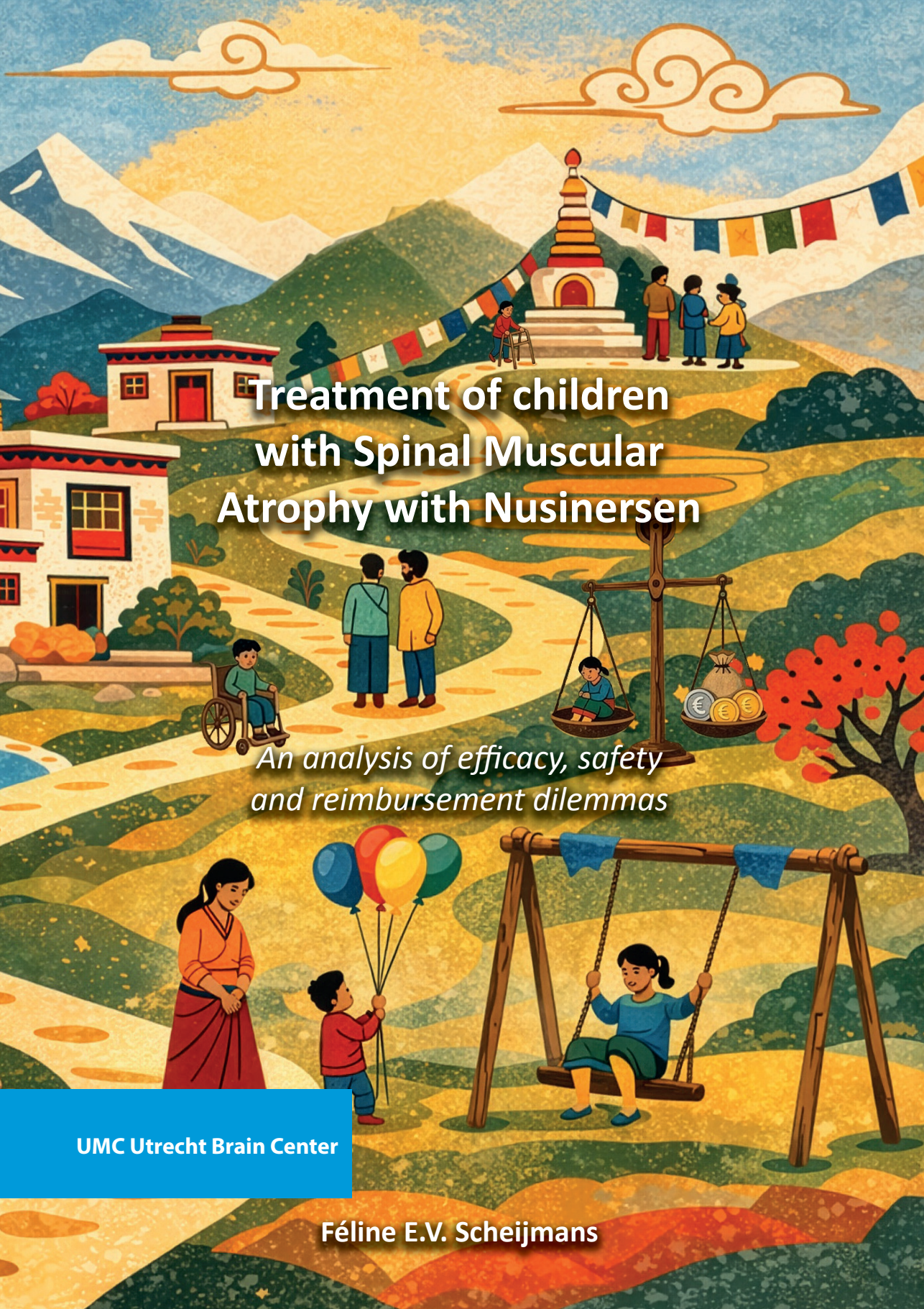




Treatment of children with Spinal Muscular Atrophy with Nusinersen

*An analysis of efficacy, safety
and reimbursement dilemmas*

UMC Utrecht Brain Center

Féline E.V. Scheijmans

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Colophon

Treatment of children with Spinal Muscular Atrophy with Nusinersen - An analysis of efficacy, safety and reimbursement dilemmas

PhD thesis, University Medical Center Utrecht, Utrecht University, The Netherlands

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Treatment of children with Spinal Muscular Atrophy with Nusinersen

An analysis of efficacy, safety and reimbursement dilemmas

Behandeling van kinderen met spinale spieratrofie met Nusinersen

Een analyse van de effectiviteit, veiligheid en vergoeding dilemma's
(met een samenvatting in het Nederlands)

Proefschrift

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Voor Tim en Boris,

Aan mijn ouders

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Chapter 1

General introduction and thesis outline

Spinal muscular atrophy; pathophysiology and clinical characteristics

Hereditary proximal spinal muscular atrophy (SMA) is a severe autosomal recessive, hereditary neuromuscular disorder with onset in infancy, childhood or rarely adulthood caused by the loss of function (most often a homozygous (partial) deletion) of the survival motor neuron (*SMN*) 1 gene on chromosome 5q. The pathological hallmark is progressive dysfunction and death of alpha-motor neurons that connect spinal cord and muscle tissues. The estimated incidence is 1:6000-1:10,000 newborns (1, 2). This implies that every year approximately 15-25 children are born in the Netherlands (population size 17.7 million, approximate number of newborns per year 170.000), who will develop symptoms of SMA during life. Although SMA is a rare disease, it is one of the more common genetic disorders that affects infants and young children and the most common genetic cause of infant mortality and severe childhood disability.

SMA was described for the first time in the last decade of the 19th century by several authors, but the names of Guido Werdnig and Johann Hoffmann have remained best known, mostly because of the Werdnig-Hoffmann eponym that was used until the 1990s to refer to the most common and severe form of SMA with infantile onset (3-6). The use of such eponyms or the adjectives infantile, intermediate and mild, that were used from the 1960s, to capture the broad range of SMA severity, were replaced by a clinical classification scheme designed in the 1990's. Using age of disease onset and the highest achieved motor milestone to initially distinguish 3 and ultimately 5 SMA types (**table 1**) (7, 8). More recent amendments allow the distinction of subtypes that reflect variation in severity that is clinically relevant. Since the introduction of the newborn screening program for SMA in the Netherlands and elsewhere, most children are identified before the onset of symptoms ('presymptomatic' cases). Obviously, classification of presymptomatic cases requires another approach, i.e., the number of *SMN2* copies that the newborn carries (see below).

The identification of the genetic defect underlying SMA, i.e., the homozygous loss of function of the survival motor neuron 1 (*SMN1*) gene, was challenging because of the complex structure of the *SMN* locus and was finally published in 1995 (9). Follow-up studies identified the most important genetic modifier of SMA severity, i.e. the copy number variation of the second and highly homologous human *SMN* gene (*SMN2*) that due to a critical point mutation in exon 7 that alters mRNA splicing only produces small amounts of full length SMN protein (10). Human genomes show broad variation in the number of *SMN2* gene copies. The presence of more copies generally results in higher residual SMN protein levels, which partially explains the variety in SMA severity (11-14). The presence of 2 *SMN2*

copies is associated with SMA type1, while 3 and 4 *SMN2* copies correlate with SMA type 2 and 3, respectively – although with much broader overlap (13). Partial deficiency of the SMN protein in human cells is thus the cause of SMA. Although SMN protein is expressed by all cells and is essential for embryonal development and for a wide range of generic cell biological functions, motor neurons are particularly vulnerable to SMN protein deficiency, most likely due to cell-type specific ribosomal dysfunction that causes translational disturbances in motor neurons (15-17).

Despite advances in supportive care, SMA remained a severe disorder. Recently, advances in genetic medicine have resulted in the successful development of no less than three therapies that have entered the European market since 2017 (see below for overview). SMA became part of the Dutch newborn screening program in 2022, which allows the identification of patients before the onset of symptoms and the start of treatment before extensive damage to motor neurons has occurred (18).

Table 1. Clinical classification of SMA (7, 12, 19)

SMA type	0	1	2	3	4
Age at onset	Pre- and neonatal	0-6 months 1a: neonatal 1b (“classic”): 1–6 months 1c: 3-6 months	6-18 months	>18 month 3a: 18-36 months 3b: >36 months	During adulthood, i.e., ≥18 years
Incidence	1-5%	50%	25-30%	15%	5%
Highest motor milestone	None	Never achieves ability to sit unsupported 1a: no head control 1b: No head control and no ability to roll over 1c: Will usually acquire additional motor skills, such as head control or rolling from supine to prone, or at least to one side at any stage in life.	Able to sit unsupported, not able to walk 2a: Unsupported sitting 2b: In addition to unsupported sitting, able to stand or walk supported	Able to walk unsupported	Able to walk unsupported
Survival without treatment (median) (20)	Extremely short; intra-uterine	Severely shortened or depending on mechanical (invasive) ventilation	2a: shortened 2b: probable close to	Normal life expectancy	Normal life expectancy

	death or within the first days		normal life expectancy		
SMN copy number (13)	1	Usually, 2 Range 1-3	Usually, 3 Range 2-4	Range 3-4	Range 4-5

SMN protein enhancing therapies

The inverse correlation of *SMN2* copy number and severity and its reproduction in an SMA mouse model (10, 21) suggested that experimental strategies that increase SMN protein levels could change the natural history of SMA. First attempts to use existing drugs to this end, for example salbutamol and valproate, were unsuccessful (22-30). However, the advances in genetic medicine allowed the development of more specific treatment strategies, more specifically two *SMN2* mRNA splicing modifiers and one *SMN1* gene replacement therapy.

Nusinersen (Spinraza®), an antisense oligonucleotide (ASO) that increases the inclusion of exon 7 in *SMN2* mRNA by binding to a sequence upstream of exon 7, was the first *SMN2* splicing modifier that became available in 2017 (31). An ASO does not pass the blood-brain barrier and therefore nusinersen needs to be administered by repeated intrathecal injections.

In randomized clinical trials nusinersen improved survival of infants with SMA (type 1) and motor function development in children up to 12 years with SMA (type 1 and 2) (32-34). This led to regulatory approval in the United States (2016) and Europe (2017) for all SMA types and all ages (35, 36). Following market authorization of nusinersen, an increasing number of observational studies and one meta-analysis documented beneficial effects on motor function also in adolescents and adult patients with SMA types 2 and 3 (37-50). The results from phase two and three trials indicated that treatment with nusinersen was safe and well tolerated in young children with SMA (32, 34, 51). However, these studies focus either on small, selected patient cohorts or on adolescents and adults, and have a limited follow-up time. In **chapter 2** we therefore analyze the efficacy and safety of nusinersen in a cohort of Dutch children for a longer time of period, in order to answer the question “*What is the efficacy of nusinersen is on the motor function, bulbar and respiratory function of children with SMA types 1, 2 and 3a treated in the Netherlands?*”.

A body of literature supports that treatment with nusinersen is safe e.g., (52-59). However, two serious adverse events have been reported in the first year after the introduction of nusinersen, i.e., hydrocephalus unrelated to bleeding or infection and aseptic meningitis (60, 61). These adverse events might be triggered by an inflammatory process of the

meninges, occurring after the start of treatment. The reports on nusinophages, macrophages containing granules with nusinersen (62-64), were additional indications of an immunological response to nusinersen administration, and raised concerns regarding the longer-term safety of the treatment.

In **chapter 3** we therefore aim to answer the question *“Is nusinersen safe, or are there markers in the cerebrospinal fluid suggesting a prolonged inflammatory response to treatment?”*.

While writing this thesis, a second *SMN2* splicing modifier (risdiplam (Evrysdi[®]) and a gene replacement therapy (onasemnogene abeparvovec, Zolgensma) were granted market access by the European Medicines Agency (EMA). Risdiplam is an orally administered small molecule that promotes the inclusion of exon 7 in het pre-mRNA of the *SMN2* gene (65). EMA granted risdiplam market authorization in March 2021 for SMA patients from the age of 2 months, and with SMA type 1, 2 or 3, or with one to four *SMN2* copies (66). Onasemnogene abeparvovec (Zolgensma[®]) is a one-time intravenous gene replacement therapy that employs adeno-associated virus (AAV) serotype 9 with tropism for motor neurons as a vector. The *SMN1* gene is delivered to the nucleus as an (extrachromosomal) episome, although there are reports that do not exclude the possibility of low levels of chromosomal integration of *SMN1* (67-69). This therapy was approved for both the US and EU market in 2020, but with different indications. The EMA has approved treatment for patients with SMA type 1 and presymptomatic cases with up to three copies of *SMN2* gene (70). The FDA has approved treatment for pediatric patients less than two years old with SMA (71).

At the start of the studies in this thesis, nusinersen was the only reimbursed SMA treatment in the Netherlands and we therefore focus on treatment with nusinersen in this thesis.

In addition to their potential to increase SMN levels, the three genetic therapies share the characteristic of extraordinary pricing. The list price of nusinersen is €93,448.48 per injection, amounting to first year costs of €499,900.00 per patient followed by a life-long maintenance treatment costs of €280,345.45 per patient per year. Onasemnogene abeparvovec is a one-time treatment with a list price of €1,900,000 per patient. Risdiplam costs are broadly similar to those of nusinersen. SMA treatment is an example of the dilemma surrounding rare diseases: there is a high medical need for therapies, but the high pricing of these effective therapies leads to pressure on healthcare budgets. Governments generally aim to make a fair choice in the reimbursement of treatments. However, access to these life-saving treatments is delayed or even limited due to the high prices and limited budgets.

Allocation in solidarity-based healthcare systems

The growing number of expensive treatments for oncology and rare diseases (72) are a challenge for policy makers in the allocation of health-care budgets (73-78) given the fact that the capacity of societies to bear healthcare costs has limits. Increasing expenses on orphan drugs could lead to crowding out other healthcare priorities (79).

Healthcare systems in the Netherlands and many other EU countries are solidarity-based. This implies that healthcare is available for all citizens and that the healthy support the sick by contributing to costs. Financing is through taxes and compulsory healthcare insurance. The Dutch government ensures basic health insurance coverage also for citizens with a low income by income dependent allowances. Healthcare coverage is regulated by law and covers a broad range of care, including treatment with expensive drugs. In order to maintain the solidarity within the healthcare budget, the Dutch government decided to reassess the policy of automatically reimbursing expensive drugs in 2015. This reassessment led to the Coverage Lock (CL) policy (80-82).

The CL policy as allocation instrument

The CL policy halted direct reimbursement of expensive drugs. The rationale was that a growing percentage of the healthcare budget (80) spent on expensive therapies would crowd out other healthcare needs from the basic insurance package. The expensive drugs became therefore a “target” in the struggle to manage the costs and maintain solidarity within the system (83). The purpose of the CL was to make new, expensive drugs, that are used in hospitals (inpatient drugs), *affordable and accessible* within basic health insurance (84).

The current CL policy works as follows (**Figure 1**). New drugs that exceed a certain budget limit – a budget impact of more than €20,000,000 in total or more than €50,000 per patient resulting in total costs exceeding €10,000,000 – are placed in the CL directly after market authorization by the European Medicine Agency (EMA) (85). Despite market access, drugs placed in the CL are not reimbursed and therefore patients with high medical need do not have access to treatment. The CL implies that the new drug will undergo an additional scientific assessment focusing on four criteria for reimbursement: efficacy, cost-effectiveness, necessity and feasibility (82, 86). The scientific assessment includes a dimension of societal appraisal, i.e., stakeholders’ interests and opinions are taken into account and weighed. The CL procedure has different possible outcomes (**table 2**).

Table 2. Possible outcomes of the Coverage Lock

	Positive cost-benefit ratio	Negative cost-benefit ratio
Proven efficacy	Reimbursement from basic health insurance	Price negotiations
Unsure efficacy	Conditional reimbursement or reimbursement for limited patient groups	Conditional reimbursement or reimbursement for limited patient groups

Conditional reimbursement is an agreement between the government, manufacturer and often a specialized clinic. The aim is to ensure access to a new and innovative treatment, while gathering data on efficacy and safety. This type of agreement typically lasts for 7 to 14 years, after which efficacy is re-assessed prior to a decision on final reimbursement (87, 88).

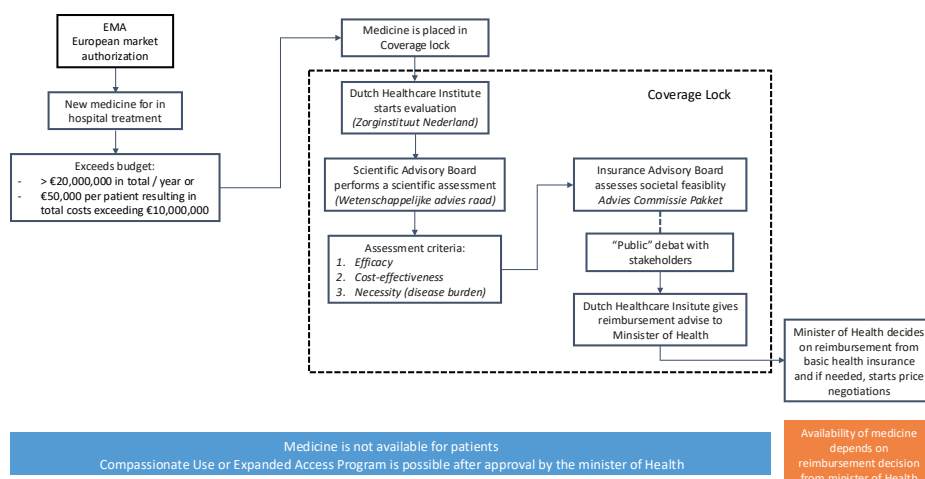


Figure 1. Flowchart for new medicine entering the European market after approval by the EMA. In the dotted box is the flowchart of the Coverage Lock.

Nusinersen and the CL

Nusinersen received accelerated market authorization from the EMA and not all efficacy data were published at the moment of market authorization in May 2017. Nusinersen was placed in Coverage Lock at the time of EMA approval and because the manufacturer had to wait for efficacy data to be published, the reassessment started with some delay in October 2017.

The Dutch Healthcare Institute (DHI) decided in February 2018 based on cost-efficacy analysis that nusinersen did not meet reimbursement criteria. DHI reported that efficacy of

nusinersen was proven in selected patient cohorts (with a limited disease duration, age and genetic background) and the cost-effectiveness ratio was poor. Nusinersen would exceed the limit of €80,000/QALY for all SMA types. The advice of the DHI to the minister of Health was to start price negotiations and aim for a significant price reduction in line with the QALY threshold.

Price negotiations lasted until June 2018 and from the 1st of August 2018 nusinersen was reimbursed for a subgroup of patients. Reimbursed treatment was limited to the patient groups in which treatment was proven effective, according to the reassessment:

1. SMA type 1 and a disease duration no longer than 26 weeks
2. SMA type 2 or 3 and a disease duration no longer than 94 months
3. Presymptomatic infants with a maximum of 3 *SMN2* copies.

This led to an age limit for the start of treatment was set at 9.5 years. This reimbursement agreement implied that a large part of the SMA population was excluded from treatment. This decision also led to differences in access in families with two (or more) children with SMA, in which younger siblings could be treated but their (slightly) older siblings not.

The more inclusive conditional reimbursement program repaired this imbalance. From the 1st of January 2020 all SMA patients in the Netherlands were invited to participate in the conditional reimbursement program that combined treatment with assessments for efficacy and safety in a population with a longer disease duration. This program will end in 2026, followed by re-evaluation of efficacy and safety in this older SMA population

Exploring the intrinsic fairness of the CL

The CL was introduced as a policy instrument to control costs of expensive medicines, primarily for oncology and rare diseases, arguing that this would honor the values of solidarity and justice of the Dutch healthcare system. However, the CL also excludes patients from treatments that are beneficial.

The CL has not been evaluated since its introduction in 2015. The age limit for reimbursement of nusinersen, apparently different from neighboring countries, prompted us to start an evaluation of the CL. Since public support for policy measures is important for the legitimacy (89-92), we evaluated the CL from several perspectives.

In **chapter 4** we aimed to gain a better understanding on how stakeholders experienced the CL procedure of nusinersen and to summarize lessons learned.

In **chapter 5** we investigated how the Dutch public appreciates the CL and assessed opinions regarding expensive (orphan) drugs.

Finally, in **chapter 6** we aimed to gain a better understanding of the international differences in access to orphan drugs such as nusinersen by assessing (procedural) differences in the decision-making process of neighboring countries.

Summary of the outline of this thesis;

This thesis has two main aims. In the first part I aimed to gain insight in the efficacy and safety of intrathecal treatment with nusinersen, based on real-world data up to 2019.

In the second part I used the reimbursement process of nusinersen as a case-study to gain insight in the values that play a role in the allocation of reimbursement when introducing an expensive medicine in a solidarity-based healthcare system in order to assess if the CL can be considered a fair decision-making process.

Part I: Efficacy and safety of nusinersen in a real-world cohort of Dutch children with SMA

Chapter 2: What is the efficacy of nusinersen is on the motor function, bulbar and respiratory function of children with SMA types 1, 2 and 3a treated in the Netherlands?

Chapter 3: Is nusinersen safe, or are there markers in the cerebrospinal fluid suggesting a prolonged inflammatory response to treatment?

Part II: Coverage Lock as policy instrument: experiences, opinions and ethical arguments in the reimbursement decision on nusinersen

Chapter 4: How was the coverage lock procedure of nusinersen experienced by different stakeholders and what can we learn for future CL procedures?

Chapter 5: What are the views and opinions of the general public on the reimbursement of expensive medicine and the CL as policy instrument for reimbursement decisions?

