a public authority told the same procedure and indicated that that`s how they could monitor the number of patients who had Zolgensma abroad:

> We know the number of families who applied for Spinraza after Zolgensma and I think there are no patients who do not continue Spinraza in their return. That's the only way we could follow up as the public authority, because in some cases they do not even inform their own physicians in Turkey about their plans to take Zolgensma (Interview with public authority, 18 May 2022)

As one interviewed patient association mentioned, they also wanted to talk with patients who received Zolgensma abroad, in order to learn whether they benefited or not, but they encountered with a difficulty in monitoring the patient outcomes: “The patient took 8 doses of Spinraza and 3 months later had Zolgensma abroad; 4 months later they went to the Court and started taking Spinraza again. You cannot differentiate which therapy led to the benefit or harm” (Interview with patient association, 17 May 2022).

Another point of discussion related to Zolgensma campaigns among patient representatives was concerns of equality and solidarity. As one association mentioned, supporting the campaigns in the administrative or funding process would create inequality among children, since there are many kids with similar situation and the association do not have enough capacity to support them all. The representative indicated their concerns about the fairness:

> There are various families who live in suburban and do not have the means or digital literacy to organize campaigns. So, if we decide to help them in campaigns, it would be unfair to those we cannot support. Our goal is to make the therapy available in the country and ensure all patients have equal access. (Interview with patient association, 16 May 2022)

Another association also pointed that they believed they should collectively negotiate for equal access as in the case of Spinraza, instead of organizing individual fundraising campaigns. He added that having access to Zolgensma through campaigns was not a smart approach, by pointing to the marketing strategy of Novartis:

> In case that the company would have applied for the authorization and reimbursement in Turkey, it had had to sell the therapy a lot cheaper than its list price, which was 2.1 million dollar. I know that the company has sold its therapy to more than 100 patients so far through the campaigns at that price. If the drug had been covered under reimbursement by the SSI, it would have made the same money from 300 patients. I think that`s why they do not try to negotiate with the public authorities anymore. Actually the families are shooting themselves in their own foot with these campaigns. (Interview with patient association, 17 May 2022)

He also touched upon another aspect of this access and marketing strategy. This was how the representative viewed the relationship between the actors of Zolegensma:

> If the company and public authorities had had come to terms about price and reimbursement, and marketing therapy through regular channels; access would have been provided to a very narrowly defined patient population. Then we would see the real battle of access between families and public authorities (Interview with patient association, 17 May 2022).

The similar critical reflection about the company`s strategy was also expressed by a public authority representative. Talking about how reimbursement decisions are made by SSI, he indicated that if a company entered the market as the second therapy targeting the same disease; its price could not be higher than the first therapy unless it manifested a clinical added value (Interview with public authority, 17 May 2022). As the representative mentioned, the manufacturer of Zolgensma put a really high price tag in the negotiation process compared to Spinraza`s price offered to Turkey. The public representative criticized this strategy in the following manner:

> What the company has applied by selling its products through campaigns is a *seeding* strategy, where you deliver free samples to promote new products. In pharmaceuticals, companies in the authorization process can provide their products

> free through early access programmes such as *compassionate use*, in order to introduce the product to the healthcare professionals. However, *seeding* without free provision of the product is indecency (Interview with public authority, 17 May 2022).

The representative juxtaposed marketing strategies of two companies. Accordingly, the manufacturer of Spinraza did involve Turkey to its early access programme and provided the treatment for free to a certain number of patients in Turkey within the scope of *compassionate use*; it reduced the price considering to the purchasing power of the country and applied for the market authorization in time. As he mentioned, the company "played it by the book" (Interview with public authority, 17 May 2022). Yet, as he indicated, the manufacturer of Zolgensma did not involve Turkey to its early access program, although it initiated a *compassionate use program*, and provided the therapy free in countries such as Italy, Germany and Netherlands. Besides, it did not apply for the market authorization in Turkey (Interview with public authority, 17 May 2022). These discussions have shown that the valuation concerns were not limited to safety and clinical efficiency of the therapies, but there were also political and economic aspects to consider which could not be disentangled from the policy relevant scientific discussions that shaped the life of citizens.