Chapter 6: Are moral reasons taken into account in the reimbursement decision of nusinersen and are they explaining a difference in access to nusinersen between neighboring European countries?

Chapter 7: General discussion, I will discuss our findings in a broader context.

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Chapter 2

Population-based assessment of nusinersen efficacy in children with spinal muscular atrophy: a three-year follow-up study

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Abstract

Background: Nusinersen (Spinraza®) improves survival of infants with hereditary proximal spinal muscular atrophy (SMA) and motor function in children up to 12 years. Population-based assessments of treatment efficacy are limited and confined to select cohorts of patients.

Methods: We performed a nationwide, population-based, single-center cohort study in children with SMA younger than 9.5 years at start of treatment in line with reimbursement criteria in the Netherlands. We assessed age-relevant motor function scores, the need for tube feeding, hours of ventilatory support and documented adverse events. We used linear mixed modeling (LMM) to assess treatment effects. We compared motor function during treatment with natural history data and to individual trajectories of muscle strength and motor function before the start of treatment.

Results: We included 71 out of 72 Dutch children who were treated (median age 54 months; range 0-117) and followed them for a median of 38 months (range 5-52). We observed improvement of motor function in 72% and stabilization in another 18% of the symptomatic children, which differed from the natural disease course in a matched cohort of which we had previously collected natural history data. Longitudinal analysis showed that motor function improved up to a median of 24 months (range 12-30) of treatment after which it stabilized. Shorter disease duration at start of treatment resulted in better treatment efficacy ($p < 0.01$). Sixteen children (23%) achieved new motor milestones. Bulbar and respiratory function did not improve significantly during treatment. In 15 patients from whom treatment-naïve data were available, the pre-treatment trajectory of motor function decline changed to stabilization or improvement after the start of treatment. We documented 82 adverse events after 934 injections (9%) in 45 patients. None of the adverse events led to treatment discontinuation.

Discussion: Intrathecal nusinersen treatment is safe and improves or stabilizes motor function in 90% of young children with SMA types 1c–3a. We did not observe improvement of respiratory and bulbar functions.

Introduction

Hereditary proximal spinal muscular atrophy (SMA) is caused by deficiency of survival motor neuron (SMN) protein due to loss of the *SMN1* gene function (1). Its natural history is characterized by deteriorating muscle strength and motor function throughout life (2-6). SMA has a striking variability in disease severity. Ranging from an early infantile-onset form with severely impaired motor development (type 1), childhood-onset forms type 2 and type 3 with delayed gross motor development and progressive loss of motor function, to an adult-onset form with generally limited disability (type 4) (7). Variability in disease severity between patients is partly explained by the inverse correlation with the *SMN2* copy number. (3, 8, 9).

Nusinersen (Spinraza®) is an antisense oligonucleotide that modifies *SMN2* splicing, thereby increasing SMN protein production. It is the first approved drug for the treatment of patients with SMA. Clinical trials showed that nusinersen improves survival of infants with SMA type 1 and motor function of infants and children with SMA types 1 and 2 (10,11). After the regulatory approval of nusinersen in the United States (2016) and Europe (2017), an increasing number of observational studies and one meta-analysis documented beneficial effects on motor function in adolescents and adult patients with SMA types 2 and 3 (12-24). Population-based, real-world data from larger cohorts of children with SMA would allow evaluation of the real-world efficacy of nusinersen but are still scarce (24-26). We here present data on motor, respiratory and bulbar function, and adverse events of 98% of the Dutch children with SMA types 1, 2 and 3a, eligible for reimbursement, who started treatment with nusinersen before July 2019.

Materials and methods

Patients

Treatment of SMA is centralized in the Netherlands at the SMA center in the University Medical Center Utrecht (UMCU). We therefore enrolled all patients with SMA who fulfilled the Dutch reimbursement criteria (i.e., patients younger than 9.5 years at start of treatment and 2 or 3 *SMN2* copies) between May 2017 and July 2019. All patients in this cohort had previously been included in an ongoing prospective population-based prevalence cohort study in the Netherlands and had agreed to have their clinical data included in the national SMA registry (2,3,5).

We used historical natural history data from the Dutch SMA Registry (2,3,5). All patients in this natural history cohort were treatment naïve. Our natural history study started in September 2010 and it now contains data of the very large majority of patients with SMA

who live in the Netherlands. Follow-up of included patients continues until today. Motor function of all included patients was assessed at inclusion (baseline) and during follow up every one to five years. For this study, we matched patients from the natural history cohort based on SMA type and age and included only patients for which at least two longitudinal treatment naïve assessments were available.

We used age at onset and acquired motor skills to define SMA types 1-3 according to the SMA classification (3,5,7). In case of discrepancy between age at onset and reached motor milestones, the latter determined the final diagnosis. SMA type 1 (a, b, c) was defined by an onset before six months and the inability to sit independently at any time. Patients with type 1b show signs of hypotonia after the neonatal period and will never have head control or will ever be able to roll. Type 1c includes patients who meet the criteria of type 1, and not type 2, but show a relative better performance in motor skills, including head control or rolling from supine to prone, or at least to one side at any stage in life. Patients with SMA type 2 had onset between the age of six and 18 months and learned to sit (type 2a) or even stand but not walk assisted (type 2b). Patients with SMA type 3 developed weakness after the age of 18 months and learned to walk independently. Patients with type 3 were further divided into SMA type 3a (disease onset before the age of 3 years old) and type 3b (disease onset after the age of 3 years old).

We used multiplex ligation-dependent probe amplification (SALSA MLPA kit P021-B1-01 (MRC-Holland) to confirm the homozygous deletion of the *SMN1* gene and to determine *SMN2* copy number in all patients.

Assessments of motor function, respiratory function and bulbar function

Three pediatric physical therapists (MAGCS, DW, BB) assessed motor function in all patients using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) (27,28) and Hammersmith Infant Neurological Examination-2 (HINE-2) for patients with SMA type 1 (29), and Hammersmith Functional Motor Scale Expanded (HFMSE) (30, 31) for patients with SMA types 2 and 3. We used WHO definitions for acquired motor milestones (32). We assessed motor function prior to treatment and after three, four and five injections. After the fifth injection we repeated assessments with every injection in presymptomatic children and those with SMA type 1. Children with SMA type 2 and 3 were assessed every six months. Patients were usually assessed at the day of intrathecal injection, with a maximum interval of two weeks.

We documented respiratory (i.e., hours of (non-)invasive ventilation) and bulbar functions (i.e., need for tube feeding) at least every 6 to 12 months.

Adverse events were systematically assessed using a questionnaire at every visit for nusinersen administration as well as during the yearly outpatient follow-up visits.

Treatment

Treatment with nusinersen was available from May 2017 for children with SMA type 1 (as part of an expanded access program) and from January 2018 for children up to six years of age with SMA types 2 and 3 (preliminary reimbursement arrangement). The final reimbursement arrangement included children with SMA younger than 9.5 years, including presymptomatic children, with 2 or 3 *SMN2* copies came into effect in August 2018 (33). Exclusion criteria for nusinersen treatment were as prescribed by the manufacturer (34). We applied lidocaine/prilocaine cream prior to lumbar intrathecal administration of nusinersen in patients less than one year old and general anesthesia with inhalation anesthetics or intravenously administered propofol at the intensive care unit or operation theatre for children of one year and older. No children required consistent angiography or CT guidance for their lumbar puncture. Treatment as per protocol started with a loading dose at days zero, 14, 28 and 63 followed by intrathecal injections every four months (34).

We defined treatment response as an improved disease trajectory in comparison to the known natural history patterns, defined by slow but continuous deterioration of motor function (2,4-6). Response to treatment therefore included both improvements of motor function and stabilization, i.e., remaining within the day-to-day variation of specific motor function scales (e.g. 4 points on the CHOP-INTEND scale, 2 points on the HINE-2 scale for type 1, 2 HFMSE points for types 2 and 3). With no progressive decline on 2 consecutive assessments (2,5,10,11).

Ethical approval

This cohort is part of an ongoing study. The local Medical Ethical Committee approved the study protocol, which is registered at the Dutch registry for clinical studies and trials (NL29692.041.09). We obtained written and oral informed consent of both parents or legal guardians of each patient.

Statistical analyses

We used descriptive statistics to describe baseline characteristics. Continuous variables were presented as median (range), and categorical variables as frequency (percentage). We used linear mixed models (LMM) to estimate the population-average change in motor

function from baseline to 36 months of treatment for the CHOP-INTEND, HINE-2 (SMA type 1) and up to 30 months of treatment for the HFMSE total score (SMA types 2 and 3). The fixed part of the model contained the baseline score and time since first injection in months. A random intercept and slope for time since first injection per patient were added as random effects. We evaluated the effect of time both as linear and as non-linear (quadratic) pattern. Likelihood ratio tests were used to determine significance. Bootstrapping ($n = 1,000$) was used to estimate 95% confidence intervals.

We performed separate linear mixed models (LMM) to analyse response to treatment based on disease duration before treatment for SMA types 1, 2 and 3. We dichotomized patients on the median disease duration before treatment and added the interaction between disease duration and time since first injection. We used R software (R-3.5.1 for Windows with RStudio version 1.1.456, R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses. Significance level was set at $p < 0.05$.

Data availability

The presented model summary statistics allow full reproduction of all LMMs. Additional data supporting our findings are available upon reasonable request.

Results

Eighty-one patients were screened for eligibility of nusinersen treatment. Ten children were excluded from this study, due to the following reasons: palliative care was initiated in 5 infants (6%) with SMA type 1b who were already severely affected at presentation, three patients (4%) were excluded due to clinical trial participation elsewhere (one with nusinersen, one with onasemnogene abeparvovec-xioi, and one with risdiplam), in one patient (1%) with SMA type 1c intrathecal injections were technically impossible due to complete thoracolumbar fusion after scoliosis surgery, and finally the parents of one child (1%) did not give informed consent for participation.

Patient characteristics of symptomatic children ($n=69$) and their baseline values of motor, respiratory and bulbar function are presented in **table 1**.

Five children (1 with type 1c, 3 with type 2a and 1 with type 2b) ended treatment with nusinersen during follow-up and switched to oral risdiplam as part of the JEWELFISH study (NCT03032172). One child (type 1c) died due to a non-treatment related event after 10 injections. All available follow-up data from these six children are included in our analyses.

Table 1. Baseline characteristics of symptomatic patients treated with nusinersen

	All patients (n=69)	SMA type 1 (n=23)	SMA type 2 (n=30)	SMA type 3 (n=16)
SMA type n (%)				
A		0 (0)	20 (67)	16(100)
B		5 (25)	10 (33)	0 (0)
C		18 (75)	n.a	n.a.
Male sex n (%)	42 (60.9)	18 (78)	15 (50)	9 (56)
Age at disease onset in months	9 (0-36)	4.5 (0-13)*	10.3 (0-20)	19 (12-36)
Age at diagnosis in months	16 (0-82)	8 (2-22)	18 (0-36)	36 (0-82)
Disease duration at start of therapy	43 (0-114)	28 (0.5-113)	48 (5-114)	46.5 (6-95)
Age at first dose in months	54 (2-117)	37 (2-117)	55.5 (18-115)	68 (39-113)
SMN2 copy number n (%)				
2	7 (10)	6 (26)	0 (0)	1** (6)
3	52 (75)	17 (74)	30 (100)	5 (31)
4	10 (15)	0 (0)	0 (0)	10 (62)
CHOP-INTEND score	31 (6-46)	31 (6-46)	n.a.	n.a.
HINE-2 score	0 (0-7)	0 (0-7)	n.a.	n.a.
HFMSE score	19 (0-62)	n.a.	11 (0-38)	47.5 (34-62)
WHO motor milestone score	1 (0-6)	0 (0)	1 (0-4)	6 (2-6)
None	24 (40)	23 (100)	1 (3)	0 (0)
Sitting without support	20 (31)	0 (0)	16 (53)	0 (0)
Standing with assistance	5 (7)	0 (0)	4 (13)	3 (19)
Hands and knees crawling	0 (0)	0 (0)	4 (13)	0 (0)
Walking with assistance	1 (1)	0 (0)	3 (10)	0 (0)
Standing alone	1 (1)	0 (0)	2 (7)	1(6)
Walking alone	12 (18)	0 (0)	0 (0)	12 (75)
Use of ventilator support n (%)				
None	53 (77)	11 (48)	26 (87)	16 (100)
Non-invasive ventilation	13 (19)	9 (39)	4 (13)	0 (0)
Hours per day of non-invasive ventilation	12 (8-16)	13 (8-16)	10.5 (10-12)	n.a.
Invasive ventilation	4 (6)	4 (17)	0 (0)	0 (0)
Hours per day of invasive ventilation	22.5 (12-24)	22.5 (12-24)	n.a.	n.a.
Dependent on feeding tube n (%)	24 (35)	16 (30)	9 (30)	0 (0)
Nasogastric tube	6 (8)	5 (22)	2 (7)	0 (0)
Gastrostomy	18 (26)	11 (48)	7 (23)	0 (0)

Legend Table 1. SMA= spinal muscular atrophy; n= number; n.a. = not applicable; *SMN2*= survival motor neuron 2 gene; CHOP-INTEND= Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Hammersmith Infant Neurological Examination 2; WHO= World Health Organization; HFMSE= Hammersmith Functional Motor Scale Expanded. All outcomes are given in median (range) unless otherwise stated. *= Age at onset was between 8-13 months in 4 infants with SMA type 1c. Age at onset was particularly

late in one infant (13 months) due to delay of symptom recognition. **= One patient with confirmation of two *SMN2* copies and c.859G>C mutation in exon 7 of *SMN2*

Survival, motor function and milestones in SMA type 1

We included 23 patients with SMA type 1 (5 with type 1b, 18 with type 1c). Nine patients (39%) learned to sit after 3 to 13 injections (**table 2**), of whom 4 had SMA type 1b (baseline CHOP INTEND range 17-46) and 5 type 1c (baseline CHOP-INTEND range 29-42). One patient with type 1c lost the ability to sit due to scoliosis progression.

Table 2. Clinical outcome measures in patients with SMA type 1 treated with nusinersen

	SMA type 1b (n=5)	SMA type 1c (n=18)
Follow-up in months	41 (29-46)	45.5 (19-52)
Number of injections	13 (10-15)	14 (7-16)
CHOP-INTEND score	56 (23-58)	40 (15-54)
Δ CHOP-INTEND score	25 (12-39)	8 (1-18)
HINE-2 score	16 (15-19)	4 (0-9)
Δ HINE-2 score	15.5 (12-19)	3.5 (0-9)
WHO motor milestone score	1 (0-1)	0 (0-1)
Use of ventilator support n (%)		
None	3 (60)	4 (22)
Non-invasive ventilation	2 (40)	10 (56)
Hours of non-invasive ventilation	13.5 (13-14)	12 (11-13)
Invasive ventilation	0 (0)	4 (22)
Hours of invasive ventilation	n.a.	12 (12-24)
Dependent on feeding tube n (%)		
None	1 (20)*	4 (22)
Nasogastric tube	0 (0)	0 (0)
Gastrostomy	4 (80)	9 (50)

Legend Table 2. SMA= spinal muscular atrophy; n= number; CHOP-INTEND= Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; Δ CHOP-INTEND = difference in CHOP-INTEND score between baseline and last follow-up assessment; HINE-2= Hammersmith Infant Neurological Examination-2; Δ HINE-2 = difference in HINE-2 score between baseline and last follow-up assessment; WHO= World Health Organization

Outcomes present the data of last follow up assessment, unless otherwise stated. All outcomes are given in median (range) unless otherwise stated.

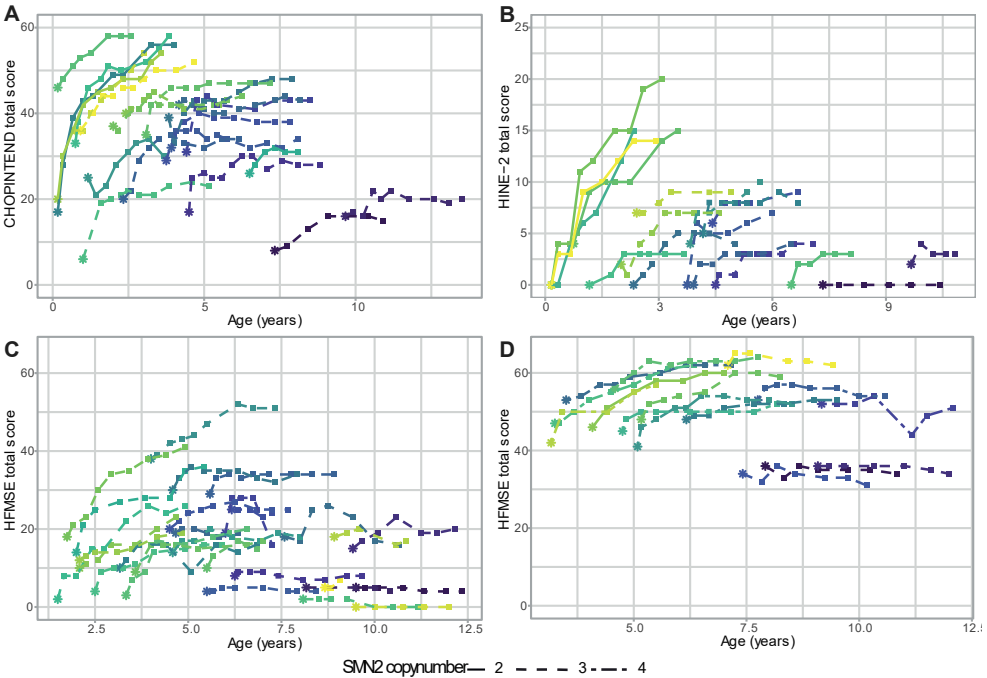
* Swallow examination shows silent aspiration, parents refused feeding tube.

CHOP-INTEND scores for 21 patients with SMA types 1b and 1c are shown in **figure 1A**. Eighteen children (85%) showed an improvement of ≥ 4 points on the CHOP-INTEND scale. CHOP-INTEND increments varied, were not linear ($p < 0.001$) and depended significantly on

disease duration before start ($p<0.001$). There was a mean increase in CHOP-INTEND scores from baseline of 3.3 (CI 2.7-4.0) points after six months of treatment, 6.0 (CI 4.8-7.1) points after 12 months, 8.0 (CI 6.3-9.7) points after 18 months, 9.6 (CI 7.5-11.6) points after 24 months, 10.4 (CI 7.8-12.9) points after 30 months and 10.6 (CI 7.5-13.7) after 36 months of treatment, all in comparison to baseline scores (**figure 2A**). After 30 months of treatment, group analysis showed a plateau of motor function gains.

HINE-2 scores of 17 patients did not deteriorate during follow-up and are shown in **figure 1B**. Increases in HINE-2 scores were non-linear in the first 18 months, i.e. a mean increase of 1.8 (CI 1.3-2.2) points after six months of treatment, 3.2 (CI 2.3-4.1) points after 12 months, 4.4 (CI 2.9-5.7) points after 18 months, 5.1 (CI 3.4-6.8) points after 24 months, 5.6 (CI 3.5-7.8) points after 30 months and 5.7 (CI 3.1-8.3) points after 36 months of treatment (**figure 2B, table 2**). Shorter disease duration at treatment initiation was associated with better treatment response ($p<0.001$). None of the children showed a decline of motor function during treatment.

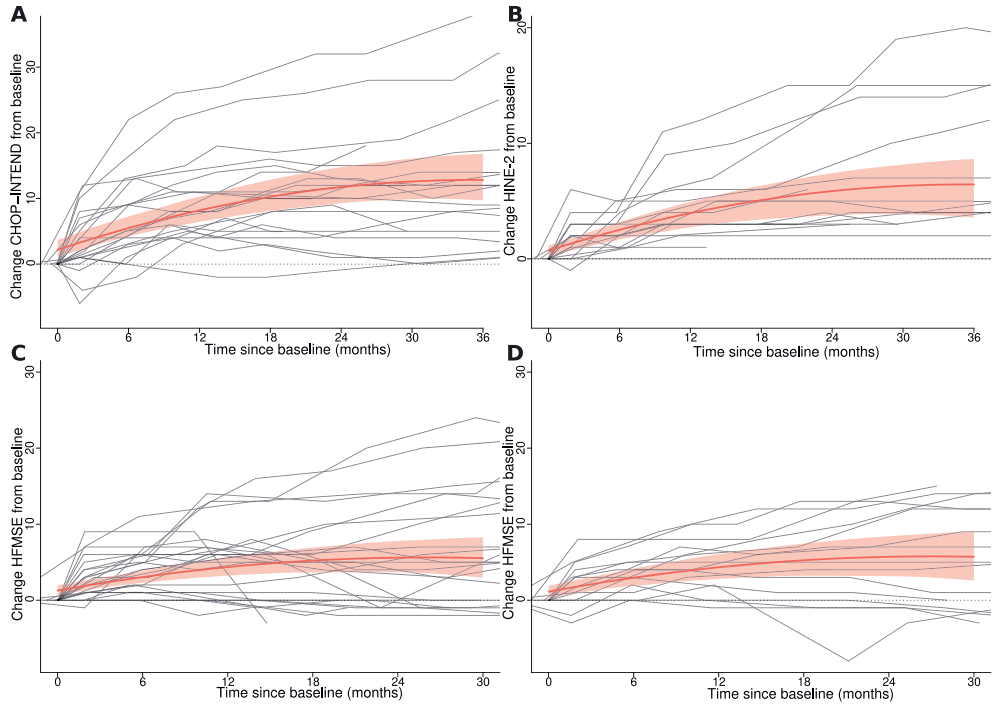
Figure 1. CHOP-INTEND, HINE-2 and HFMSE scores of individual patients during treatment with nusinersen



Legend figure 1

Motor function trajectories reflected by CHOP-INTEND, HINE-2 and HFMSE scores in symptomatic children with SMA types 1b-3a. Each coloured line represents one patient. Baseline assessment is indicated by asterisks, while follow-up assessments are indicated by squares. Effects of nusinersen treatment were associated with disease duration at treatment initiation and age at the start of treatment (likelihood ratio test: $p < 0.001$). A) CHOP-INTEND scores in patients with SMA type 1, including types 1b and 1c. B) HINE-2 scores in patients with SMA type 1, including types 1b and 1c. C) HFMSE scores in patients with SMA type 2, including types 2a and 2b. D) HFMSE scores in patients with SMA type 3a.

Figure 2. Linear mixed model trajectory of motor function in patients with SMA types 1, 2 and 3 treated with nusinersen



Legend figure 2ABCD

Motor function trajectories analysed with a linear mixed model with repeated measures, including bootstrapping ($n = 1,000$) to estimate 95% confidence intervals. The grey lines represent individual trajectories. The red line and grey area reflect the mean changes in motor function over time with confidence interval, respectively. A) Change from baseline in CHOP-INTEND score in all patients with SMA type 1 during treatment. B) Change from baseline in HINE-2 score in patients with SMA type 1 during treatment. C) Change from baseline in HFMSE score in patients with SMA type 2 during treatment. D) Change from baseline in HFMSE score in patients with SMA type 3a during treatment.

Motor function assessments and milestones in SMA type 2

We included 30 patients with SMA type 2 (20 with type 2a, 10 with type 2b). Four children with SMA type 2a regained the ability to sit independently (after 3-7 injections), one child with type 2a gained the ability to walk with assistance (after 9 injections). Two children with SMA type 2b learned to stand without support (after 4 and 7 injections, respectively) (**table 3**). None of the children lost these new milestones during follow-up.

HFMSE scores increased in a non-linear fashion ($p < 0.001$) with a mean increase of 1.8 (CI 1.2- 2.4) points after six months, 3.1 (CI 1.9-4.3) points after 12 months, 3.9 (CI 2.3-5.6)

points after 18 months, 4.3 (CI 2.2-6.5) points after 24 months and 4.1 (CI 1.6-6.9) after 30 months of treatment, all in comparison to baseline scores (**figure 1C and 2C, table 3**). After 12 months motor function reached a relative plateau. Shorter disease duration at treatment initiation was associated with better treatment response ($p<0.001$). Sixteen children (57%) showed an improvement of ≥ 3 points on the HFMSE. Seven children (25%) showed a decline of motor function during treatment compared to baseline, with a maximum decline of 3 points on the HFMSE. Six patients lost 1 or 2 points on the HFMSE, either because of increasing severity of contractures ($n=2$) or inability to perform one specific item on the HFMSE ($n=5$). One child lost 3 points after scoliosis surgery. Motor function in all seven children remained stable afterwards.

Motor function assessments and milestones in SMA type 3

Twelve out of 16 children (75%) with SMA type 3a were ambulant at start of treatment, one was able to stand without support and three were able to stand with help. One child regained the ability to stand alone after 7 injections, but lost this milestone 4 months later. Increases in HFMSE scores were non-linear ($p<0.001$), with a mean increase of 1.8 (CI 1.2-2.5) points after six months, 3.2 (CI 1.9-4.5) points after 12 months, 4.1 (CI 2.4-5.9) points after 18 months, 4.6 (CI 2.2-6.9) points after 24 months and 4.6 CI (1.7-7.5) points after 30 months of treatment, all in comparison to baseline scores (**figure 1D and 2D, table 3**). After 24 months motor function reached a relative plateau. Shorter disease duration at treatment initiation was associated with better treatment response ($p<0.001$). Ten (63%) children showed an improvement of ≥ 3 HFMSE points. Four patients (25%) showed a decline of motor function, losing up to 3 HFMSE points. All four children lost points on specific items due to increasing hip flexor contractures, but stabilized in the consecutive assessments.

Table 3. Clinical outcome measures in patients with SMA types 2 and 3 treated with nusinersen

	SMA type 2a (n=20)	SMA type 2b (n=10)	SMA type 3a (n=16)
Follow-up in months	34.5 (5-44)	36 (13-40)	33.5 (21-41)
Number of injections	11.5 (4-14)	11.5 (6-15)	11 (8-13)
HFMSE score	16 (0-41)	20 (4-51)	55.5 (31-64)
ΔHFMSE score	5 (-3-24)	4 (-2-13)	6 (-3-15)
WHO motor milestone score	1 (0-4)	1 (1-5)	6 (2-6)
Use of ventilator support n (%)			
None	15 (75)	10 (100)	16 (100)
Non-invasive ventilation	5 (25)	0 (0)	0 (0)
Hours of non-invasive ventilation	12 (12)	n.a.	n.a.
Invasive ventilation	0 (0)	0 (0)	0(0)
Dependent on feeding tube n (%)			
None	16 (80)	7 (70)	16 (100)
Nasogastric tube	0 (0)	1 (10)	0 (0)
Gastrostomy	4 (20)	2 (20)	0 (0)

Legend Table 3. SMA= spinal muscular atrophy; n= number; HFMSE= Hammersmith Functional Motor Scale Expanded; ΔHFMSE = difference in HFMSE score between baseline and last follow-up assessment, WHO= World Health Organization

Outcomes present the data of last follow up assessment, unless otherwise stated.

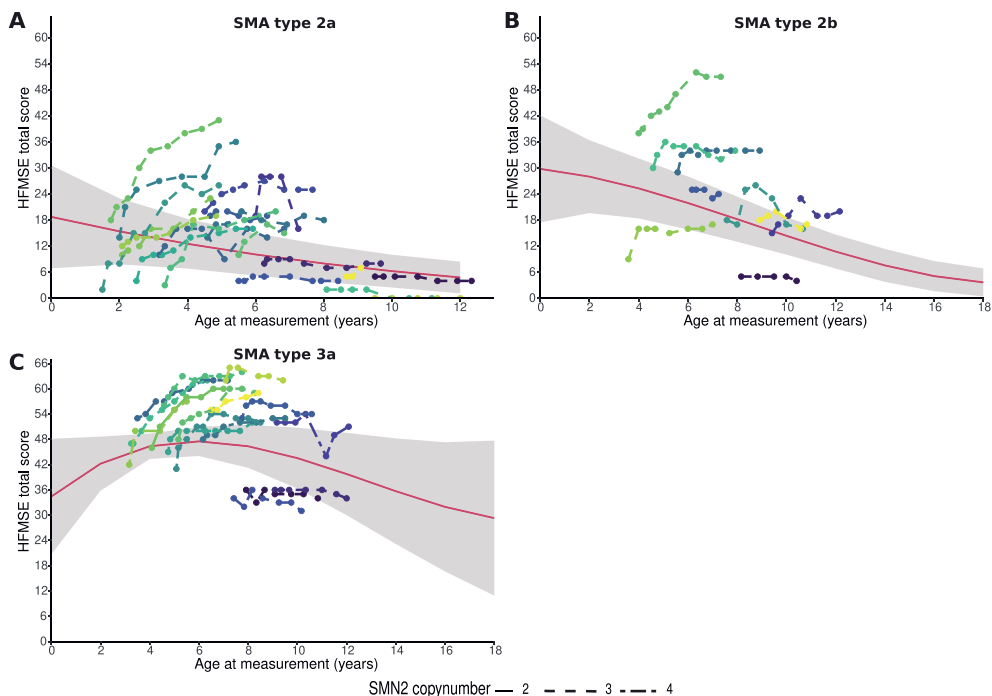
All outcomes are given in median (range) unless otherwise stated.

Natural history of SMA compared to disease course with treatment

We compared the disease course of children treated with nusinersen to data from our natural history cohort (2,3,5). We included all children from the natural history cohort with available longitudinal follow-up data available (28 with SMA type 2, 16 with SMA type 3). Median age at baseline was 6.2 years (range 1.4-17.2 years). Median follow-up was 45 months (range 3-90) in SMA type 2 and 38 months (range 3-74) in SMA type 3a. Disease course during treatment with nusinersen differed from natural history (**figure 3, supplementary figure 1**). We additionally compared the disease course of 15 children before and after start of treatment (3 SMA type 2a, 4 type 2b and 8 type 3a) with a median pre-treatment follow-up of 14 months (range 1-68). One patient with SMA type 2a, with a stable HFMSE score prior to treatment, showed an increase of 1 point after the start of nusinersen. Two children with type 2b with decreasing scores prior to treatment showed an increase in the HFMSE score after the start of nusinersen: one (67 months of age at baseline) had an increase of 5 points after six injections, the other (94 months of age at baseline) had an increase of 8 points after six injections. Two children with SMA type 3a with decreasing HFSME scores prior to treatment also improved after six injections: one 10 points (61

months of age at baseline), the other 4 points (92 months of age at start of treatment) respectively.

Figure 3. Disease course with nusinersen treatment and natural disease course in children with SMA type 2a, 2b and 3a



Legend figure 3.

Individual motor function trajectories of symptomatic children treated with nusinersen ($n = 42$) are represented as coloured lines. Each line represents an individual child treated with nusinersen. The individual motor function scores of children treated with nusinersen improved or remained stable (as shown in figure 2) in 42 out of 44 (95%). This reflects a change from the natural history of SMA that is reflected by the red line with the 95% confidence intervals in grey. This natural history trajectory was reconstructed from 44 age group -matched, treatment-naïve Dutch SMA patients with SMA types 2a ($n=16$), 2b ($n=12$) and 3 ($n=16$) included in the Dutch natural history cohort. We analysed their motor function scores using a linear mixed-effects model with age, SMA type and an interaction term of these two predictors as fixed factors, whilst dependency in the data due to repeated measures was accounted for by a random intercept per individual, as previously published (2). As a result, this natural disease course trajectory shows that a child with SMA type 2a of four years old has a mean HFMSE score of 12 points, while at age of six the score will have deteriorated to approximately 10 points. A) Individual trajectories of the HFMSE scores of 19 children with SMA type 2a, treated with nusinersen. The median increase of the HFMSE score during treatment was 5 points. Twelve (63%) children showed improved motor function, six (31%) remained stable and one (5%) showed a decline of 3 points during treatment. B) Coloured lines are individual HFMSE score trajectories of 9 children with SMA type 2b, treated with nusinersen. The median increase of the HFMSE during treatment was 4 points. Five children (55%) showed improved motor function and four (45%) remained stable during treatment. C) Coloured lines are individual HFMSE score trajectories of 16 children with SMA type 3a, treated with nusinersen. The median increase of HFMSE

scores during treatment was 6 points. Eleven (68%) children showed improved motor scores, four (25%) remained stable and one (6%) showed a decline in motor function. For a more detailed motor function trajectory of the natural history cohort see supplementary figure 1.

Bulbar and respiratory function during treatment

Ten children with SMA type 1 did not receive mechanical ventilation at treatment initiation. Three of them (1 type 1b, 2 type 1c) started non-invasive mechanical ventilation (NIV) during treatment (age 2 months for type 1b and 11 and 46 months for type 1c at treatment initiation, respectively), despite improvements of motor function in all three. Two out of 4 children with SMA type 1c who received invasive ventilation prior to treatment, reduced their ventilation time from 22h/d to 13 and 12h/d, respectively (**table 2**). Three children (2 type 1b, 1 type 1c) had to start tube feeding during treatment, all after 6 injections. One child with SMA type 2 (type 2a) started nocturnal NIV (8h per night) after four injections at the age of 9.5 years. One child with SMA type 2b required nasogastric tube feeding after 12 injections to prepare the child for scoliosis surgery (**table 3**); two children with type 2a did no longer need tube feeding after seven and eight injections, respectively. None of the children with SMA type 3a required tube feeding or mechanical ventilation prior to treatment, which did not change during treatment.

Motor function and milestones after start of treatment in two presymptomatic patients

Two infants were diagnosed before onset of clinical symptoms and were therefore classified as 'presymptomatic'.

The first infant (two *SMN2* copies) was diagnosed prenatally because of an older sibling who died of SMA type 1b. The infant showed no signs of SMA after birth and had a baseline CHOP-INTEND score of 43 points. The infant started treatment at day four. The infant was able to sit independently at the age of 11 months, to stand with support at 19 months and walk with support at 30 months. He needed NIV (13 hours/day) and nasogastric tube feeding from the age of 18 months.

The second child (three *SMN2* copies) was diagnosed at the age of three months after a recent diagnosis of SMA type 3 in an older sibling. This presymptomatic infant showed no clinical signs of SMA and had a baseline CHOP-INTEND score of 62 points. The infant started treatment at day 102. He was able to walk with support at the age of 10 months and to walk without support at the age of 21 months. Respiratory and bulbar function remained normal until last follow-up (34 months).

Safety

We observed 82 treatment-related adverse events in 45 patients (63%) on a total of 934 injections (9%) (**table 4**). The most reported side effects were headache, back pain, pyrexia and discomfort. One patient developed aseptic meningitis one day after his first injection. He fully recovered and continued treatment with nusinersen without further complications. One child had an allergic skin reaction with angio-edema of the lips shortly after the second and fourth injection. Skin allergy tests with nusinersen and drugs used for anesthesia were normal. Despite the use of clemastine, the skin rash occurred twice more without angio-edema. Two children showed an increased intracranial pressure measured prior to their injection of nusinersen. Both children were without concomitant clinical symptoms. Investigation with MRI and fundoscopy showed no signs of hydrocephalus. Both children continued treatment with nusinersen.

Table 4. Reported adverse events during treatment with nusinersen

Adverse event	Number of reported AE (n of patients)
(Allergic) skin reaction	5 (3)
Aseptic meningitis	1 (1)
Increased intracranial pressure (without hydrocephalus)	3 (2)
Headache	24 (20)
Back pain	10 (9)
Tingling feeling in back/leg	4 (4)
Discomfort	13 (6)
Pyrexia	13 (10)
Proteinuria	9 (8)
Legend table 4. Number of reported AEs in 934 injections	
AE= adverse event; n= number	

Discussion

This study is a population-based assessment of efficacy of intrathecal treatment with nusinersen in Dutch children with SMA types 1-3a. We observed improvement of motor function scores in 72% of patients with SMA types 1b-3a and 23% of the patients gained new motor milestones. In another 18% of the patients, motor function scores stabilized during treatment. This is a clear difference from the expected natural history patterns, observed in 90% of young symptomatic children. Importantly, we did not observe a consistent decline of motor function in any of the enrolled patients. Longitudinal analysis showed that motor function changes after the start of treatment are non-linear, with the most pronounced improvement within the first 12 months of treatment, followed by a relative stabilization of motor function after 30 months. In contrast, bulbar and respiratory function did not improve during treatment. Shorter disease duration at time of treatment initiation was associated with a better treatment response. The national single center treatment setting minimizes the risk of inclusion bias and reduces variability in outcome measure assessments. Our data therefore provide an important insight in real-world treatment efficacy of nusinersen for children with SMA.

Response to treatment as previously defined as improvements of ≥ 4 CHOP-INTEND or ≥ 3 HMFSE points (10, 11, 38), was observed in 85% of children with SMA type 1, 57% of those with type 2, and 63% of those with type 3.

Nine children (39%) with SMA type 1 learned to sit independently during treatment. The percentage of children that achieved this motor milestone is higher than in the randomized controlled ENDEAR trial and other reports (10, 26, 35,36) and may reflect differences in baseline characteristics, in particular disease duration and condition at the start of treatment. The median CHOP-INTEND baseline scores of children with SMA type 1 who learned to sit was 32 (range 20-46) which is in line with previous findings (26). Parents of babies with SMA type 1b in already poor condition often opted for best supportive care. This explains the underrepresentation of this group of patients in our treatment cohort.

The percentage of children with SMA type 2 and 3 improving ≥ 3 HMFSE points in our cohort is in line with the results of the randomized CHERISH study. However, the responder rate in children with SMA type 2 in our cohort is higher in comparison to another study which had a shorter follow-up time (i.e. 12 months) (25). The extended follow-up time of our study revealed that treatment response is reflected by incremental improvements up till 30 months of treatment followed by stabilization of motor function scores.

An increase of ≥ 1 on specific items or, an increase in the score for kicking of ≥ 2 points on the HINE-2, ≥ 4 points on the CHOP-INTEND or ≥ 3 points on the HFMSE were previously defined

as evidence for treatment efficacy in the sham-controlled clinical trials with nusinersen, because this is uncommon in the natural course of disease (10, 11, 38).

Various motor scales and assessments are validated and used to follow up on SMA patients. Still there is no consensus on what changes are clinically significant or meaningful (39, 40). However, any improvement of functional motor scales above the age of 5 years or even stabilization is change from the natural course of SMA and should therefore be interpreted as a treatment effect (41). This is further illustrated by the comparison of the historical cohort of children enrolled in the Dutch natural history study.

We observed temporary functional decline under treatment most often in children with progressive contractures or scoliosis. This underscores that pro-active treatment of contractures is essential to maintain and optimize motor function in children who are treated with new therapies for SMA (42, 43).

The pattern of treatment response – improvement followed by a plateau – was similar in all SMA types, but the time-to-plateau differed. We assume that this pattern is best explained by accelerated maturation or activation of ‘hibernating’ motor units (44), while the plateau phase reflects the limitation in the number of motor units that can be revived. We cannot exclude that the longer time to plateau in SMA type 1 is explained by the longer treatment time needed for motor neurons to recover. However, properties and limitations of motor scales may provide an alternative explanation, including ceiling effects and the non-continuous nature of motor function scales that may mask subtle improvements, in particular in non-ambulant children with SMA type 2 and 3a.

The percentage of treatment responders differed between SMA types. This is probably due to the selection of patients with SMA type 1 (as outlined above) and the relatively long disease duration of children with SMA type 2 at the start of treatment. Disease duration was the most important predictor of the magnitude of treatment effect. Children with SMA type 2 starting after the age of 5.5 years and type 3a starting after 7.5 years showed limited or no improvement. However, we observed clinical stabilization in these patients, which is an important change from the natural disease course that likely reflects treatment effects. The importance of early treatment and its effect on motor response was shown in our data from symptomatic patients with SMA types 1-3 and underlined by the motor performance of our two presymptomatically diagnosed and treated infants. Newborn screening programs would make presymptomatic treatment the rule rather than the exception and should be a priority in all countries with reimbursement arrangement for genetic therapies (45,46).

Combinatorial therapies that would target SMN and other, non-SMN targets that support the neuromuscular system (i.e., pyridostigmine for neuromuscular junction (NMJ) function, and myostatin inhibitors currently in clinical trials to support muscle function) might have a synergistic effect on motor function and daily life performance. Combining multiple SMN-targeting therapies remains controversial as it is unclear if there are limits to up-regulating SMN levels (see e.g., 47).

Treatment effects of nusinersen on respiratory and bulbar function are limited and clearly fall behind the observed motor function changes. We previously reported the lack of persistent improvement of bulbar function in children with SMA type 1 treated with nusinersen (48). Although the hours of mechanical (non-)invasive ventilation declined on average during follow-up in a cohort of 123 French children with SMA type 1, effects on respiratory function were clearly less pronounced than those on motor function (16). Other studies also report limited effects of nusinersen on respiratory and bulbar function (49-57). We compared the hours of ventilation or the need of tube feeding before and after the start of treatment. We acknowledge that this approach to assess respiratory and bulbar function may lack sensitivity to detect subtle, but relevant changes. Parents frequently reported changes, including a louder voice or cry, a decreased mealtime or improving intake and fewer respiratory infections during nusinersen treatment. Patient reported outcome measures might therefore provide valuable insights but need to be standardized and validated for future use.

The overall occurrence of adverse events in our cohorts was low and the procedure well tolerated. None of the children discontinued treatment because of adverse events. Anesthesia and sedation were well tolerated. Intrathecal injections could be performed without complications in 45 patients with either (severe) scoliosis or previous spinal surgery, without the use of radiologic assistance, e.g., CT-, fluoroscopy- or radioguidance (58-62).

This study has several important strengths. First, this is a single-center population-based SMA cohort. We systematically obtained motor function data prior to the start of and during treatment, which minimizes inclusion bias and contributes to the real-world evidence for nusinersen efficacy. We applied longitudinal analyses and showed a non-linear pattern of improvement. This allowed us not only to show improvement after the start of treatment, but also and for the first time, stabilization in children who had longer disease duration. The comparison of treatment effects with natural history data in patients with the same supportive care strategy (e.g. same country and treating physicians) has not been reported

before. Limitations of our work include the sample size and the selection bias of children with SMA type 1b.

We conclude that intrathecal nusinersen treatment of patients with spinal muscular atrophy is safe and results in modest to large effects in the large majority of young patients with SMA types 1, 2 and 3a. The effect of nusinersen treatment is most evident in the first year of treatment. Short disease duration at treatment initiation is related to a larger treatment effect. Uncertainties regarding the longer-term duration of these effects and effects on respiratory and bulbar function remain to be resolved in future studies.