7. Analysis and Discussion

Developments related to the SMA disease showcases the understanding of personalized medicine and genetic approach to the diagnosis and treatment as Sunder Rajan and Lakoff have put it: In 1995, the disease was defined with reference to a genetic cause and responsible genes were determined. With the development of gene-based diagnostic tests, these genes were used like a coding mechanism for distinguishing the heterogeneous groups of patients (Lakoff, 2008, p.752). Then the therapies targeting these genes were developed, either through making the SMN protein produced by the SMN2 gene functional (Spinraza) or delivering a functional copy of SMN1 gene (Zolgensma). In the clinical trials, marketing authorization and reimbursement decisions, the technological platform of *pharmacogenetics* and stratification of patients as SMA sub-populations were used for tailoring the use and reimbursement. Although genetic diagnosis made it possible to see differences and similarities between the cases, it did not put an end to the discussions related to classification of SMA disease. "Persistent tensions in medicine between the variation and standardization" revealed itself in the market authorizations and reimbursement decisions of national authorities (Green et.al., 2022, p.1).

While innovation in pharmaceutical industry has been welcomed by all stakeholders especially since they have addressed a disease without any treatment, it has come at the expense of high prices and challenges of affordability and access. SMA treatments Spinraza and Zolgensma, known as the most expensive genetic based medicines so far have been a text book example of challenges in governing novel health technologies. Manufacturers attempted to maximise the prices to recoup their R&D costs from relatively smaller number of patients. National authorities tried to negotiate according to their domestic pricing and reimbursement policies; and patients and their families were waiting with the hopes of cure and aspired to have optimal access to any available innovation. This made the valuation of these therapies an issue that has been shaped in the relationship between a range of stakeholders in different jurisdictions particularly the regulatory authorities, pharmaceutical companies, patients and patient organizations. Different values and expectations related to these technologies were negotiated and contested with diverging or coalescing concerns particularly the safety, efficacy, cost-effectiveness or equality. All stakeholders have used and shaped the scientific knowledge related to the disease and therapies based on *stratification* of disease population in line with the understanding of personalized medicine (Wadmann & Hague, 2021).

Different forms of stratification with reference to genotypic or/and phenotypic characteristics of patients were firstly visible in the authorization decisions of EMA. Through the evaluation of safety and efficacy of Spinraza, EMA annotated that the clinical trials did not indicate efficacy in all patient sub-types, yet it issued a positive opinion on authorization for all types with reference to the shared genetic defect on SMN1 gene, due to the *high unmet medical need*. On the other hand, despite the limitations of evidence, it approved Zolgensma for certain sub-groups of SMA patients (SMA type 1) with reference to both clinical diagnoses by leaving space for judgements beyond genotypic characteristics and also the number of copies of SMN2 genes. Based on the potential *therapeutic added value* of the therapy (as it is the requirement to issue conditional approval, if there is a treatment for the disease in place), Zolgensma has been given 'conditional authorisation', which implies the company should submit further evidence, to be reviewed by the Agency. Its application method, being a one-time infusion was regarded as the main added value.

Three themes came to the forefront by reading the case through discourses and practices of valuation: *Valuation of therapies vis-à-vis each other* with reference to their therapeutic added value and price; *the significance of early access*, *contestations over the expected progress*. *Therapeutic added value* and the logic of *comparison between the two therapies* have become outstanding discussion lines in the valuation of therapies. In

their assessment of Zolgensma, influential neurology experts were concerned especially with the safety of the therapy in heavier patients, and referred to the Spinraza`s availability and longer period of time used in the market, associated with more real world evidence. This positioned Spinraza as a relatively more *conventional* therapy vis-à-vis Zolgensma. When it comes to assessment of national authorities, values of therapies were articulated usually through a two level comparison: Firstly a comparison between their potential *efficacy* based on the available data for each patient group and the *price* suggested by the company; and secondly a comparison between the alternative therapies. As a result, therapies were regarded as either not *cost effective* or *uncertain* in terms of efficacy such as considering the long term effects. For national authorities, this entailed the risk of paying high prices without generating the promised benefits. However, the comparison between therapies in terms of efficacy and therapeutic added value was not easy, since clinical trials which included certain sub-group of patients did not cover the same groups; or their trial subjects could not be easily attached to the same disease type. These uncertainties about clinical efficacy and therapeutic added value of the therapies prompted public authorities to create novel strategies regarding to the negotiations with the industry such as *joint negotiations* with the involvement of a couple of Member States and regarding to the reimbursement policies such as *outcome based reimbursement* models.