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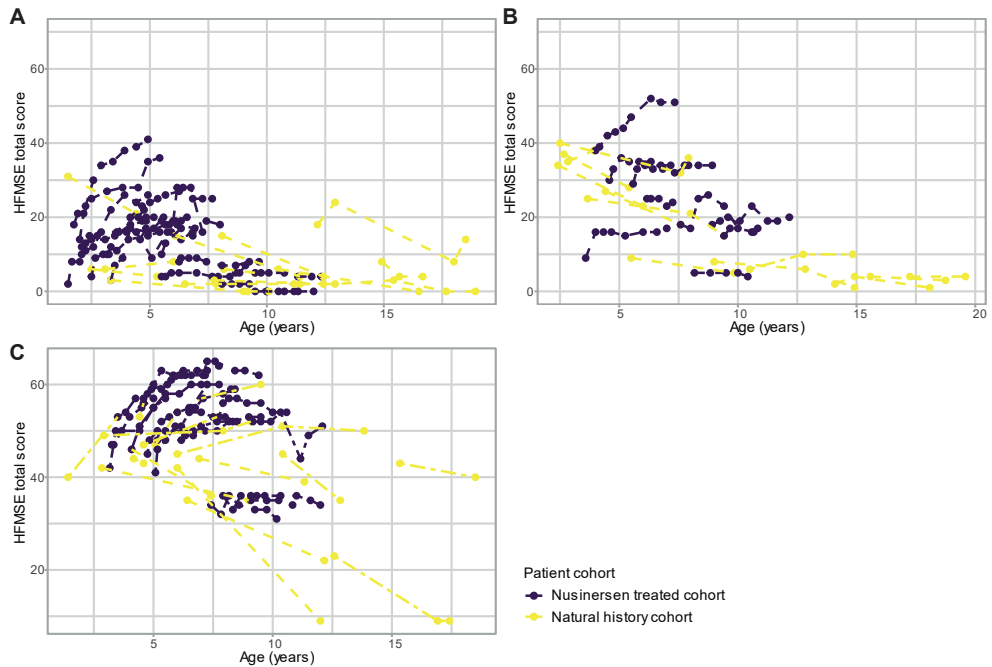
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Supplementary files chapter 2

Supplementary figure 1: Individual data of treated (with nusinersen) and non-treated patients with SMA



Legend Supplementary Figure 1:

A) Motor function trajectories of children with SMA type 2a without treatment (purple, $n=16$) and with nusinersen treatment (yellow, $n=20$). Showing a different disease trajectory between both groups: children with treatment show an increase of motor function where patients without treatment show a clear decline of motor function. B) Motor function trajectories of children with SMA type 2b without treatment (purple, $n=12$) and with nusinersen treatment (yellow, $n=10$). Showing a different disease trajectory between both groups: children with treatment show an increase followed by stabilization of motor function, where patients without treatment show a clear decline of motor function. C) Motor function trajectories of children with SMA type 3a without treatment (purple, $n=16$) and with nusinersen treatment (yellow, $n=16$). Showing a different disease trajectory between both groups: most children with treatment show an increase of motor function followed by a stabilization, where patients without treatment show a lower maximal motor function score (if there was an increase compared to baseline) followed by a decline of motor function. Children with a lower baseline HFMSE show stabilisation, while patients with the same age without treatment show a clear decline of motor function, which supports the idea that treatment with nusinersen at least gives stabilization of motor function.



Chapter 3

Inflammatory markers in cerebrospinal fluid of paediatric spinal muscular atrophy patients receiving nusinersen treatment

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Abstract

Introduction: Spinal muscular atrophy (SMA) is a progressive motor neuron disease with onset during infancy or early childhood. Recent therapeutic advances targeting the genetic defect that underlies SMA improved survival in patients with infantile onset SMA (type 1) and improved motor function in SMA type 1-3. The most commonly used therapy for SMA, the antisense oligonucleotide nusinersen, is delivered by repeated intrathecal injections. The long-term safety effects of this procedure, however, have not yet been investigated in detail. We here present case reports of three children with SMA in which routine laboratory investigation revealed increased leukocyte counts in cerebrospinal fluid (CSF) collected during the course of nusinersen treatment.

Methods: To further characterize this observation, we used a multiplex method to analyse a broad spectrum of inflammatory markers in the CSF of these patients.

Results: We found that interleukin-10 (IL10) was consistently elevated in CSF with increased leukocyte counts, but other inflammatory markers were not. Based on this analysis we selected 7 markers for further analysis in a cohort of 38 children with SMA and determined their expression during the course of nusinersen therapy. No consistent association was found between levels of inflammatory markers and the duration of nusinersen therapy in individual patients. However, monocyte chemo active protein 1 (MCP1 / CCL2) - a neuroprotective protein secreted by astrocytes and previously associated with SMA- levels increased over the course of nusinersen treatment, indicating a possible neuroprotective mechanism associated with nusinersen therapy.

Conclusion: In summary, our findings confirm that repeated intrathecal injections are safe and do not trigger unwanted immune responses.

Introduction

Hereditary proximal spinal muscular atrophy (SMA) is characterized by stalled early gross motor development and deterioration of muscle strength throughout life, including of respiratory and bulbar muscles (1). SMA is caused by deficiency of the survival motor neuron (SMN) protein due to the homozygous loss-of-function of the *survival motor neuron 1* gene (*SMN1*) (2). A point mutation in exon 7 of the highly homologous *SMN2* causes exclusion of exon 7 in the majority of *SMN2* mRNA, leading to a truncated protein with limited functionality (3, 4). A minority of *SMN2* mRNA transcripts, however, includes exon 7 and leads to the production of full-length SMN protein. As such, SMA severity is inversely correlated with *SMN2* copy number, although this correlation is incomplete and up to 40% of clinical variability cannot be explained by variation in *SMN2* copy number alone (5).

Understanding the mechanisms underlying exon 7 splicing in *SMN2* has led to the development of two *SMN2* splicing modifiers that have now been approved for the treatment of SMA. One of these drugs, nusinersen (Spinraza), is an antisense oligonucleotide (ASO) that increases *SMN2* exon 7 inclusion by binding to a sequence (ISS-N1) upstream of exon 7 (6). Although the long-term efficacy of nusinersen therapy will need to be further established in the coming years, an increasing number of post-marketing studies amongst multiple populations, age groups and SMA types now all indicate that nusinersen therapy leads to disease stabilisation or meaningful clinical improvements in the vast majority of SMA patients, as determined by motor function and development (see for example refs. (7-10)).

Nusinersen is an ASO that cannot pass the blood-brain barrier and therefore needs to be administered by repeated intrathecal injections. The need for repeated intrathecal injections at the scale and frequency required for nusinersen treatment represents a relatively novel concept in (paediatric) neurology. It is therefore important to implement routine, long-term monitoring of any adverse events that may be related to the procedure. The clinical trials that led to the approval indicated that the procedure was safe and well-tolerated (7, 8, 11, 12), and did not report side-effects other than those commonly associated with lumbar puncture (e.g., post-puncture headache). However, since the approval of nusinersen, specific, other adverse events have been reported, including communicating hydrocephalus (13) and aseptic meningitis (14). Although the incidence of these adverse reactions is unknown, they may indicate an inflammatory process of the meninges after nusinersen administration. Moreover, other groups have described so-called nusino-phages, macrophages with granules containing nusinersen (15-17), similarly pointing towards an ongoing immune response. Despite these observations, a systematic

investigation of the presence and levels of inflammatory markers over the course of nusinersen therapy has not yet been reported.

In our cohort of children with SMA patients receiving nusinersen therapy, we observed three patients with elevated leukocyte counts in CSF during treatment, without clear clinical signs of inflammation. This finding led us to systematically investigate the expression of a range of inflammatory markers in patient cerebrospinal fluid (CSF) in these patients using multiplex immunoassays. Based on an initial screen to determine which inflammatory markers could reliably be measured, we subsequently performed a larger-scale experiment in a cohort of 38 paediatric SMA patients to identify possible inflammatory markers associated with nusinersen therapy and, additionally, investigate their suitability as candidate biomarkers.

Materials and methods

Patients

All patients had been included previously in a prospective population-based cohort study on SMA in the Netherlands (18-20). Patient characteristics were collected during interviews with parents using standardized questionnaires and physical examination as described before (18-22). We distinguished patients as SMA types 1–3 based on age at disease onset and best of two acquired WHO motor milestones (i.e., sitting and walking independently), and further classified patients into SMA subtypes (1, 18, 20). In short, patients with type 1c achieve the ability to roll or lift their head in prone position, patients with type 2a learn to sit independently, while those with type 2b also learn to stand or take a few steps with support. Patients with type 3 learn to walk independently and have a disease onset before (type 3a) or after (type 3b) the age of three years (1, 18, 20). A genetic diagnosis of SMA and *SMN2* copy number was confirmed using multiplex ligation-dependent probe amplification (SALSA MLPA kit P021–B1, MRC-Holland) as described in detail previously (5).

CSF collection and multiplex immunoassay

Five millilitres of CSF was collected at each injection according at the time points indicated in the standard nusinersen treatment protocol, starting with loading doses at baseline (day zero, T0), day 14 (T1), day 28 and day 63, and followed by intrathecal injections every four months (T5 in this study was at 10 months after the start of therapy) (23). At each injection, 3 mL of CSF was sent for routine clinical laboratory analysis that included determination of blood cell counts, protein and glucose levels. Moreover, 2 mL of CSF was centrifuged at 1,000x *g* at 4 °C for 10 minutes, aliquoted and stored at -80 °C until analysis. Prior to multiplex immunoassay on the Luminex platform, samples were passed through a .22 µm

filter to remove debris. Multiplex analysis of 16 proteins was performed as described previously (24). Briefly, color-coded magnetic beads (Luminex) were conjugated to antibodies that had previously been validated to specifically detect the protein of interest. After incubating our CSF samples with color-coded, antibody-coated beads, a mix of biotinylated antibodies was used for detection of the analytes and fluorescence intensity was determined on a Flexmap 3D system (Luminex).

Experimental design

In this study we used a two-stage experimental design. In the first stage, as it was unclear which proteins could reliably be measured in CSF, we analysed CSF samples from patients with increased leukocyte counts and patients without increased leukocyte counts (matched for sex, age, SMA type, disease duration and remaining motor function) for a broad range of analytes. All analytes we included had previously been validated on our multiplexing platform (24) and that could thus be reliably and reproducibly quantified. We included proteins of which the expression is thought to be linked to the activity or regulation of key parts of the immune system including interleukin-1 beta (IL1B), IL3, IL6, IL10, IL12, IL13, IL17, IL18, and interferon gamma (IFNG) (25, 26). Also, we included proteins that had been previously linked to SMA, motor neuron function or the neuromuscular system including brain-derived neurotrophic factor (BDNF), FAS, vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNFA), angiopoietin-1 (ANG1), complement C5 alpha chain (C5a) and monocyte chemoattractant protein 1 (MCP1; also called C-C motif chemokine 2, CCL2) (27-33). For the second stage of our analysis, we selected 7 of the above proteins based on the results of the first stage experiment. We analysed these proteins at three different time points during the course of nusinersen treatment (T0, T1 and T5) in 38 patients for whom we had samples from these time points available. Graphs were generated in Rstudio (version 1.3.959) using ggplot 2. Statistical tests were performed in Graphpad Prism (version 9.3), by comparing the means of multiple groups with a one-way ANOVA followed by post hoc Tukey t-test with correction for multiple testing.

Ethical approval

Patients included in this study participate in an ongoing prospective population-based cohort study on SMA in the Netherlands, approved by the UMC Utrecht Medical Ethical Committee (No. 09-307/NL29692.041.09). We obtained written and oral informed consent from both parents of each patient.

Results

Rare observations of elevated leukocyte count in paediatric SMA patients

The cohort of SMA patients receiving nusinersen therapy in the Netherlands was initially limited to children up to the age of 9.5 years and consisted of 72 patients. From this cohort, we noticed elevated leukocyte counts in the CSF of three children during routine laboratory monitoring. Other variables that were monitored included CSF protein, glucose and erythrocyte levels and were generally all within the normal range. The first child started treatment presymptomatically (four days after birth). This child has two *SMN2* copies and a baseline CHOP INTEND score of 43. Elevated leukocyte counts were observed in the first three CSF samples, and elevated protein levels in the first four CSF samples (sample taken prior to injection 1: leukocytes $7 \times 10^6/L$, 70% monocytes, 25% lymphocytes; protein 1.91 g/L; injection 2: leukocytes $9 \times 10^6/L$, 77% lymphocytes, 16% monocytes; protein 1.52 g/L; injection 3: leukocytes $6 \times 10^6/L$, 53% lymphocytes -within range-, 23% monocytes, 9% macrophages; protein 1.05 g/L; injection 4: leukocytes $2 \times 10^6/L$ -within range-; protein 0.77 g/L). There were no clinical symptoms accompanying these laboratory findings. After the fourth injection, no abnormalities were found in the CSF of this patient again. Later during treatment, the parents have occasionally reported increased body temperature after nusinersen injection, unrelated to elevated leukocyte counts. The second child started treatment at the age of 30 months, has SMA type 2a with three *SMN2* copies and a baseline HFMSE score of 4. In total this child has now received 12 injections without complications. Elevated CSF leukocyte counts ($20 \times 10^6/L$; 75% lymphocytes, 19% monocytes) was observed once, prior to the fifth injection. The CSF was colourless. Other variables were within normal range. The third child started treatment at the age of 50 months, has SMA type 1c with three *SMN2* copies and a baseline CHOP INTEND of 42. In total this child has had 13 injections, without complications. We observed elevated leukocyte levels in the CSF once ($6 \times 10^6/L$; 86% lymphocytes, 13% monocytes), prior to the sixth injection. The CSF was colourless and erythrocyte and protein levels were within the normal range (0.22 g/L).

Other than mildly elevated body temperature in the first child, no clinical signs associated with inflammation or immune response were reported for these patients. Also, no chronic leucocytosis was observed in these patients (increased leukocytes were present during the first 4 weeks of nusinersen therapy in patient 1). Although it is therefore likely that the clinical effect of increased leukocytes in CSF during nusinersen therapy is limited, we decided to study in more detail if this phenomenon was associated with the activation of specific parts of the immune system as this has not been systematically characterised before.

Increased interleukin-10 (IL10) expression is associated with increased leukocyte count

As generally protein makes up only a small proportion of CSF (on average 0.2 gram per litre of CSF) and reference values available for CSF cytokines have mainly been reported based on adult cohorts, we first asked what proteins could be reliably detected in the CSF of children with SMA. For this, we used a multiplex assay based on the Luminex platform, as this allowed us to make efficient use of scarce patient material while reliably detecting proteins at a high sensitivity using reproducible assays that have been validated previously (see materials and methods). The human immune response is regulated through a complex interplay of many (extracellular) elements, including chemokines, cytokines, growth factors, peptides and complement factors. We here tried to cover a broad range of the human immune response by selecting analytes that are known to be markers or regulators of key elements of the immune system. Moreover, we included proteins that were part of pathways that had previously been linked to SMA or motor neuron function. We analysed CSF samples from time points at which elevated leukocytes counts were observed and compared those to samples taken from the same patients at baseline and after leukocyte counts were back within normal range. Moreover, we analysed CSF samples from age-matched patients from the same time points but without CSF anomalies. The results from this initial screen are presented in **table 1**. First, we looked for associations between the expression of inflammatory markers and the of elevated CSF leukocytes. Interleukin-10 (IL10) was consistently elevated in each sample in which increased leukocyte levels were found but could not be detected in any of the other samples. Although patient 2 showed higher IL6 and IFNG levels when elevated leukocyte counts were reported, we did not observe a further consistent association between increased leukocyte levels and other proteins included in our analysis. Second, because protein levels in CSF are low, we found that most other proteins included in our analysis were below the detection limit of the Luminex platform or could only be detected in a limited number of samples. However, MCP1 (CCL2), C5A and ANG1 could reliably and consistently be detected in almost all samples and were therefore selected for further analysis in a larger cohort of SMA patients.

MCP1 (CCL2) expression increases during nusinersen treatment

We included all children with SMA who started treatment with nusinersen between May 2017 and July 2019 and for whom CSF samples were available at baseline (T0), two weeks after the start of therapy (T1) and 10 months after starting treatment (T5), providing a total cohort of 38 patients for these analyses. We chose these timepoints to capture key phases of nusinersen: T0 samples may possibly contain SMA-dependent, treatment-unrelated immunological markers; whereas T1 and T5, respectively, respectively contain acute or chronic immunological responses to nusinersen treatment or repeated intrathecal

injections. The patient characteristics of the patients included in this analysis are summarized in **table 2**. We again used a multiplex assay based on the Luminex platform to determine proteins levels of MCP1, C5A and ANG1 in 114 CSF samples. We also included IL1B, IL6, IL10 and TNFA as a representative sample of inflammatory markers we were able to measure in our initial screen. We included analysis of the protein RANTES as a quality control for possible cell contamination in our samples, in particular contamination with erythrocytes. Based on the presence of detectable levels of RANTES in 5 samples, we excluded those from further analysis, leaving 109 results from CSF samples for further analysis. The results from this experiment are presented in **table 3**. Further association between inflammatory markers (IL1B, IL6, IL10, TNFA) and nusinersen therapy was also absent in this larger cohort.

Table 1. Screen for detectable cytokines and other proteins in SMA patient CSF

Patient	Description	IL10	IL1B	IL6	MCP1	C5A	ANG1				
1	Elevated leukocytes (after 1st injection)	3.26	7.72	ND	1314.75	468.21	41.38				
2	Elevated leukocytes (after 4th injection)	34.06	7.49	327.91	764.58	175.48	56.7				
3	Elevated leukocytes (after 5th injection)	5.83	7.07	4.87	192.73	39.06	69.91				
Average baseline		ND	5.90	2.60	1227.47	221.90	100.27				
(total n=3)	Range (min - max)	--	4.56 - 7.39	--	369.95 - 2909.38	9.05 - 644.53	82.71 - 121.53				
	ND (not detected) in n samples	3	--	2	--	--	--				
Average control		ND	6.48	4.74	538.10	26.68	90.03				
(total n=8)	Range (min - max)	--	4.56 - 10.92	2.53 - 6.95	372.7 - 856.38	6.41 - 99.15	52.04 - 138.92				
	ND (not detected) in n samples	8	--	6	--	--	--				
Patient	TNFA	IL12	IL13	IL18	VEGF	FAS	IL17	IL3	IFNG	BDNF	
1	ND	ND	2.62	18.31	9.92	86.04	ND	73.49	ND	ND	
2	1.79	11.95	3.16	1.91	4.41	61.18	ND	65.71	2.89	ND	
3	2.11	15.32	2.76	1.56	4.81	65.93	ND	103.69	ND	ND	
Average baseline		1.69	13.64	2.87	25.25	8.65	70.83	96.27	0.94	ND	ND
(total n=3)	1.42 - 2.07	10.43 - 16.06	1.08 - 4.79	-	3.78 - 17.5	37.96 - 115.52	--	46.72 - 145.82	--	--	--
	--	--	--	2	--	--	--	1	2	3	3
Average control		1.54	10.75	3.45	2.73	3.59	52.80	55.28	2.86	--	--
(total n=8)	1.26 - 1.99	5.74 - 13.05	0.27 - 6.05	2.56 - 3.42	2.62 - 6.95	32.16 - 74.52	--	29.6 - 85.51	--	--	--
1	3	1	5	--	--	--	7	3	--	--	8

Table 1. Screen to determine detectable cytokines and other proteins in SMA patient CSF.

CSF samples from patients with increased leukocyte counts (patients 1, 2 and 3) were analysed for 16 cytokines and proteins to determine what samples could reliably be measured. For each patient, baseline control samples and age-matched controls were included in the analysis. Because not all analytes could be measured in all samples, the table indicates the number of samples for which this was not possible (ND; not detected). The average values for each analyte and the range (min – max) are presented.

IL: interleukin (1N, 3, 6, 10, 12, 13, 17, 18); MCP1: monocyte chemoattractant protein 1 (also known as C-C motif chemokine 2 or CCL2); C5A: complement C5 alpha chain; ANG-1: angiopoietin-1; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; FAS: Fas cell surface death receptor; BDNF: brain derived neurotrophic factor; IFNG: interferon gamma.

Table 2. Patient characteristics

	All patients (n=38)	SMA type 1 (n=4)	SMA type 2 (n=22)	SMA type 3 (n=12)
Male sex n (%)	22 (58)	4 (100)	11 (50)	7 (58)
Age disease onset	12 (0-36)	3.5 (0-13)	9 (2.5-18)	19 (12-36)
Disease duration start therapy	47 (2-108)	24 (2-101)	47.5 (12-108)	47 (9-95)
Age at first dose	59 (2-115)	27.5 (2-114)	55.5 (21-115)	68 (39-113)
SMN2 copy number n (%)				
2	3 (8)	3 (50)	0	0
3	27 (71)	1 (50)	22 (100)	4 (33)
4	8 (19)	0 (0)	0	8 (67)
CHOP INTEND at baseline	33 (20-46)	33 (20-46)	n.a.	n.a.
HFMSE at baseline	19.5 (2-56)	n.a.	13 (2-38)	47.5 (34-56)

Table 2. Patient characteristics

A cohort of 38 patients for which baseline, T1 and T5 CSF samples were available were included for further analyses. N= number; n.a. = not applicable; SMN2= survival motor neuron 2; CHOP INTEND= Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE= Hammersmith Functional Motor Scale Expanded. All ages and disease duration are given in months, unless otherwise stated. All outcomes are given in median (range) unless otherwise stated.