On the other hand, patient organizations were cautious about any evaluation of medical and regulatory authorities that could limit the already difficult choices of families and clinicians. Besides, how they valued the therapies indicated differences: For patient organizations, even stabilization was an improvement. They attached values to therapies with reference to *stabilization* they would bring to the patients. On the other hand, these authorities were keen on seeing an improvement in their respiratory and muscle functions. Despite the contestations on the values and how to value these therapies, one shared concern with regard to the value of therapies was the need for early access, articulated by referring to the scientific knowledge on the disease. As better outcome was linked to the early application for both therapies, the importance of early diagnosis and treatment was reflected in the discourses and practices of all stakeholders. This analysis pointed that narratives of different actors could be coalesced, as much as they collide in enacting the values of therapies. Besides, it underlined that stakeholders articulated their concerns with reference to scientific underpinnings, even though their valuation was shaped with the political or economic concerns.

Issues discussed in Europe particularly with regard to evidence gaps, safety and efficacy had repercussions in Turkey, notwithstanding the local specificities of the national

case. One of the striking aspects of the Turkish case was the over-emphasis on non-economic considerations in the valuation of the public authorities. Minister of Health made all announcements regarding the therapies after SMA Scientific Board meetings, highlighting that he spoke for the name of science; despite the decision making process implicated multi-layer institutions and responsibilities. Besides, he stressed that only scientific reasons were taken into account in the assessments by the Scientific Board. His narratives embodied boundaries among epistemic (scientific) and economic values to justify the desired policy acts (Dussauge et.al., 2015, p.9). Whether or not there were political and economic underpinnings of the regulatory decisions including the price and reimbursement negotiations between the public authorities and pharmaceutical companies, they have never been revealed and articulated at the public sight. Since, economic considerations might have depicted the country incapable of providing the available therapies to its citizens, according to their views. The announcements of public authorities seemed to suggest that they mobilized a distinction between the scientific considerations that they associated with themselves and economic calculations that they attached to the industry.

Secondly, values of the therapies were articulated and enacted in relation to each other. While there were increasing visibility of Zolgensma campaigns and pressures on the public authorities for adopting Zolgensma in the country, authorities responded to this by extending the indication of Spinraza, and announced that they repealed the conditions of access based on patients` clinical progress. Through this action, they *cooled out* the patients` and patient organizations` resistance to a certain extent and aimed to change citizens` perception about Zolgensma as the only treatment option (Wadmann & Hauge, 2022). In the announcement of these policy changes, they only referred to recent scientific studies that generated further evidence on Spinraza, made a hierarchization between the therapies and positioned Spinraza as a secure and available treatment. As authorities reflected, if Spinraza was made available for a wide range of patient sub-groups, there was no need for another therapy for any sub group of patient, contrary to the added value defined by EMA in its authorization of Zolgensma.

In the meantime, families were taking decisions about treatments, organizing campaigns for reaching Zolgensma, contacting people for raising the whole amount and for finding hospitals that administer the therapy abroad. The articulation and portrayal of the value of Zolgensma in the campaigns were contested by the public authority. Shaped with the hope of finding a better treatment, their individual and collective actions were significant in the enactment of values about both therapies. Within the scope of their campaigns for reaching the required amount of Zolgensma, their actions and all public

interactions not only depended upon, but also intensified the hope associated with the therapy (Rose & Novas, 2005, p.452). This was illustrated eloquently by the *urgency narrative* that families employed during their campaigns. Since patients could exceed the age and weight limits stipulated by certain hospitals for the safe application of Zolgensma, families conducting the campaigns were in a race against the time to ´save the life of their children´. These narratives of families were criticized by the Minister of Health, as they positioned Zolgensma as the only therapy option for the disease and misguided the public opinion.

On the other hand, patient organizations reflected a more cautious standpoint regarding the Zolgensma campaigns: They articulated that they supported the campaigns neither financially nor administratively. SMA patient organizations indicated that funding campaigns was a wrong *strategy* firstly because they could not bring equal access to patients; secondly they led the company not to further negotiate the price and reimbursement issues with the public authorities. Accordingly, patients could succeed only if they could collectively act, similar to the solidarity shown in advocacy for achieving extended access in Spinraza. Pharmaceutical industry was not out of the picture while pointing at the responsible actors; its marketing strategy and choices were critically held with reference to ethical concerns by the representatives of patient organizations. Besides, referring to the global scientific discussions on the efficacy and safety of the therapy, such as limitations on the age and weight and respiratory conditions of the patients, organizations embodied a balanced and sophisticated understanding on the value of Zolgensma.