Table 3. Protein expression in CSF per timepoint and per SMA type

Baseline (detected in <i>n</i> samples)				After 1st injection (detected in <i>n</i> samples)				After 5th injection (detected in <i>n</i> samples)				
Per SMA type (<i>n</i>)				Per SMA type (<i>n</i>)				Per SMA type (<i>n</i>)				
IL1B (95% CI)	All SMA (37)	1 (3)	2 (22)	3 (12)	All SMA (35)	1 (3)	2 (21)	3 (11)	All SMA (37)	1 (4)	2 (21)	3 (12)
	1.51 (1.31 – 1.71)	2.06	1.51	1.41	1.62 (0.94 – 2.29)	1.53	1.92	1.4	1.58 (1.28 – 1.88)	1.33	1.66	1.75
	(8)	(1)	(2)	(5)	(3)	(1)	(1)	(1)	(11)	(3)	(7)	(1)
IL6	6.34	--	6.34	--	--	--	--	--	11.51	--	11.51	--
	(1)	--	(1)	--	(0)	--	--	--	(1)	--	(1)	--
IL10	2.55	--	--	2.55	--	--	--	--	--	--	--	--
	(1)	--	--	(1)	(0)	--	--	--	(0)	--	--	--
TNFA	2.75 (-1.58 – 7.09)	4.05	1.46	--	2.07 (-0.80 – 4.95)	2.34	--	1.55	1.35 (1.24 – 1.46)	1.26	1.34	1.38
	(4)	(2)	(2)	--	(3)	(2)	--	(1)	(9)	(1)	(5)	(3)
MCP1	756.6 (668.2 – 845.1)	1123.0	737.9	699.3	904.5 (705.9 - 1103)	2078.5	829.8	726.8	1001 (887.4 – 1115)	1176.8	1001.2	941.9
	(37)	(3)	(22)	(12)	(35)	(3)	(21)	(11)	(37)	(4)	(21)	(12)
ANG1	33.17 (27.52 – 38.81)	26.67	40.32	21.28	33.66 (27.16 – 40.17)	12.98	38.98	23.55	26.81 (22.08 – 31.54)	36.75	30.04	15.93
	(35)	(3)	(21)	(11)	(31)	(1)	(21)	(9)	(33)	(3)	(21)	(9)
C5A	44.64 (30.08 – 59.19)	123.78	32.33	47.41	41.83 (26.96 – 56.71)	146.21	31.30	33.47	32.24 (27.13 – 37.36)	51.54	27.55	34.01
	(37)	(3)	(24)	(12)	(35)	(3)	(21)	(11)	(37)	(4)	(21)	(12)

Table 3. Protein expression in CSF per timepoint and per SMA type.

Overview of protein expression levels in 38 SMA patients. Initially, 114 CSF samples were analysed, after quality control 5 were excluded from further analysis. The average (mean) for all SMA patients at each time point is presented with the 95% confidence interval. As not all analytes reached detectable levels in each sample, the number of samples on which each average value is based is presented below the average between brackets. IL: interleukin (IL1B, IL6, IL10); MCP1: monocyte chemoattractant protein 1; CSA: complement C5 alpha chain; ANG1: angiopoietin-1; TNF: tumor necrosis factor

The expression of MCP1, ANG1 and C5A for each of the time points included in our analysis is shown in **figure 1**. For ANG1, levels were highly variable, and we did not observe an association between ANG1 levels and treatment timepoints or SMA types (**figure 1A**). For C5A and MCP1 (**figure 1B-C**), we noticed particularly high protein levels in the youngest patients included in our cohort, that decreased quickly after therapy start. Because we had limited availability of baseline CSF samples for type 1 patients in our centre, we were not able to analyse this observation in more detail. It seems to represent a similar pattern of high CSF protein levels shortly after birth, as has been previously observed in studies of CSF from SMA patients (see e.g. (34)). Because we were able to include more type 2 (n=22) and type 3 (n=12) patients in our study, we analysed the pattern in which the expression of MCP1 and C5A changed over time with treatment in more detail (**figure 2**). When normalising the expression of these proteins to baseline levels, to control for variability in expression between patients at the start of therapy, we observed that MCP1 expression showed an increased trend over time with treatment (**figure. 2A-B**). For patients with type 3, this increase was significant compared to baseline levels (**figure 2B**; T0: 699.3 pg/mL, T5: 941.9 pg/mL, $P = 0.0014$). Compared to MCP1, C5A levels remained stable over time with treatment, and we did not observe significant changes (**figure 2C-D**). Finally, we investigated if increased MCP1 levels over the course of nusinersen treatment correlated with other clinical characteristics of the patients included in our analysis. However, we did not identify a correlation between MCP1 levels and age at disease onset, delay of therapy start, HFMSE score or *SMN2* copy number.

Figure 1. MCP1, ANG1 and C5A in CSF in individual patients treated with nusinersen

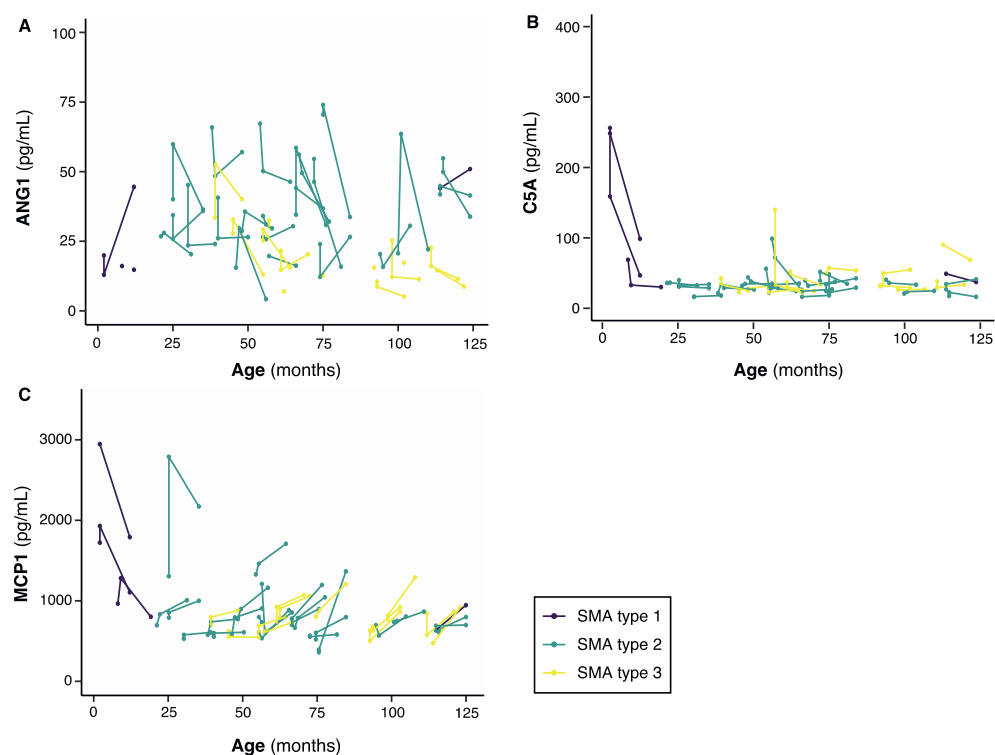


Figure 1. Legend

ANG1 (A), C5A (B) and MCP1 (C) expression levels were measured using multiplex immunoassays in patients with SMA type 1 ($n=4$, dark blue), type 2 ($n=22$, green) and type 3 ($n=12$, yellow). For each patient, three time points were included in our analysis (baseline, 14 days after the first injection, and after 10 months of therapy). Although protein levels were measured at 3 time points for each patient, after quality control 109 samples were included for final analysis and therefore for some patients for some proteins only 1 or 2 data points could be included in this figure.

Figure 2. Change from baseline in cytokines MCP1 and C5a in CSF of patients treated with nusinersen

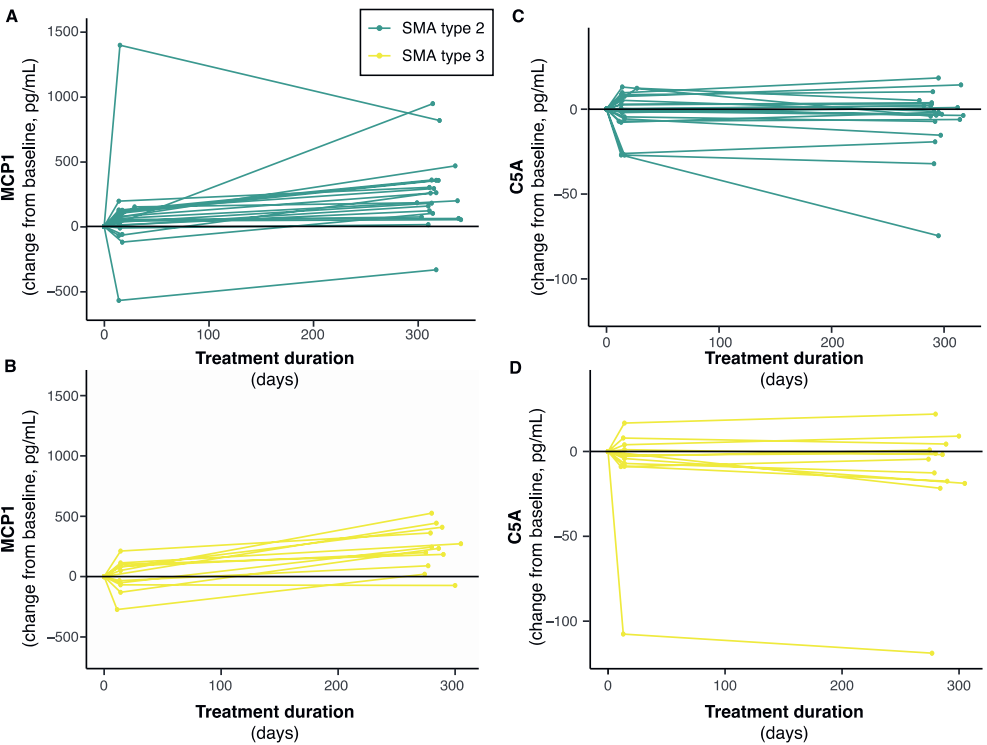


Figure 2. Legend

To illustrate the development of MCP1 (A, B) and C5a (C, D) expression profiles over time, protein expression values were plotted as change compared to baseline measurements. This illustrates that MCP1 expression in type 3 patients (A) increased over time compared to baseline in all but one patient. A similar trend is visible in type 2 patients for MCP1 (B), but is absent in C5a (C, D).

Discussion

Our knowledge about the long-term effect and safety of repeated intrathecal injections to treat neurological diseases is still limited. At the same time, the number of genetic therapies for neurological diseases in advanced stages of clinical development and requiring intrathecal delivery is rapidly increasing (35). Because SMA is at the forefront of these developments, and we occasionally noticed elevated CSF leukocytes in the cohort of children with SMA receiving nusinersen, we decided to focus on characterising expression profiles of inflammatory markers in response to repeated intrathecal injections. Our results further confirm that repeated intrathecal delivery of gene-targeting therapies is safe, also when focusing on markers of inflammation.

IL10 was the only cytokine included in our analyses that was consistently upregulated in response to increased leukocyte counts. IL10 is a cytokine with an anti-inflammatory function and is expressed by different cells from the adaptive and innate immune system (36, 37). Previous work suggests that IL10 is required to prevent host damage after infection or to inhibit an immune response (36). Its exact *in vivo* role remains incompletely understood, but it has been suggested that IL10 downregulates the production of other, pro-inflammatory cytokines (36, 37) and can protect against tissue damage caused by inflammatory diseases of the CNS (37). The anti-inflammatory function of IL10 is a possible explanation of the association between elevated leukocytes counts in the CSF and increased IL10 that we observe in our current study. As such, it may contribute to our observation that increased leukocyte counts did not lead to infection or inflammation. Of note, the increased leukocyte counts observed in our studies seemed to be mainly lymphoid, although the youngest patient displayed a shift from monocytic to a lymphoid reaction. Unfortunately, we did not have access to a larger number of CSF samples for this patient to further detail the cytokines that may be regulating this change in CSF leukocyte counts.

In the publication reporting the results of the phase I clinical trial of nusinersen, the analysis of cytokine levels in CSF (IL6, TNFA, MCP1) was mentioned (11). This study was performed in small numbers of SMA patients receiving lower doses of nusinersen and found no abnormalities for these cytokines at day 7 and 28 post-dose, although no further details were provided (11). Importantly, changes in e.g., MCP1 expression in our studies were only measurable after longer treatment durations, which illustrates that it may be important to measure molecular markers for longer follow-up intervals. Furthermore, several other studies have previously reported typical laboratory values (e.g., protein levels, erythrocyte counts, glucose levels) for CSF samples from adult and adolescent patients with SMA (38-41). These studies reported an overall increase in protein levels over the course of

nusinersen therapy, which we did not generally observe in our study. However, in the youngest patients included in our analysis (SMA type 1) we noticed higher overall CSF protein, and also higher levels of specific proteins (e.g., MCP1 and C5A) levels at the start of treatment, that decreased over time. Interestingly, protein levels in CSF have previously been found to be increased in young infants (up to 6 months) compared to older children and adolescents, independent of underlying pathology (42). Possible explanations for increased protein levels in young infants are birth trauma, an immature blood-brain barrier or different CSF flow rate. This observation is an example of our limited knowledge about reference values for CSF of (very) young children. In addition to basic reference values such as leukocyte counts and protein levels, reference values for specific proteins (including C5A, MCP1 and ANG1) have not been reported for the age groups investigated in our current study. This warrants care in interpreting results, as many studies, including our current study, reported results on CSF analyses of SMA patients only, as dedicated control groups are not often available.

Other than for diagnostic purposes, CSF samples were previously not regularly obtained and collected from children. With the arrival of genetic therapies that need intrathecal delivery also comes the possibility to readily obtain CSF without extra invasive procedures to the children receiving nusinersen therapy. This now highlights CSF as a source for determining longitudinal molecular markers of disease progression and therapy efficacy. This is especially relevant for nusinersen treatment, as the long-term clinical efficacy, safety and cost-effectiveness remain unclear. Indeed, a growing number of previous studies have reported findings on both specific and unbiased approaches to determine and identify CSF-derived biomarkers for monitoring treatment efficacy. Many groups have focused on various forms of neurofilament as a biomarker for SMA severity and treatment response (e.g., (34, 39, 43-47)). Especially children with SMA type 1 show very high neurofilament levels, that sharply decrease with treatment (39, 43, 47). It should be noted, however, that neurofilament levels also decrease with age and that differences in neurofilament levels between treated and untreated patients in older SMA patients (e.g., type 2 and type 3) is less pronounced. Moreover, recent studies have used unbiased approaches to determine on a large scale what protein (38), extracellular RNAs and micro RNAs (miRNAs) could be measured in CSF obtained from SMA patients (48). These approaches highlighted e.g., miR-146a, a known miRNA associated with astrocyte function in SMA. Interestingly, in our current paper, we identified MCP1 as a promising candidate for monitoring nusinersen efficacy, as it increased significantly over time in nusinersen-treated type 2 and type 3 patients. MCP1 levels did not correlate with clinical outcomes, including motor scale improvement in these patients, but we cannot exclude that this is partially due to subtle phenotypic improvements that may

currently not be adequately captured by existing motor scales. MCP1 has been linked to SMA previously, when it was shown to be secreted by astrocytes and thereby protect against degeneration of motor neurons (32), possibly by interacting with an axonal isoform of the SMN protein (33). Our results may therefore reflect a nusinersen-induced improvement of astrocyte function in SMA, which may prove an interesting insight both for biomarker research and further understanding of the role of astrocytes in SMA pathogenesis (49).

Conclusions

We confirm that repeated intrathecal injections of nusinersen to treat children with SMA are well-tolerated and safe, also when investigating markers of inflammation. In rare patients with elevated leukocyte numbers, we were able to measure IL10, suggesting that IL10 may be a promising candidate to monitor immune response to intrathecal injections in patients for which this is relevant. MCP1 (CCL2) showed a modest but consistent increase with treatment over time, especially in type 3 children, and may therefore be an interesting biomarker candidate for future research.

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Chapter 4

The reimbursement for expensive medicines:

stakeholder perspectives on the SMA medicine nusinersen and the Dutch Coverage Lock policy

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Abstract

Background: The reimbursement for expensive medicines poses a growing challenge to healthcare worldwide. In order to increase its control over the costs of medicines, the Dutch government introduced the Coverage Lock (CL) policy in 2015. The CL postpones decisions regarding reimbursement of expensive medicines until detailed advice on i.e., cost-effectiveness has been given. The CL has been in place for six years, has raised many questions and concerns, but currently, no evaluation is known to the authors. A better understanding of the effects of the CL on all stakeholders involved may contribute to reflections on the CL process and help find ways to improve it. An evaluation of Dutch policy will also be relevant for other countries that aim to optimize reimbursement procedures for expensive treatments. To perform this evaluation, we focused on the CL procedure for the medicine nusinersen. Nusinersen is the first treatment for spinal muscular atrophy (SMA). Following EMA approval in May 2017, it was placed in the CL. The analysis of cost-effectiveness and added therapeutic value resulted in an advice for reimbursement limited to children younger than 9.5 years at the start of treatment; this was implemented from August 2018 onwards.

Methods: Qualitative stakeholder perspective analysis of the CL procedure focusing on nusinersen with 15 stakeholders.

Results: Stakeholders raised key issues of the CL based on their experience with nusinersen: emotional impact of the CL, duration of the CL procedure, appropriateness of the CL procedure for different types of medicines, transparency of the CL, a wish for patient-centred decision-making and the lack of uniformity of access to expensive treatments.

Discussion: Stakeholders supported measures to control healthcare expenses and to ensure reasonable pricing. They considered the delay in access to therapies and lack of procedural transparency to be the main challenges to the CL. Stakeholders also agreed that the interests of patients deserve more attention in the practical implementation of the reimbursement decision. Stakeholders suggested a number of adjustments to improve the CL, such as a faster start with conditional reimbursement programs to ensure access and intensify European collaboration to speed up the assessment of the medicine.

Background

A relatively new challenge for solidarity-based healthcare systems is to incorporate very expensive medicines for rare diseases (1-6). In the Dutch healthcare system, based on solidarity, citizens pay taxes and mandatory health insurance premiums to finance accessible healthcare for everyone. However, the growth in the number of medicines for rare diseases requires an increasing percentage of the healthcare budget, which risks crowding out other types of healthcare (2, 3, 7-10).

Governments need policy-instruments to guide decisions on which medicines should be reimbursed. The Coverage Lock (CL) is an example of a policy-instrument that was implemented in the Netherlands in 2015 (11). The purpose of the CL is to evaluate new, expensive medicines, that are used in hospitals (inpatient medicines) before inclusion in the basic health insurance. Price negotiations are also part of the CL. New medicines that exceed a certain budget limit – a budget impact of more than €40,000,000 in total or more than €50,000 per patient resulting in total costs exceeding €10,000,000 – are placed in the CL directly after market authorization by the European Medicine Agency (EMA). In the CL the new medicines undergo an additional scientific assessment and appraisal by the Dutch Healthcare Institute (DHI) based on four criteria: efficacy, cost-effectiveness, necessity and feasibility (financial and practical). This results in an advice to the minister of Health on the reimbursement and pricing. Subsequently, the ministry of Health may decide to start price negotiations with the pharmaceutical company involved (11). The CL postpones reimbursement, and with that, access to treatment, until these steps have been finalized and a final decision has been made by the Minister for Health. Access to treatment during the CL is sometimes possible, but only by participating in a clinical trial (if available) or a compassionate use program, financed by the manufacturer.

The CL was used in 2017 for the first available treatment, nusinersen, for hereditary proximal spinal muscular atrophy (SMA). SMA is an autosomal recessive neuromuscular disorder caused by the loss-of-function of the survival motor neuron 1 (*SMN1*) gene. With an incidence of 1:6000-1:10,000 new-borns, it is a rare disease but still one of the more common genetic disorders that affects infants and young children. The most common and severe form, SMA type 1, causes respiratory failure in the first years of life, whilst the slightly milder chronic forms, types 2 and 3, cause stalled gross motor development followed by gradual deterioration in muscle strength and severe levels of disability (12-14). The efficacy of nusinersen was demonstrated by two small studies on the basis of which the EMA granted market access in May 2017 (15, 16). Nusinersen has a list price of €499,800 in the first year for six injections, followed by €249,900 for three injections per year per patient.

In the Netherlands, the CL procedure for nusinersen lasted 15 months (May 2017-August 2018) and resulted in a reimbursement arrangement for children with SMA who started treatment before the age of 9.5 years, thus excluding older children and adults, in contrast to all neighbouring countries (Germany, Belgium, United Kingdom). The duration of the procedure and the medicine being available through a special arrangement for only a very small group of children caused concerns for parents of other children with SMA and older patients. When the final reimbursement was arranged and an age limit was set, it split families with two children with SMA in half. These cases generated media attention for the CL and gave rise to a public debate (see e.g., (17-19)). The case of nusinersen was a high-profile case and therefore interesting to evaluate the CL. As far as we know, the CL has not been evaluated since its introduction in 2015. Because of the increasing use of the CL due to the growing number of expensive treatments, we decided to evaluate the experiences and perceptions of stakeholders in the CL procedure of nusinersen in the Netherlands. An evaluation of Dutch CL policy is also relevant for other countries that aim to optimize reimbursement procedures for expensive treatments (5, 20).

Methods

Identification and inclusion of participants

In order to better understand similarities and differences in the experience and perception of stakeholders regarding the exact same procedure, we screened participants in the CL procedure for nusinersen (FS, WLP, GvT). We used purposive sampling to find parties and persons representing these parties who were specifically involved in the nusinersen dossier and are well known with the CL policy (21). Parents of patients were contacted through the SMA centre of expertise in Utrecht.

All parties involved in a CL procedure were represented by the selected stakeholders. The identified stakeholders were contacted through email and after obtaining informed consent, an interview was scheduled. All invited participants accepted to participate. Informed consent was validated and reconfirmed orally at the start of the interview and recorded.