Thinking through the concepts of *bio-constituionalism* and *subject-constitution*, SMA case indicated that value constitution goes alongside the subject constitution within diverse, social, institutional, and organizational relations. The discussions on the valuation of therapies especially focusing on the national context revealed significant aspects with regard to the three strands of *subject constitution* defined by Sunder Rajan (2011, p.210): ´how patient families and organization thought about their enrolment´ and the institutional and epistemological aspects of subject constitution. Yet, those aspects incorporated valuation practices beyond the national context and pointed at the globally interconnected regimes of knowledge and value production. This particularly hints at the definition and classification of the disease and thereby the patient populations according to their genetic and physically observable characteristics and neoliberal regulatory tendencies that left a considerable part of the evidence production to the post marketing process.

Development of therapies represented a *bio-constitutional* moment (Jasanoff, 2011) which prompted patient families to establish patient organizations for their disease and

take actions according to their needs. Values of the therapies were enacted both through the individual decisions of patient families and through *the biological citizenship* represented in their practices, particularly mobilization of their collective identity based on the disease, institutionalization under SMA organizations and negotiations on the values of therapies (Rose & Novas, 2005). This aspect of *subjectivity* was related to "how one becomes the subject (agent)" in response to emergent technologies (Sunder Rajan, 2011, p.195). Families employed *biological citizenship* firstly in their contestations of limited access to Spinraza as the first available therapy. Access for the all types of SMA patients without any limitation was defined as the `right to life`. Some families could engage with the campaigns for Zolgensma, involved in judicial procedures to obtain that `right´ and shaped the life of their children through their acts of choice.

Patient families and patient organizations have become the agents in valuation through their individual and collective actions. They pressured public authorities for the application and reimbursement of Spinraza in the country, then for extending its indications so as to cover all patients and ameliorate the conditions of access, and configured the market through their choices and actions in Zolgensma. Therefore, they shaped the governance and knowledge in techno-scientific developments and had a say in the circulation of pharmaceuticals. On the other hand, SMA patients and patient representatives including the families as *subjects* were also constructed in different ways "in the emergent relationships between state and capital" (Sunder Rajan, 2011, p.195). Firstly state constituted patient families as the responsible subject for sustaining the life of their children, particularly through maintaining the physical and administrative procedures to maintain the treatment with Spinraza. Secondly, it configured the possibilities for the *subjects* by regulating Spinraza in a certain way, by stratifying access, and stipulating the necessity to show improvements in the tests to continue the application of doses and *cooling out* their resistance through legal and institutional channels (Wadmann & Hauge, 2022). As indicated in the interviewees with the patient representatives, administrative and physical hurdles of the processes in access to Spinraza including the multiple layers of responsibility played a key role in the families´ valuation of Zolgensma. Since it was a one-time treatment, families positioned Zolgensma as the less effortless option compared to the demanding procedure of access to Spinraza.

On the other hand, in view of the valuation practices for Zolgensma, the industry conjured up patient families as *sovereign consumers* who could put together the money no matter how; strive for and achieve access to the therapy with the hopes of better treatment. Hence, *subjects* were constituted as "always already a source of potential market value" by the corporate interests (Sunder Rajan, 2011, p.202). Here, it is not easy

to imagine them as the agents exercising their free choice among the available therapy options. Since, families have encountered the stress of completing the increasing amount due to the depreciating local currency before it is too late and muddling through various unknowns such as long terms effects and risks of the consecutive therapies if they manage to access Zolgensma through the campaigns. As indicated by one public representative and patient organization, networking and communication possibilities of families and solidarity among citizens which facilitated the collection of the required money were utilized by the company as a way to bring the product to the market. Besides, as patient organizations indicated, there were patients who received Zolgensma in some hospitals abroad, even though they were beyond the limits of adjusted doses studied by the company. Here, the subjects were *epistemologically constructed* in certain ways with reference their genotypic and phenotypic characteristics, who could show expected responses to the therapy. This complicates the reading that whether these healthcare institutions can be regarded as *experimental* or *therapeutic sites*. In voew of Turkish Minister of Health about Zolgensma, patients were constituted as *experimental subjects* and the state positioned itself as the ´guardian´ that aimed to prevent its citizens becoming the "targets of experimental therapeutic intervention" (Sunder Rajan, 2011, p.205).

Therefore, subjectivity of patients/families in Turkey was congruent neither entirely with the *therapeutic consumer* of the US, nor with the *experimental subjects* portrayed in the Indian case by Sunder Rajan (2011). It was rather somewhere in between, thereby their *subjectivity* were provisional and transitionary, but not contingent, since it was configured according to the dynamics of global capital, as well as the European and national regulatory regimes. Considering the agency and subjectivity through the national case, patients` perspectives were not entirely dismissed; they found channels to raise their concerns regarding to access to therapies. Although they were not formally incorporated into the decision making process, they took part in shaping the values and markets of therapies by benefiting from the ambiguities of disease categorization in different terms. However, patients and patient advocacy could easily become "imaginable as *valuable*" to the corporate capital and their agency took form according to the state`s interests (Sunder Rajan, 2011, p.210).

8. Conclusion

In this thesis, I studied mutual constitution of subjectivities and values by focusing on the therapies targeting a rare disease, Spinal Muscular Atrophy. My initial research has primarily led me to understand that the values of emergent technologies are constituted along with emergent institutional structures and individual and collective

practices of patients. This prompted me to link question of *subjectivity* to *valuation* of techno-scientific objects and to study the agency of patients (their families in this case) alongside the *valuation practices*. Apart from that, my research has revealed that values are not only constructed in the relationship between different actors, but also in relation to each other. That is why I studied the *valuation practices* about the first two approved medicines of the disease, which in a sense share the market.

First and foremost, I showed how the regimes of knowledge and value co-produce each other, as also highlighted by Sunder Rajan (2011). The definition and classification of the disease, which were configured with the development of genetic technologies, were used in various ways by different actors in the valuation of these therapies. Then I underlined that the institutional and epistemological aspects of the valuation have transcended the borders of national context, as valuation and knowledge making at the European level have implications on the values and valuation practices about the therapies in Turkey. The case highlighted that assessments of national authorities on the cost effectiveness of therapies cannot be separated from their assessments on the clinical efficacy. However, while technology assessments of some countries could reveal this relationship between scientific and economic matters; authorities could also deny any economic concerns, and employ a boundary between scientific aspects and economic/commercial interests, in line with the political identities that they would like to promote as in the case of Turkey. Concerning to the valuation studies, this stressed the need for paying attention to potential intersections between different values and how those values are made separate in practices as also suggested by Dussauge et.al. (2015).

I concluded that regulatory frameworks at the national and European level, marketing strategies of corporations and valuation practices of medical and public authorities and patient families have been all performative in enacting and shaping values as well as subjectivities. In this regard, *valuation practices* have ordering effects in the relationship among the actors, namely these technologies, families and public and medical authorities. These effects that were shaped in complex global and national dynamics were palpably manifested in the analysis of the national case, specifically the discussions about the disease and therapies in Turkey and negotiations between the patient organizations and public authorities. By highlighting different modalities of *subject constitution*, be fashioned as *consumer subject* or the *experimental subject*, the study invites researchers to think through the nuances of patient engagement and participation in governance of biomedicine, with the following guiding questions: What kind of an agency of patients or patient representatives would not be considered as

epistemologically or *ethically silenced* (Sunder Rajan, 2011)? What kind of participation can be regarded as *emancipatory* (Prainsack, 2017a) so that we can consider technologies in concern were developed with a sense of *humility* (Jasanoff, 2003)?

This work has opened up the way for a comparative inquiry involving different countries to observe valuation practices and the views of patient`s organizations on high priced advanced therapies. Besides, as it has raised certain questions, they can be discussed in a potential future work: Who owns and regulates the issues related to data when patients from a country have their treatment abroad? For which purposes patient`s outcomes would be used in the post-market phase of medicines lifecycle? Who accepts responsibility in case of a safety issue: the manufacturer company, the hospital, or no one? Following such questions, the governance of real-world patient data after market approval -especially for medicines marketed through conditional approval- is also a relevant matter that deserves exploration with an STS perspective.

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English:
Declaration of Authorship

I hereby declare that the thesis submitted is my own unaided work. All direct or indirect sources used are acknowledged as references. This paper has not previously been presented to another examination board or published.

German:
Ehrenwörtliche Erklärung

Ich erkläre hiermit ehrenwörtlich, dass ich die vorliegende Arbeit selbständig angefertigt habe. Die aus fremden Quellen direkt und indirekt übernommenen Gedanken sind als solche kenntlich gemacht.
Die Arbeit wurde weder einer anderen Prüfungsbehörde vorgelegt noch veröffentlicht.

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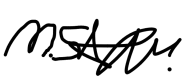

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