Interviews and data collection

We conducted semi-structured interviews. The interview guide was designed by two authors (MO, SF) and evaluated by two other authors (GT, FS). It consists of questions about the role participants had in the procedure, their experiences, the perceived necessity and strong and weak elements of the procedure (see supplementary file 1 and 2). After carrying out three interviews, we analysed the transcripts to ensure the interview guide fitted the research aim (MO, SF, FS, GT). No adjustments were made. The interviews were conducted

by three authors (MO, SF, FS), one of whom (FS) was present at all interviews to ensure continuity. Data collection was stopped when respondents from all stakeholder perspectives had been included. Thematic saturation was reached after interviewing 15 stakeholders. The interviews were transcribed verbatim for further data analysis by one of two authors (MO, SF) or a professional organisation (uitgetypt.nl).

Data analysis

The first nine transcripts were independently coded by two authors (MO, SF) using Nvivo 12. The code-tree was constructed by inductive coding. Two other authors (MZ, FS) (re-)read the transcripts and adjusted the code-tree. Using the adjusted codes, all interviews were re-coded by one author (FS) and randomly checked by two authors (MZ, GT). Thematic analysis followed after comparison across the interviews and the identification of higher order themes (22). The stakeholders were divided into three groups representing a patient, clinical and policy perspective. The patient perspective consisted of parents of young SMA patients and a representative from a patient organization. The clinical perspective consisted of caregivers involved in the treatment of SMA patients in the Netherlands. The policy perspective consisted of stakeholders from different organizations, governmental, manufacturer and healthcare insurers point of view. If views within one of the perspectives differs, we make this clear in the result section.

Themes that were common to these three perspectives were identified as the key issues of the CL by two authors (MZ, FS) and discussed with four other authors (JD, WP, GT, RG). After the first analysis we organised an online stakeholder meeting to present the results and verify the themes with the stakeholders.

Ethical approval

According to Dutch law, interview studies are exempt from review by a Medical Research Ethics Committee (MREC) in case the questions are non-invasive cause no potential harm for participants. The MREC METC Utrecht (currently NedMec) confirmed this in a decision (nr. 20/696) on 11 November 2020.

Results

We conducted 13 interviews involving 15 respondents between November 2020 and April 2021. Due to COVID-19 restrictions, all interviews were conducted online and lasted 27-75 minutes. **Table 1** presents characteristics of the stakeholders. The stakeholder meeting to verify and confirm the results was attended by six stakeholders. The themes described below were shared and confirmed by the attendees. No new themes were added.

Overall, stakeholders acknowledged that healthcare expenses have to be controlled; most participants agreed that the CL might be an effective way of doing this and thus might contribute to affordable care. Further experiences and perceptions from stakeholders can be traced back to six overarching themes described below (for illustrative quotes see **table 2**).

Table 1. Stakeholder characteristics

Patient perspective
5 interviews:
4 with parents of patients with SMA
1 with a representative of the patient organisation
Clinical perspective
3 interviews:
2 with nurses involved in SMA treatment in the SMA Centre of Expertise in Utrecht
1 with a physician involved in SMA treatment in the SMA Centre of Expertise in Utrecht
Policy perspective
5 interviews: 3 with representatives of the governmental organisations involved (5 persons, Ministry of Public Health and Sports and the Dutch Healthcare Institute)
1 with representative of the pharmaceutical company involved (Biogen)
1 with a representative of one of the largest health insurance companies (Zilveren Kruis)

Emotional impact of the CL on stakeholders

Clinicians and patient representatives described their experience with the CL primarily in terms of emotional impact. Feelings of uncertainty, powerlessness and unfairness were mentioned by parents. They experienced the lengthy procedure as nerve-racking and lived between hope and fear (Q1, Table 2). Not being able to influence the procedure contributed to their feeling of powerlessness. Some parents mentioned they had been thinking of emigrating to another country to obtain access to treatment for their (severely) affected children (Q2, **table 2**). Parents whose children eventually received reimbursement for the treatment found it difficult to feel happy and relieved. They sympathised with parents and their children who had the same desperate unmet need but who were too old.

Feelings of unfairness were mentioned by parents and clinicians regarding the age limit of 9.5 years in the reimbursement arrangement. In some families, a younger child had access

while an older sibling did not. Clinicians and parents experienced this as harsh and difficult to understand.

Clinicians felt frustrated about the age limit in the reimbursement arrangement, which they found to be incomprehensible and highly theoretical. This feeling was further aggravated by the internal conflict of knowing that treatment is available but not being able to prescribe it (Q3, **table 2**). Several patient representatives described a similar experience.

Policymakers had the impression that patients or their parents had amplified expectations of the efficacy of the treatment based on examples found on social media. They thought that these high expectations fuelled the frustration of patients or their parents about the delay in access to treatment.

Duration of the CL procedure

Participants from all perspectives mentioned the duration of the decision-making as one of the key issues of the CL; it takes too long. A time-consuming procedure like the CL was considered to be undesirable in general, but certainly when it involves assessing a treatment for a progressive disease like SMA that affects children (Q4, **table 2**). Clinicians mentioned that for a child aged 1.5 years, having to wait almost 1.5 years before reimbursement is arranged, is disproportionately long. Clinicians explained that this experience with nusinersen causes uncertainty among patients and themselves about the duration of future CL procedures for SMA-treatments.

Stakeholders from all perspectives perceived the procedure to be thorough. One governmental policymaker emphasized that acceleration of the procedure in the future should not be at the expense of comprising the thoroughness and precision of the assessment.

CL procedure is not appropriate for all types of medicines

Policymakers and patient representatives explained that the EMA and the assessors in the CL procedures differ with regard to the level of unpublished data acceptable for efficacy assessment. They mentioned that the EMA accepts unpublished efficacy data for the assessment in the case of orphan medicines. They explained this is done to accelerate authorized market access, as was the case with nusinersen (Q5, **table 2**). They also stated that unpublished data have limited and relative weight in the CL; published data are required for the efficacy assessment. To avoid a delay in the CL assessment, participants from all perspectives agree that the CL should also accept unpublished data on efficacy of orphan medicines.

Patient representatives added that the methodology of cost-effectiveness, i.e., Quality Adjusted Life Years (QALYs), is rigid and less suitable for evaluating a medicine like nusinersen because this approach may undervalue effects of nusinersen on the quality of life and inflate the negative cost-effectiveness ratio (Q6, **table 2**).

Transparency of the CL

Some parents felt there was a lack of transparency; they indicated that they did not know exactly what the CL entails nor what happens behind the scenes (Q7, **table 2**). A clinician had the same experience: it was not clear who is involved in the CL nor how healthcare provision is ensured during and after the CL. Policymakers from outside the government expressed a lack of clarity about what exactly is expected of the parties involved in the CL and at what stage. They mentioned that there is no overview of what the procedure looks like, the milestones of the CL or the time it takes (Q8, **table 2**). As a result, they felt that it is impossible to hold each other accountable for carrying out tasks in the CL.

Stakeholders from all perspectives mentioned that medicine prices, not only nusinersen but other medicines too, are not transparent after the CL. This made them question how effective the CL is in cost management.

Some patient representatives attended the final public CL meeting on nusinersen and perceived this to be important for transparency. Sharing the assessment reports was considered to be an indication of transparency by one clinician. Some participants from the policy perspective, involved in governmental organizations, emphasised that they tried to maintain transparency by updating the patient organisation and families and streamlined information during the procedure.

A wish for patient-centred decision-making

Patient representatives and clinicians in particular mentioned the lack of the human dimension in decision-making about the CL (Q9, **table 2**). Patient representatives experienced that the decision-makers had no idea of the impact of decisions on families and that insufficient attention is paid to the interest of the patient or ethical considerations. This experience was confirmed by clinicians. They emphasised the unworkable practical application of CL decisions and attributed this to the focus on cost control in the CL (Q10, **table 2**).

Patient representatives and clinicians expressed a wish for greater involvement of parents, the patient organisation and clinicians in the CL procedure. In the current situation, clinicians feel the decision is imposed on them. Clinicians were asked to provide information about

the disease and potential effect of the treatment, but were not involved in the decision-making. Clinicians experienced that they were called to account for the decision that was made, while they in fact had no influence on, and were not responsible for, the final CL decision.

Some policymakers, from governmental organizations, indicated that CL decisions are often made under considerable societal pressure. Furthermore, they felt there was a constant threat that the pharmaceutical company would end the availability of the medicine in a compassionate use program. One of the policymakers, from a governmental organization, mentioned being approached personally by parents and patients, and experienced this as difficult, considering the job of a policymaker is supposed to remain impartial.

Stakeholders from all perspectives appreciated the neutrality, impartiality and independence of the governmental parties currently involved in the CL procedure (Q11, **table 2**).

The lack of uniformity in access to expensive treatments in European countries

Participants from all perspectives mentioned the lack of uniformity between EU member states in accessing expensive treatments as being an important problem. Patient representatives expressed astonishment and horror that social media showed the availability of nusinersen for a broad range of patients (including adults) in other European countries, while young children in the Netherlands did not have access (Q12, **table 2**). This astonishment was shared by clinicians. Patient representatives felt that this lack of uniformity was unacceptable.

Patient representatives considered the German policy – allowing treatment to start while further assessment and price negotiations were taking place - as an approach which did not sacrifice the interest of the patient for bureaucratic procedures (Q13, **table 2**). Policymakers from governmental organizations suggested that this approach might be attractive from the pharmaceutical company's point of view. The fact that the medicine has to be taken away from patients if the decision is negative, was seen as a disadvantage of the German policy by patient representatives and policymakers.

Some policymakers mentioned that, compared to other European countries, the Netherlands holds an overall top position with regard to the package of medicines reimbursed, the time required to ensure access to these medicines and their price.

Policymakers had the impression that the authorities of countries with faster access to expensive therapies than the Netherlands have a higher level of trust in the EMA and professionals. They also had the impression that authorities in these countries are more

open towards re-assessing the decision after some time on the basis of real-world evidence gathered in, for example, national registers.

Translating the themes into improvements of the CL in the future

Most of the stakeholders came up with suggestions for future improvements while talking about their CL experiences and perceptions.

Making a timely decision was mentioned often as an important improvement. Patient representatives suggested that timely decisions could be assured by distinguishing treatments for progressive diseases (in which time is key) from diseases that are not or less progressive and to prioritize the first group over the second. Clinicians and patient representatives suggested an alternative trajectory for treatments for (orphan) diseases with no other treatment options. An example of such a trajectory was a conditional reimbursement program (Q14, **table 2**). This solution was also proposed by clinicians and policymakers to deal with limited available efficacy data. To take uncertainty around (cost-) effectiveness into account, policymakers proposed a pay-for-performance arrangement. Stakeholders from all perspectives suggested that EU countries could collaborate (more) in the assessment of the (cost-)effectiveness of expensive medicines and join each other in price negotiations. It was thought this would be more efficient and might strengthen their position (Q15, **table 2**).

Table 2. Illustrative quotes from interviews with stakeholders

Emotional impact of the CL on stakeholders
Q1: "...For us, that was a very intense period because you just feel powerless, because you know there is something and I cannot buy it at the supermarket; how can I get it, I just want my child to get it. We were really desperate at that time because our child was getting worse." (P)
Q2: "Once that decision was made, and our child would miss out, then we actually thought: what are our alternatives? [...] So time became more and more urgent and we thought we would emigrate to Belgium. We were actually completely fed up with being in the Netherlands, so we took the necessary steps. We went to see where we could live and what was needed for that, because in Belgium all patients were reimbursed." (P)
Q3: "I mean you might be able to formulate a cut-off limit with it, but is this meaningful enough to override the doctor's duty not on improper grounds, yes, everyone's of course, but the doctor still has that duty himself and you probably feel that too. Somehow it hurts that it is not fair." (C)
Duration of the CL procedure
Q4: "Look, there was no cure for SMA. It is a progressive disease and if you yourself take 2 years, and - I'll just say - at your convenience, to reach your decision: that is unacceptable. Look, I can imagine if you have a disease of your eyes for example, and there is a drug that makes you better, but in the meantime it doesn't get worse. That it is recoverable, but with a progressive disease that is irreversible, time is just key." (P)

CL procedure is not appropriate for all types of medicine

Q5: “But what happened with spinraza: because it worked so well, it was assessed at an accelerated pace. Not only in America but also in Europe this was quickly assessed by the registration authorities. The result was that at the time there was a permit, there had been no publication yet. Because normally the process takes 10 months, then you still have time, but we were at 6 months by then. So, we had to wait for the publication. [...] At such a moment, the health care institute says: sorry, but the file is not complete. So we cannot assess it yet. This gave a month’s delay and was very frustrating.” (B)

Q6: “You will not see that in rare diseases such as a muscle disease where the muscles are simply damaged and can no longer recover. So, stabilization or slower decline is already a huge advantage. I had to explain that. [...] So, in other words, in rare diseases, stabilization, being able to turn over in bed, is a huge gain. Or being able to take three more steps, meaning you can still go to the toilet yourself. That is a huge gain. That is very difficult to explain if you do not know what the disease entails and if you look at the outcome of the data, you think: stabilization is “mwah”. At that point therapeutic value is set at less than the cost. But that is not the case, because it has an enormous therapeutic value for this disease. So, I do think you should look at data with a good eye, and I think that is fairly rigid now.” (P)

Transparency of the CL

Q7: “I do not know what happens in the time of the coverage lock. That is speculation for me too.” (P)

Q8: “But when I ask colleagues, that is what I hear a lot from guys: it’s not always that clear. What I miss in the Coverage Lock is something like: this is what the process looks like, these are the milestones, they are achieved on this day and this day.” (B)

A wish for patient-centred decision-making

Q9: “And that mainly concerns, which I find very difficult, that decisions are made about, for example, SMA typing, so type 1 yes, type 2 no, by people who have no idea at all what the typing of SMA means.” (C)

Q10: “(...) of whom you actually think: they deserve that treatment, but that is not allowed according to the rules. And that is also very difficult to explain to people. So there are, on all sides as you notice, people around the table, people who do not quite, yes, understand the human dimension or the essence of that patient, so to speak.” (C)

Q11: “That is complicated for the government, which has the formal task of doing the assessment. They should keep doing it, because they are the only ones who can do the assessment objectively.” (B)

The lack of uniformity in access to expensive treatments in European countries

Q12: “Then I found it very difficult to see on the internet that there were people in other European countries who were adults, had type 3, who were given an injection for the tenth time. While there were young children in the Netherlands who did not get anything yet.” (P)

Q13: “I myself became enamored with the German model, where they say: we are putting the patient first, so we are going to start treatment and then we take two years to make a decision. Then we will investigate. So we are not going to wait two years until we make a decision. The patient must not become the victim of our bureaucratic processes. I would find that ideal. Of course, it has drawbacks; I understand that too.” (P)

Translating the themes into improvements of the CL in the future

Q14: "I can imagine that you check: is there already a medicine on the market? If there isn't, then go ahead, then start treatment quickly and negotiate a price. And B if there are drugs on the market, but there will be a new drug that is easier in administration and also cheaper, yes then you have to be quick too, I think." (P)

Q15: "Yes, it will help, I think, because the Netherlands is simply too small if, for example, you unite as European countries and then start negotiations with a larger body with pharmaceutical companies. Then you are just much stronger. [...] Well, I think you cannot avoid critical assessment, but the question is whether that should only be done from the Netherlands. Why not do the same with a number of countries. That you say: I work together with Germany and Belgium, as is happening now, for example, with gene-therapy in the Benelux." (C)

Legend table 2: P = patient representative, C = clinician, B = stakeholder from policy perspective

Discussion

With this study we aimed to gain insight into the stakeholder perspectives on a Dutch policy measure to control reimbursement for extremely expensive new medicines, known as the Coverage Lock. Overall, stakeholders acknowledged that healthcare expenses have to be controlled; most participants agreed that the CL might be an effective way of doing this and thus might contribute to affordable care. Furthermore, we identified six overarching themes that emerged from the experiences and perceptions of stakeholders of the CL procedure for nusinersen. Our study reveals that even though stakeholders are aware of the necessity to control healthcare expenditure, the CL places strains on stakeholders of all perspectives. Patients and their parents feel powerless; waiting for a (lifesaving) treatment is very difficult. The decision of the CL is imposed on clinicians, who experience an unworkable situation in their clinic. And policymakers from governmental organisations feel societal pressure and are unsure whether treatments, available in a compassionate use program, will remain available. The reimbursement decision on expensive medicines has to be made despite all these tensions in the CL procedure. Above all, clinicians and patient representatives experienced the CL as unfair, especially in comparison to neighbouring countries, because while the procedure is in progress, a (potential) treatment is withheld.

The importance of a fair procedure to come to reimbursement decisions has been described before. An often-proposed ethical framework for such a process is accountability for reasonableness (A4R) (see **box 1**) (23-26).

Box 1. Accountability for reasonableness framework requirements.

This framework consists of four requirements to come closer to a fair decision-making process about the reimbursement of therapies (23):

1. *Publicity: meaning the reimbursement decisions must be publicly accessible and ensures clarity about reasons behind a reimbursement decision.*
2. *Relevance, also called reasonableness. This condition asks for a reasonable explanation of how the organisation provides “value for money” in meeting the varied health needs of a defined population under reasonable resource constraints. Specifically, an explanation is reasonable if it appeals to reasons and principles that are accepted as relevant.*
3. *There should be a mechanism to challenge and dispute the resolution regarding limit-setting decisions, this includes the opportunity for revising decisions in light of further evidence or arguments.*
4. *There should be a voluntary or public regulation of the process to ensure that conditions 1 to 3 are met.*

When we compare the stakeholder experiences and perceptions to A4R requirements for a fair process, some of the pitfalls of the CL become clear. Most problems expressed by the stakeholders relate to the A4R conditions, publicity (criterion 1) and relevance (criterion 2). Although the final decision in the CL procedure is made public, the CL procedure itself is not always clear and transparent for stakeholders. For some stakeholders it was not transparent to them how the procedure works, what the milestones are or who participates in the process. Governmental organisations tried to inform the stakeholders, but insights derived from other stakeholder perspectives have revealed that this information process was not sufficient. The identification of transparency as one of the key issues of the CL is in line with other literature that indicates the need for transparency about the reimbursement of expensive treatments (4, 24, 27).

With regard to relevance, it could be argued that the CL did not meet this condition in the case of nusinersen. Clinicians and patient representatives in particular were clear that they did not understand the reasoning for an age limit for reimbursement set at 9.5 years. Relevance also appeals to reasons and principles that are accepted as being relevant. For example, patient representatives argued that the CL does not take into account patient relevant outcome measures, which can be considered as relevant in a reimbursement decision. It has been described before, that the criterium relevance is not always met in reimbursement decisions for orphan medicines (28). Especially the arguments most often used to reason a reimbursement decision, cost-effectiveness, can be difficult to assess in orphan medicines (26, 29, 30).

Stakeholders expressed fewer experiences that can be related to the two other criteria from A4R, revisability (criterion 3) and public regulation (criterion 4). This might be explained by

the conditional reimbursement of nusinersen for patients older than 9.5 years that started in 2020; the eventual availability of the medicine makes these two conditions less urgent for stakeholders who are directly involved.

While discussing the strains the CL places on stakeholders and potential improvements of the CL, it is important to realize that solutions to improve the situation of stakeholders might also be found elsewhere. Ultimately, the origin of the problem is the unexplained high price of orphan medicines (9, 31-33). Pharmaceutical companies should not only clarify pricing of orphan medicines but also share a responsibility to come up with solutions that allows the incorporation of innovative medicines in realistic healthcare budgets (34, 35).

One of the strengths of our study is that we were able to identify and interview the key stakeholders in the CL of nusinersen, thus ensuring valuable insights from people actually involved in the CL rather than hypothetical or theoretical situations. Another strength is that we were able to verify the identified themes with the interviewees. A limitation is the time-interval between the CL procedure of nusinersen and our interviews, which was almost two years. This introduces a risk that stakeholders may not be able to recall the experience in full, or may remember it differently from the way they experienced it at the time of the CL. However, during the conversations with stakeholders, we did notice that details of their experiences came back. We, therefore, asked participants to contact us if anything came up later or if they remembered more after the interview. None of them did; and so we believe we managed to obtain an accurate overview of the experiences of all stakeholders.

Conclusion

In conclusion, stakeholders accept the need for cost-control. Improvements in the CL can, however, be made, especially regarding publicity and transparency. Providing more information about the CL procedure, the timeline with milestones and transparent medicine prices would contribute to a better understanding of future CL procedures. Another important improvement relates to relevance. Efficacy and cost-effectiveness analyses, as instruments in the CL, were perceived as not suitable for all types of treatment, especially not for orphan medicines. A revision of the assessment procedure for orphan medicines is recommended, taking more patient-relevant outcomes into account. Finally, what seems to be of most help to patients and clinicians, is taking timely CL decisions, and ensuring treatment access during the CL procedure.

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Supplementary files chapter 4

Interviewguide in Dutch

Introductie

Het onderwerp van dit interview is de zogenaamde Pakketsluis: het beleid van de overheid om bij dure, nieuwe medicijnen eerst nader onderzoek te doen en prijs onderhandelingen te voeren voordat ze vergoed worden via de basisverzekering. Het doel van dit interview is inzichtelijk maken wat de ervaringen en meningen zijn van mensen die betrokken zijn bij de Pakketsluis.

Dit interview wordt strikt vertrouwelijk behandeld, en de antwoorden die u geeft zullen alleen anoniem worden gebruikt. Heeft u op dit moment nog vragen? - Start opname -

Heeft u alles begrepen en geeft u expliciet toestemming voor dit interview?

1. Welke ervaring heeft u met de pakketsluis?
 - a. In welke hoedanigheid bent u betrokken geweest bij de pakketsluis?
 - b. Welke concrete ervaringen heeft u meegemaakt?
2. Wat vindt u over het algemeen van het Pakketsluis-beleid?
 - a. Bent u uiteindelijk positief of negatief gestemd?
3. Welke aspecten van de pakketsluis zijn in uw visie goed?
 - a. Wat zou niet veranderd moeten worden?
4. Welke aspecten zou u verbeterd willen zien?
 - a. Heeft u concrete suggesties hoe die verbeteringen eruitzien?
5. Denkt u dat er in Nederland een noodzaak is de Pakketsluis of vergelijkbaar beleid?
 - a. Waarom wel of waarom niet?
6. Hoe vindt u dat de uitwerking van de pakketsluis in de praktijk is?
 - a. Bereikt de pakketsluis zijn doel?
 - b. En op welke manier wel of juist niet?
7. Heeft u nog aanvullende vragen of opmerkingen over de pakketsluis?

Hartelijk dank voor uw medewerking.

Interview guide translated from Dutch to English

Introduction

The subject of this interview is the so-called Coverage Lock: a governmental policy for assessing expensive, new medicines, and negotiating about the price before deciding on whether they should be covered by basic health insurance. The goal of this interview is to gain insight into the experiences and attitudes of stakeholders involved in the Coverage Lock.

This interview is strictly confidential and the answers you give will only be used anonymously.

Do you have any questions? - Start recording –

Did you understand everything and do you give consent for this interview?

1. What is your experience with the coverage lock?
 - a. In what capacity were you involved in the coverage lock?
 - b. What actual experiences have you had?
2. What do you think of the Coverage Lock policy, in general terms?
 - a. Do you have a positive or negative attitude towards it?
3. Which aspects of the coverage lock are good?
 - a. What does not need to be changed?
4. Which aspects should be changed?
 - a. Do you have specific suggestions for these changes?
5. Do you think there is a need for the coverage lock or a similar policy?
 - a. Why? Why not?
6. What do you think about the implementation of the coverage lock in practice?
 - a. Does the coverage lock achieve its goals?
 - b. How does it? How does it not?
7. Do you have any additional questions or comments about the coverage lock?

Thank you for your contribution.



Chapter 5

Views and opinions of the general public about the reimbursement of expensive medicines in the Netherlands

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Abstract

Objectives: Solidarity-based healthcare systems are being challenged by the incremental costs of new and expensive medicines for cancer and rare diseases. To regulate reimbursement of such drugs, the Dutch government introduced a policy instrument known as the Coverage Lock (CL) in 2015. Little is known about the public opinion regarding such policy instruments and their consequences, i.e., reimbursement of some, but not all, expensive medicines. We aimed to identify the preferences of Dutch citizens regarding the reimbursement of expensive medicines, and to investigate the views of the public on the use of the CL as a healthcare policy instrument and their input for improvement.

Methods: Web-based survey of a representative sample of 1999 Dutch citizens aged 18 years and older (panel of research company Kantar Public). Potential respondents were approached via e-mail. Several policy measures, real-life cases and statements related to the CL were presented in the survey to respondents. Their responses were analysed by tabulating descriptive statistics (proportions and percentages).

Results: 1179 individuals (response rate 59%) filled in the questionnaire. Although a majority considered the CL policy unjustified, they preferred it to the alternative policy measures that were presented. In four real-life case descriptions of patients in need of expensive medicines, respondents most often indicated effectiveness, lack of availability of alternative treatment and improved quality of life due to treatment as reasons for a positive reimbursement decision. An unfavourable cost-benefit ratio was their main reason to be against reimbursement. Some argued that withholding reimbursement was a way of informing manufacturers that extremely high prices are unacceptable.

Conclusion: There is public support for patients in need of expensive medicine. Many respondents supported the CL as a reimbursement policy. However, there is a wish to optimize the interpretation of the assessment criteria and the weight these are attributed in decision making about reimbursement of expensive innovative medicine for patients.

Introduction

Solidarity-based healthcare systems face a growing challenge in the fair allocation of financial resources. One of the causes is the increasing number of expensive medicines each year and projections suggest that the growing percentage of healthcare budgets required will eventually crowd out other types of healthcare (1, 2). The balance between access to innovative yet expensive medicines and sustainable access to generic healthcare is delicate (3-6). Each country in the EU tries to manage this balance in its own way, which may cause inequalities in access to medicines for European citizens (7, 8). Furthermore, national reimbursement limits for expensive medicines may deny citizens with rare diseases in need of expensive medicines, causing feelings of unfairness (9).

Governments need policy-instruments to guide decisions on which medicines should be reimbursed and which should not. The Coverage Lock (CL) is an example of such an instrument and was implemented in the Netherlands in 2015 (10) (see **textbox 1** for background information on the Dutch healthcare and reimbursement system). Before 2015, new medicine used for in-hospital treatments were usually directly reimbursed, regardless of their price. The purpose of the CL is to regulate access to new expensive medicines in the basic health insurance package. In short, the CL limits automatic reimbursement of new medicines to those with a cumulative budget impact of more than €40,000,000 (in total for all indications), or when costs are more than €50,000 per patient and total costs exceed €10,000,000 (for only one indication) per year. When new medicines are expected to exceed these limits, reimbursement is put on hold directly following market authorization by the European Medicines Agency (EMA). This expectation of exceeding the limits is based on the so-called “Horizon scan of Medicines” in which several expert parties work together to generate an overview of the innovative medicines of which market authorization is expected in the next two years, and to predict the potential financial impact of these. The CL policy consists of an assessment of efficacy, cost-effectiveness, necessity, and feasibility of the included medicines. If outcomes of these analyses indicate that new medicines indeed add value, the advice to the Ministry of Health is to start price negotiations with the manufacturer. The whole process may take up to several years. An important consequence of the CL is, therefore, that Dutch patients, in contrast to patients in other EU countries, do not have immediate access to treatment (if at all). In the recent past, this has sparked patient protests, often covered by Dutch media.

Despite the fact that public support is vital to successful implementation of policies that may substantially affect people’s lives, the CL has not been formally evaluated, either during its design or its implementation(11-14). There is a lack of understanding of prevailing public

opinion regarding current decision-making procedures and regulations. Fortunately, there is an increasing body of literature assessing citizen's reimbursement preferences (15) with varying scopes, including reimbursement decisions in general (12, 16-18), for rare diseases (19-22) and more specifically for treatment of cancer (16, 17).

Our aim was to identify the preferences of Dutch citizens regarding the reimbursement of expensive medicines, and to investigate the views of the public on the use of the CL as a healthcare policy instrument and their input for improvement.

Textbox 1. Healthcare and reimbursement system in the Netherlands

In the Netherlands, all residents are required to have a basic health insurance package with a Dutch health insurer for which a monthly premium is charged. The coverage of the basic health insurance package is exactly the same with every health insurer and concerns, in principle, all medically necessary care, such as the care of general practitioners, hospital treatment, and medical prescriptions at the pharmacy. The government decides which care is included in the package. For most healthcare in the basic health insurance package a mandatory own risk applies and sometimes also a co-payment. As the basic health insurance package does not cover the costs of all healthcare, payers can choose for supplementary insurance at their own costs.

Healthcare in the Netherlands is largely financed by the premiums that are paid to health insurers, other (social) premiums that are paid to the government, and a governmental contribution.

Methods

Study design and participants

We conducted a web-based survey of a sample of 1999 Dutch citizens aged 18 years and older. The sample was part of the extensive Kantar Consumer panel (NIPObase). Kantar Public is a research company specialized in public consultation to assess the degree of approval of public opinion in political decision-making. The Kantar Consumer panel contains 123,534 persons. It is one of the most representative panels in the Netherlands due to several recruitment strategies aimed at also including target populations that are usually less represented in (web-based) research (e.g., older adults, people with a lower level of education and the migrant population). Kantar Public for example specifically approaches certain target populations and once persons become panellists they may be asked to recruit others from their target population. The sample for our study was drawn representative of the general Dutch population in terms of sex, age, education and region of residence. Potential respondents were approached via e-mail with a unique invitation link to fill in the survey. The survey itself was hosted on a website (CAWI – computer-assisted web interviewing). For a one-week period, the survey was distributed online (between December

8th and December 14th 2021 – 12 December a reminder e-mail was sent to those who did not respond yet).

Questionnaire

Before respondents started the survey, they received a short description of the CL and the purpose of the questionnaire. Next, they received 30 multiple choice questions and two open questions, based on relevant literature and the results from a previous interview study with stakeholders from the CL (9). Once the survey was programmed, it was tested by two researchers of Kantar Public before sending it out. **Supplementary file 3** shows the introduction of the questionnaire and all questions we asked. It also shows the answering options for each question and when it was possible to give multiple answers and to answer in free text fields. Answering options were not always mutually exclusive or entirely independent of each other. In those cases, we asked participants to indicate what is most important to them or they had the option to choose multiple answers. The first part of the survey consisted of background questions regarding participants' characteristics. In the second part, the focus was on prior knowledge of and their preferences regarding different reimbursement systems. Following this, the participants were asked whether they would vote in favour of reimbursement of four new expensive medicines. To better understand their preferences, participants were asked to support their reimbursement choice by choosing from several arguments that, amongst other values, reflected the current assessment criteria of the CL. These cases were based on real-life examples of medicines that have previously been placed in the CL and have subsequently been evaluated (**see textbox 2**). Respondents had to select their preferred option from multiple choice arguments. The next part of the questionnaire focused on the CL, to gain better insight in the preferences of the participants regarding the composition of the CL decision-making committee and the access to treatment during the CL procedure. Finally, to gain insight in the preferences regarding the reimbursement of expensive treatment we included questions about the willingness of participants themselves to contribute financially to providing access to expensive therapies for specific patient groups.

Textbox 2. Real – life examples used in questionnaire

We presented four “hypothetical” cases to participants, based on the cases of durvalumab (case 1), vedoluzimab (case 2), aducanumab (case 3), nusinersen (case 4). The descriptions of the cases were as follows:

The first described treatment with a drug for life-threatening cancer. Treatment might extend life by several months but carries the risk of side-effects, such as dyspnoea; it will primarily be used by patients aged ≥ 55 years (approximately 300 per year) with no alternative treatment options. Costs are €100,000 per patient, cumulative costs are €30 million per year.

The second described treatment for chronic inflammatory bowel disease. The treatment does not provide a cure, but often leads to a significant improvement in quality of life. The available alternatives are less effective. Patients are usually between 25 and 60 years of age (approximately 800 per year). Costs are about €20,000 per patient per year, cumulative costs are €16 million per year.

The third outlines a treatment to slow down progression of Alzheimer’s dementia. Patients are usually aged ≥ 65 years (approximately 5000 per year). Efficacy of the treatment is uncertain, similar to the available alternatives. Costs are €50,000 per patient per year, cumulative costs are €250 million.

The fourth concerns treatment for patients with a progressive neuromuscular disease, affecting mainly children (approximately 85 per year). Treatment often leads to improved gross motor development and fewer impairments later in life. There is no alternative treatment. It costs €350,000 per patient per year and cumulative costs are €30 million per year.

Data analysis

We used SPSS software, version 26.0.0.1, for all statistical analyses. We analysed the data by tabulating descriptive statistics which show frequencies in terms of proportions and percentages. We used a Fisher’s exact test to compare the answers of those who considered the CL justifiable with those who considered the CL not justifiable for the question “Do you consider yourself a patient?”. There were two Likert scale questions in the survey (**see supplementary files**). For our analysis, strongly disagree and disagree were classified as “disagree” and strongly agree and agree as “agree”.

As described under the heading “study design and participants”, the sample of our study was drawn representative of the general Dutch population in terms of sex, age, education and region of residence from one of the most representative panels in the Netherlands. However, not everyone who is invited for a survey takes part and, in this phase, some selective drop-out may take place. We applied a weighting factor in all analyses to correct for the deviations in representativity of the final sample. This weighting factor was provided by the research company Kantar Public. It is based on reference numbers of the composition of the Dutch general population concerning sex, age, education, region of residence, household size and social class.

Informed consent and ethical approval

Participants gave their written informed consent prior to the start of the questionnaire. The Medical Research Ethics committee METC Utrecht confirmed that under Dutch law, this research is exempt from review by a medical research ethics committee (dossier number 20/696).

Results

The survey was sent to 1999 individuals; 1179 (59%) filled in the questionnaire. between December 8th and December 14th 2021. We had to exclude 35 questionnaires because of missing baseline characteristics of respondents, leaving a sample size of 1144 Dutch citizens at the start of the survey. However, 69 surveys were incomplete, resulting in a sample of 1075 at the final question of the survey. For baseline characteristics **see table 1**.

In general, the final sample reflected the Dutch general population in terms of sex, age, education, region of residence, household size and social class, as shown by the comparable weighted versus unweighted composition of the participants in **supplementary table 1**. Since the final sample size did not fully represent Dutch society, we applied a weighting factor (as explained in the methods section). **Supplementary table 1**, for example, shows that compared to the Dutch general population there were relatively less low educated persons in our final sample. The weighting factor we applied corrects for this deviation by weighting the answers of lower educated persons in such a way that it represents a fully representative sample.

Table 1. Baseline characteristics

Characteristic	n = 1144
Sex	
Male	565 (49.4%)
Female	579 (50.6%)
Age (years)	
18 – 24	125 (10.9%)
25 - 34	182 (15.9%)
35 – 44	170 (14.9%)
45 – 54	208 (18.2%)
55 - 64	194 (16.9%)
65+	266 (23.3%)
Educational attainment ^a	
Low	243 (21.3 %)
Middle	455 (39.8%)
High	446 (39.0%)

Social class ^b		
	Low	346 (30.3%)
	High	797 (69.7%)
Household size (number of persons)		
	1	249 (21.8%)
	2	418 (36.6%)
	3	184 (16.1%)
	4	198 (17.3%)
	5 or more	95 (8.3%)
Residential area (Nielsen-grouping CBS)		
	Three major municipalities ^c	137 (12.0%)
	West ^c	336 (29.4%)
	North ^d	114 (10.0%)
	East ^e	239 (20.9%)
	South ^f	272 (23.8%)
	Peripheral municipalities ^g	46 (4.0%)
Legend table 1: N = number.		
^a Educational attainment: Low = lower vocational education, lower secondary education, or less; Middle = intermediate vocational education or higher secondary education; High = higher vocational education or university.		
^b Social class = The construct 'Social Class' is a matrix of education x occupation of the breadwinner.		
^c Major municipalities: Amsterdam, Rotterdam, Den Haag		
^d West = Utrecht, Noord-Holland, Zuid-Holland excl. three major and peripheral municipalities.		
^e North = Groningen, Friesland, Drenthe. ^f East = Overijssel, Gelderland, Flevoland. ^g South = Zeeland, Noord-Brabant, Limburg		
^h Peripheral municipalities = Amstelveen, Diemen, Landsmeer, Ouder-Amstel, Ridderkerk, Barendrecht, Albrandswaard, Krimpen a/d IJssel.		

Prior knowledge and patient identifiability

The vast majority (89.5%) of the respondents had no prior knowledge of the CL. More than two-thirds (69.5%) did not consider themselves patients. We asked the respondents to indicate whether or not they considered the CL to be a justified policy (**see table 2**): 64.9% considered it not justified, most often "because patients have no influence on whether they need such an expensive medicine". Respondents who considered the CL justified (35.1%), chose the reason "because prices of expensive medicines are too high" most often (42.8%) (**see table 2**). The group that considered the CL not justifiable identified themselves more often as a patient (34%) than those who agreed with the CL as a policy instrument (25%) ($p=0.002$).

Table 2. Justifiability of the CL policy

General perspective on CL policy	n = 1140
CL policy is justifiable...	400 (35.1%)
...because prices of expensive medicines are too high.	171 (42.7%)
...because extremely expensive medicines put pressure on other forms of health care.	152 (37.5%)
...because health care costs are rising too fast.	77 (19.3%)
CL policy is not justifiable...	740 (64.9%)
...because patients have no influence on whether they need such an expensive medicine.	391 (52.8%)
...because it is irresponsible to keep patients waiting for an expensive medicine during the CL procedure.	182 (24.6%)
...because it is much better to cut back on other health care costs.	96 (13.0%)
...because the Netherlands is rich enough to enable access to expensive medicines.	71 (9.6%)

Legend table 2:

Respondents were asked which of the seven options most closely resembled their views.

Preferential reimbursement system

We asked the respondents which of four different reimbursement systems they preferred (see table 3). 40.3% of the respondents chose the current CL policy. Slightly fewer respondents (36.6%) chose a system in which all medicines, even very expensive medicines, were reimbursed, meaning that the government would have to make choices in other areas of care. One-fifth (20.2%) of the respondents opted for a system in which medicines are immediately reimbursed and available until further assessment takes place. This choice included the consequence that in the case of a negative assessment outcome, the medicine would be withdrawn. A very small number (2.9%) chose a system without reimbursement and hence no access to very expensive medicines.

Table 3. Preferred reimbursement system for expensive medicines

Preferred reimbursement system*	n = 1121
System 1	410 (36.6%)
System 2	227 (20.2%)
System 3	452 (40.3%)
System 4	33 (2.9%)

Legend table 3:

*Preferred reimbursement system: respondents were presented with a realistic range of 4 different reimbursement systems.

1 = All medicines, even if they are very expensive, will be reimbursed and become available to all patients who need them. However, the government will be forced to make choices in other areas of care.;

2 = Initially, during the assessment period, very expensive medicines will be reimbursed and made available. But after this, reimbursement can be withdrawn depending on the outcome of the assessment.;

3 = This is the current CL policy: consisting of a waiting period during which assessment takes place, the medicine is not reimbursed nor available yet. This will only happen once full assessment has led to this decision.

4 = No compensation or availability of very expensive medicines at all.

Reimbursement decisions of participants in response to real-life examples of CL medicines

A large majority of respondents supported reimbursement in response to the case descriptions of chronic inflammatory bowel disease (89.3%) and the neuromuscular disease (79.2%) (**see table 4**). Important reasons to support reimbursement were prevention of suffering, increasing quality of life, their shown efficacy and the lack of equivalent alternatives (**see table 4**).

On the other hand, the majority of respondents did not support reimbursement in the case of life-threatening cancer (72.0%) or Alzheimer dementia (73.6%) (**see table 4**). Important reasons were uncertainty about efficacy and a negative cost-effectiveness ratio (**see table 4**) coupled with excessively high pricing. Respondents indicated that manufacturers should receive a signal that extremely high prices are not acceptable.

Table 4. Real-life examples of medicines evaluated in the CL

Reimbursement of medicine?	Most important reason	n = 1109
Case 1: Life-threatening cancer		
Yes		311 (28.0%)
	The fact that the medicine is effective.	93 (29.9%)
	The absence of alternative treatment options.	86 (27.7%)
	There is a chance that this medicine is life-saving.	83 (26.6%)
	The medicine is reasonably priced if you consider the health benefits it provides for the patient.	23 (7.5%)
	The duration of treatment is relatively short, which limits the costs.	16 (5.2%)
	Other.	10 (3.1%)

No		798 (72.0%)
	The medicine is too expensive if you consider the health benefits it provides for the patient.	338 (42.5%)
	Manufacturers of medicines must receive a signal that high prices are not acceptable.	165 (20.8%)
	The medicine only offers a chance of prolonging life, but no certainty.	159 (20.0%)
	The government should give priority to cheaper treatments that benefit a larger group of patients.	45 (5.7%)
	Other.	44 (5.5%)
	Healthcare becomes unaffordable if treatments are reimbursed at this price.	43 (5.4%)
Case 2: Chronic inflammatory bowel disease		n=1100
Yes		982 (89.3%)
	The medicine prevents a great deal of suffering because it is for patients who have to live with this disease for a long time.	381 (38.9%)
	The medicine improves quality of life.	306 (31.2%)
	The medicine is reasonably priced if you consider the health benefits it provides for the patient.	152 (15.5%)
	The fact that the medicine is effective.	130 (13.3%)
	Other	11 (1.1%)
No		118 (10.7%)
	A less expensive treatment is available for these patients.	31 (26.0%)
	Manufacturers of medicines must receive a signal that high prices are not acceptable.	24 (20.3%)
	The disease for which this medicine is intended is not life-threatening.	18 (15.7%)
	The medicine is too expensive if you consider the health benefits it provides for the patient.	13 (10.9%)
	The government should give priority to cheaper treatments that benefit a larger group of patients.	9 (7.5%)
	Health care becomes unaffordable if treatments are reimbursed at this price.	9 (8.1%)
	Other	7 (6.2%)
	The duration of the treatment is long which contributes to extra high costs	7 (5.8%)
Case 3: Alzheimer dementia		n=1091
Yes		287 (26.4%)
	The medicine offers a chance for improvement, even if this is uncertain.	134 (46.7%)
	The medicine is intended for patients with a disease that causes more and more disabilities.	73 (25.4%)
	The medicine is reasonably priced if you consider the health benefits it provides for the patient.	69 (24.0%)
	Otherwise	11 (3.9%)
No		804 (73.6%)

The medicine only offers a chance of slowing down progression of the disease, but there is no certainty.	342 (42.5%)
The medicine is too expensive if you consider the health benefits it provides for the patient.	166 (20.7%)
Manufacturers of medicines must receive a signal that high prices are not acceptable.	104 (12.9%)
A less expensive treatment is available for these patients.	64 (8.0%)
Health care becomes unaffordable if treatments are reimbursed at this price.	41 (5.1%)
The government should give priority to cheaper treatments that benefit a larger group of patients.	36 (4.5%)
Other	30 (3.7%)
The disease for which this medicine is intended is not life-threatening.	20 (2.5%)
Case 4: Progressive neuromuscular disease	N=1087
Yes	861 (79.2%)
The fact that the medicine is effective.	177 (20.5%)
For these patients, no alternative treatment option exists.	166 (19.3%)
The medicine is intended for patients with a disease that causes more and more disabilities.	159 (18.5%)
The medicine treats patients with a disease for which no other treatment is available.	136 (15.8%)
The medicine is reasonably priced if you consider the health benefits it provides for the patient.	125 (14.5%)
The medicine is also suitable for children.	78 (9.1%)
Other	20 (2.3%)
No	226 (20.8%)
Manufacturers of medicines must receive a signal that high prices are not acceptable.	60 (26.5%)
Health care becomes unaffordable if treatments are reimbursed at this price.	50 (22.3%)
The medicine offers improvement, however, no certainty.	36 (16.0%)
The medicine is too expensive if you consider the health benefits it provides for the patient.	35 (15.5%)
The government should give priority to cheaper treatments that benefit a larger group of patients.	31 (13.6%)
Other	14 (6.1%)
Legend table 4:	
In addition to being for or against reimbursement (yes/no), participants were asked to give their most important reason to support their choice. Only one answer possible per person.	

The CL policy and patient access to new medicines

If a medicine is in the CL, the additional assessment and negotiation with the manufacturer to lower the price of the medicine takes on average around 11 months. We asked the respondents whether they believed that a medicine should be available during the CL procedure and who should bear the costs. A majority, 85.6%, believed that during the CL procedure, medicines should be available to all eligible patients. About two-thirds (63.1%) of this group thought that the manufacturer should bear the costs of making drugs available. When patient groups were described more specifically (see statements 2-5 in **table 5**), there was a shift towards more support for the availability of the medicine during the CL. This support went up to 96.2% when it concerned a life-threatening disease. Respondents varied regarding who should bear the costs of the medicine, depending on the case presented (**table 5**).

Table 5. Availability of medicines and financial responsibility during Coverage Lock (CL) period

Statement	N = 1082		
During the (assessment) time that a medicine is still in the CL, it should already be available...	No	Yes: the government bears the costs.	Yes: the manufacturer bears the costs.
...to all eligible patients.	155 (14.4%)	347 (32.0%)	580 (53.6%)
...to patients with a life-threatening disease.	42 (3.9%)	590 (54.5%)	451 (41.6%)
...to patients with no alternative treatment option.	71 (6.6%)	577 (53.3%)	434 (40.1%)
...to patients who would have irreversible worsening of symptoms or disabilities if treatment is delayed.	71 (6.6%)	592 (54.7%)	419 (38.7%)
...to patients who are children.	89 (8.2%)	637 (58.9%)	357 (32.9%)

Legend table 5:

Specified in the introduction to this question: 'The process of additional assessment and negotiations between pharmaceutical companies and the Ministry of Health regarding the medicine takes time, about 11 months on average.'

Decision-making procedure and committee

Respondents thought that physicians (88.5%), scientific researchers (79.8%) and patients (60.3%) should be part of the decision-making committee. There was less support for ethicists (39.6%), representatives of pharmaceutical companies (29.0%), citizens (26.5%), legal experts (20.5%), economists (19.0%) and representatives from the hospital board (16.1%) (see **supplementary table 2**).

If the decision-making committee was unable to come to an agreement, the final decision should follow the majority of the votes in the committee, according to 39.8% of the respondents. 25.9% thought physicians should have the deciding vote, while 15.9% chose scientific researchers (**see supplementary table 3**).

Future self and self-funded access to expensive treatments

We asked respondents to indicate on a Likert scale the extent to which they agree or disagree with statements on their future selves and self-funded access to expensive treatments. They were asked if they would be against reimbursement of expensive medicines, even if it meant that they would not be able to receive this treatment in the future. One-fifth (20.3%) replied they would be against reimbursement even at the expense of their future selves (**see supplementary table 4**). According to 44.9% of the respondents, self-funded access to expensive treatments should not be an option (**see supplementary table 4**).

Willingness to bear extra costs for access to expensive new medicines

We asked respondents if they would support the crowdfunding of an expensive treatment in another European country for their neighbour's 1.5-year-old child when that treatment is not available in the Netherlands due to the CL. The majority (76.7%) was willing to contribute, mainly (57.1%) because they could imagine themselves being in the same situation. Of the respondents not supporting crowdfunding initiatives (23.3%), the main reason (42.8%) was that it promotes inequality compared to patients who are not able to raise the funds required (**see supplementary table 5**).

Finally, we asked if the respondents were willing to pay higher healthcare insurance premiums to finance expensive treatments for all children suffering from the same disease as their neighbour's child (**see table 6**). A small majority was against higher healthcare insurance premiums (51.2%). Within this group, 26.7% used the open answer option to explain their choice. The three most given reasons in the open answers were: 29.8% thought money should be allocated differently in healthcare instead of increasing the premium, 27.6% thought increasing the premium would cause financial problems for others, 14% of the respondents considered it the responsibility of the pharmaceutical industry to charge reasonable prices. For more details on the priority of reasons, see **table 6**.

Table 6. Health insurance premium

Willingness to increase the compulsory health insurance premium		n = 1075
Yes	What is the maximum acceptable increase in the health care premium for you?	525 (48.8%)
	5%: this is about €75 per year and €6.25 per month.	208 (38.5%)
	2%: this is about €30 per year and €2.40 per month.	202 (39.6%)
	10%: this is about €150 per year and €12.48 per month.	100 (19.0%)
	25%: this is about €375 per year and €31.20 per month.	12 (2.2%)
	> 25%	4 (0.8%)
No	What is the most important reason for being unwilling to pay a higher health insurance premium?	550 (51.2%)
	Other.	147 (26.7%)
	Because I do not have money for it	138 (25.0%)
	Because only children with this disease are helped by this and other patients who need expensive medicines are not.	135 (24.6%)
	Because the money could be better spent on cheaper treatment for a larger group of patients.	70 (12.8%)
	Because, in my opinion, this treatment is too expensive.	41 (7.5%)
	Because I do not feel inclined to help pay for the treatment of children with this rare disease.	19 (3.4%)

Legend table 6:

People were asked if they would support an increase of the compulsory healthcare premium in order to not only treat their neighbour's child, but also other children with the same disease.

Discussion

With this study we obtained insight into the preferences of the Dutch general public regarding the reimbursement of expensive medicines and the use of the CL to streamline reimbursement decisions. There is solidarity among the Dutch public with patients in need of expensive medicines, only 2.9% of the respondents was against reimbursement of all expensive drugs. On the other hand, there was not too much support for increasing the healthcare insurance premiums. Consequently, the regulation of reimbursement remains important. Participants showed they are able to appraise and make choices in the reimbursement of innovative expensive medicine in the real-world cases. While they were not obliged to choose between the four cases, only two got support for reimbursement. This implies a certain consciousness and critical attitude towards innovative and expensive medicines and their costs. There was a high level of agreement between participants on which medicine to reimburse and which medicine not. We will evaluate and compare the chosen arguments that support their reimbursement decision with the assessment criteria in the CL. The used assessment criteria in the CL procedure, which are equally important, are cost-effectiveness, efficacy, necessity and feasibility. We found public support for the CL as a regulating policy for reimbursement in this study. However, there is room for improvement in the assessment criteria and the access to treatment during the procedure. Important reasons to decide against reimbursement were high pricing and/or limited or uncertain health benefits. Respondents also indicated that manufacturers should receive a signal from societies that extremely high pricing of innovative drugs is not acceptable.

Cost-effectiveness

Cost-effectiveness is a widely used reimbursement criterion (23, 24) and is a measure to weigh gained health by the treatment versus the costs of the treatment. It reflects a utilitarian idea of fair distribution of healthcare budgets. The gained health is often (25) expressed and quantified in quality adjusted life years (QALY), with one QALY reflecting one life year in perfect health (25, 26). Although the QALY methodology has been criticised before(27), for example in their use for orphan diseases(28), there is some level of public support for cost-effectiveness as a reimbursement criterion in this and other studies (17). However, it should be taken into account that expensive medicine are quite often treatments for orphan diseases and thus placed in the CL or under restrictions while further assessment takes place after entering the market. With only some public support and the critics on QALY's before, it might not be the most suitable assessment criterium in the CL for some medicines, orphan medicines in particular. Alternatives might be for example weighed QALY's (29).

Efficacy

Public support for efficacy as reimbursement criterion, expressed either as a cure or a significant increase in quality of life in chronic diseases, is described more often (15, 17, 21) and confirmed by our study. In some cases, there might be uncertainty about the efficacy due to limited randomized clinical trials because of the limited patient numbers, as is the case in orphan diseases and their treatments. However, uncertainty regarding efficacy is not always a reason to deny orphan drugs reimbursement (13). A practical example of how to deal with uncertainty is a form of conditional reimbursements (30, 31).

Necessity

In addition to efficacy and cost-effectiveness, necessity - formalized as disease severity - is a third prerequisite for reimbursement in the CL (32). Disease severity is defined as a shortfall of health compared to someone in perfect health in future years of life (33). With an increasing disease severity, the costs per QALY threshold increases in the Dutch reimbursement system (34). So, in a way, there is a correction for disease severity, allowing more expensive treatment for more severe disease.

Necessity as a reimbursement criterion finds public support as is reported by others (22). In the literature, necessity is an umbrella-term that can be interpreted in many ways (35). Kleinhout-Vliek and colleagues (35) proposed a broader definition of 'necessity', including definition of illness, morbidity/severity, need, (no) alternative treatment, societal functioning and the rule of rescue. Previous studies reported societal support to reimburse medicine for diseases with an unmet medical need (36-38). In this study, two of these necessity-related arguments were prioritized by participants, i.e., prevention of suffering and the lack of alternative and equivalent treatments. The CL as a policy instrument probably fails to meet a broader interpretation of necessity that is preferred by citizens, since only disease severity is taken into account.

Access to treatment

Access to treatment was of importance for our participants. Only a very small percentage (2.9%) was against reimbursement of all expensive medicine, meaning most of our participants support access to and reimbursement of expensive medicines. Cumulative more than half (56.8%) of the participants opted for one of the two reimbursement systems having the new expensive medicine directly available for patients. A large majority (85%) thinks it is important to ensure access to treatment during the CL period. This shows a clear public preference to make medicine accessible during the CL period or ensure access to

treatments in different ways. Early access programs or compassionate use programs can be a solution (39).

Assessment committee

Although previous studies suggested that there is growing support for public involvement in reimbursement decisions (11-13, 40), only 27% of the participants supported a role of citizens in assessment committees for reimbursement of new drugs. The difference between literature and our results might be explained by the incorrect deduction that involvement in reimbursement choices implies active participation in an assessment committee. Why there was less support for having citizens in these committees remains unclear as we did not explore this in more detail.

Practical recommendations

The results of this study might be used to inform the government about the preferences of the general public regarding reimbursement decisions (e.g., take the availability of alternative treatment options into account and explore ways to make medicines available during the CL assessment period). If the government aligns with these public preferences, citizens' support may grow for the difficult reimbursement decisions that have to be made. As the vast majority of the respondents had no prior knowledge of the CL, the results of this study might also be used to raise awareness among Dutch citizens about how we approach the reimbursement of expensive medicines in the Netherlands. Insight into the different considerations that may play a role in reimbursement decisions could foster societal debate on how such decisions should be made.

Strengths and limitations

As far as we are aware, our study is one of the first to describe public preferences regarding the reimbursement of expensive medicines in general, and the opinions and views on a practical policy instrument in particular. This is an addition to previous studies that mostly focused on willingness to pay, and reimbursement opinions regarding expensive cancer treatments or orphan drugs (see e.g., (17, 22, 41, 42)). We used real-life examples to examine reimbursement preferences for expensive medicines. This gives valuable insights into public opinion and its rationale regarding the reimbursement of expensive medicine. A limitation is that a large majority of our participants had no prior knowledge of the CL. We informed our participants about the CL before the start of the survey. However, we cannot rule out that people might have been inconsistent in their choices during the survey, due to a lack of (broader) knowledge about the CL (43). Another limitation is that, even though we have worked with one of the most representative panels in the Netherlands, there is always

a chance that some views and opinions of the general public are missing. For example, it should be taken into account that some perspectives of people who are more difficult to reach by means of an online survey may not be represented. However, as described in the methods section, Kantar Public applies several recruitment strategies aimed at also including target populations that are usually less represented in (web-based) research (e.g., older adults, people with a lower level of education and the migrant population).

Conclusion

Our study offers an insight into the preferences of the Dutch general public regarding the reimbursement of expensive medicines and the current CL reimbursement policy. There is public support for patients in need of expensive medicine. Participants do support the CL as a reimbursement policy. However, there is a wish to ensure early access to new innovative medicine for patients. And the weighing and interpretation of the assessment criteria can be adjusted to better fit the public preferences.

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Supplementary files chapter 5

Table 1. Weighted (representative) versus unweighted composition of the participants

Baseline characteristics		Weighted	Unweighted
Age category			
	18 to 24 years of age	10.9%	10.2%
	25 to 34 years of age	15.9%	15.9%
	35 to 39 years of age	14.9%	13.9%
	45 to 49 years of age	18.2%	17.9%
	55 to 59 years of age	16.9%	17.5%
	65 to 69 years of age	23.2%	24.5%
Sex			
	Male	49.3%	50.3%
	Female	50.7%	49.7%
Educational level			
	Low	21.3%	12.2%
	Middle	39.7%	47.1%
	High	39.0%	40.8%
Residential area (based on Nielsen distribution)			
	Three major municipalities: Amsterdam, Rotterdam, The Hague	11.9%	12.4%
	West (Utrecht, North-Holland, South-Holland excl. three largest municipalities and surrounding municipalities)	29.4%	27.7%
	North (Groningen, Friesland, Drenthe)	10.0%	10.8%
	East (Overijssel, Gelderland, Flevoland)	20.9%	21.3%
	South (Zeeland, Noord-Brabant, Limburg)	23.8%	23.7%
	Surrounding municipalities (Amstelveen, Diemen, Landsmeer, Ouder-Amstel, Ridderkerk, Barendrecht, Albrandswaard, Krimpen a/d IJssel, Capelle a/d IJssel, Schiedam, Westland, Rijswijk, Leidschendam-Voorburg, Wassenaar)	4.0%	4.2%
Household size (number of persons)			
	1 person	21.8%	20.0%
	2 persons	36.6%	37.1%
	3 persons	16.0%	14.5%
	4 persons	17.3%	21.0%
	5 persons or more	8.3%	7.4%
Social class			
	High	69.7%	71.3%

Table 2. Participation in assessment committee during CL

Person or party		N = 1079
Who should participate in the assessment committee?	Yes	No
Physicians	955 (88.5%)	124 (11.5%)
Scientific researchers	861 (79.8%)	218 (20.2%)
Patients	650 (60.3%)	429 (39.7%)
Ethicists	467 (43.3%)	612 (56.7%)
Representatives of pharmaceutical companies	342 (31.7%)	737 (68.3%)
Citizens	286 (26.5%)	793 (73.5%)
Legal experts	222 (20.5%)	857 (79.9%)
Economists	205 (19.0%)	874 (81.0%)
Representatives from the hospital board	174 (16.1%)	905 (83.9%)

Legend table 2:

Participants were asked who should take part in the CL assessment committee and thus have a vote in the reimbursement decision.

Table 3. Participation in assessment committee during CL: which vote should be decisive?

Person or party		N = 1079
Who should get the deciding vote if the different parties cannot reach an agreement?		Deciding vote
The majority		429 (39.8%)
Physicians		280 (25.9%)
Scientific researchers		171 (15.9%)
Patients		88 (8.1%)
Ethicists		47 (4.4%)
Citizens		21 (1.9%)
Representatives from the hospital board		14 (1.3%)
Representatives of pharmaceutical companies		11 (1.0%)
Economists		9 (0.9%)
Legal experts		9 (0.8%)

Legend table 3:

Participants were asked which should be the deciding vote if the assessment committee does not reach consensus on the reimbursement of a medicine

Table 4. Future selves and option for private payment

Statement	n = 1079		
	Disagree	Neutral	Agree
I do not support reimbursement of expensive medicines...			
...even if that means I would not have access to the drug if I needed it myself in the future.	585 (54.2%)	273 (25.3%)	220 (20.4%)
...however, patients who pay for the medicine themselves should be able to receive the treatment.	484 (44.9%)	246 (22.8%)	349 (32.3%)

Legend table 4:

Participants were asked if they would support a negative reimbursement if this means their future selves might not be able to get that treatment. They were also asked if they thought patients should be able to receive treatment if they want to pay for it themselves.

Table 5. Financial contribution to crowdfunding: scenario of a neighbour's child, aged 1.5 years with a rare disease

Financial contribution to crowdfunding action?	Most important reason	N = 1076
Yes		825 (76.7%)
	That I imagine myself to be in that situation.	471 (57.1%)
	That I feel the need to help others if they appeal to me.	219 (26.6%)
	That I can afford it financially.	84 (10.2%)
	Other.	51 (6.2%)
No		250 (23.3%)
	That this crowdfunding action increases inequality between patients because there are parents who cannot manage to get the amount together.	107 (42.8%)
	That I have no money for this.	51 (20.5%)
	That, in my opinion, this treatment is far too expensive.	34 (13.8%)
	Other.	27 (10.7%)
	That I do not feel the need to help pay for the treatment of my neighbour's child.	15 (6.1%)
	That I would rather spend my money on a cheaper treatment that is given to a larger group of patients.	15 (6.1%)

Legend table 5:

We asked participants if they would support a crowdfunding action and presented them with the following case: Your neighbour's child is 1.5 years old and has a rare disease. If he does not receive treatment he won't be able to walk, might even be dependent on respiratory support and die at a young age.

There is a very expensive treatment available that will give the child the chance of surviving, have a normal life expectancy with fewer disabilities.

However, in The Netherlands, this treatment is in the Coverage Lock. It costs 1.9 million euros per patient which is not reimbursed. In The Netherlands, patients are not able to receive the treatment when they want to pay for it themselves. Your neighbours, the boy's parents, are starting a crowdfunding action to pay for and receive the treatment somewhere else in Europe.

Questionnaire translated from Dutch to English as used for this study.

Questionnaire translated from Dutch to English

INTRO: General introduction

Everyone in the Netherlands, rich and poor, young and old, healthy and sick, has access to the care included in the basic package. We all contribute to this through premiums and taxes. As a result, people in the Netherlands are reimbursed for the care provided in the basic package.

The minister decides on the basic package and determines which care is covered by insurance. Most new medications are allowed into the basic package without obstacles. However, some medications cannot be included in the basic package due to their high price.

Patients who need these very expensive medications have to wait for an additional assessment to be carried out. This assessment determines whether the price of the medication is reasonable for what it does. Negotiations are also conducted with the manufacturer to lower the price. This assessment process is called the "Pakketsluit" (Coverage Lock).

With this survey, we want to know your opinion on the reimbursement of expensive medications.

Section A

Q003 - A2:

If medications are very expensive, they are assessed in the "Pakketsluit" (Coverage Lock). During this period, patients generally cannot access the medication. The Pakketsluit procedure usually lasts from months to a year.

Were you aware of the existence of the Coverage Lock?

1. Yes
2. No

Q002 - A1:

Do you consider yourself a patient?

1. Yes
2. No

Q004 - A2:

Which of the following responses best applies to you?

1. The Coverage Lock is justified because prices of expensive medicines are too high.
2. The Coverage Lock is justified because the prices of expensive medications are too high.
3. The Coverage Lock is justified because extremely expensive medicines put pressure on other forms of health care

4. The Coverage Lock is unjustified because patients have no influence on whether they need such an expensive medicine.
5. The Coverage Lock is unjustified because it is irresponsible to keep patients waiting for an expensive medicine during the CL procedure
6. The Coverage Lock is unjustified because the Netherlands is rich enough to enable access to expensive medicines.
7. The Coverage Lock is unjustified because it is much better to cut back on other health care costs.

Q005 - A3:

If you have to choose between the following systems, which one would you choose?

1. In system 1, even very expensive treatments are all reimbursed and made available. Patients in need of these treatments can all receive them, but the government will be forced to make choices in healthcare in other areas.
2. In system 2, an expensive medication is initially reimbursed and made available to patients. However, at a later stage, an assessment follows. As a result, this decision can be revoked, and the treatment of patients may be discontinued.
3. In system 3, patients must first wait for a period until an expensive medication is reimbursed and made available. However, once this decision is made, patients do not risk their treatment being discontinued at a later stage.
4. In system 4, medicines that are very expensive are no longer reimbursed and made available to patients. Patients who require these expensive medicines are deprived of this treatment.

Section B

In the following section, we will provide several examples of medicines that are currently in the Coverage Lock or have been in the past. For each example, we will ask you a series of questions to understand your thoughts on expensive medicines.

Imagine that you have to decide whether the medicines from the examples should be reimbursed through the basic insurance.

Q007 – B1

Medicine A

This is a medicine for the treatment of a life-threatening form of cancer that predominantly affects older individuals (>55 years). The medicine provides the patient with a chance of extending their life by a few months. The medicine also has side effects, with shortness of breath, fatigue, nausea, vomiting, and fever being the most common ones. There are no other life-extending treatments available. Patients typically undergo the treatment for a maximum of a few months. The average cost per patient is €100,000. It is estimated that approximately 300 patients are eligible for this treatment per year. If all patients were to be treated, it would cost the government nearly 30 million euros annually.

Would you reimburse this drug from the basic health insurance?

1. Yes
2. No

Ask only if Q007 was yes

Q008 - B1a:

Choose from the following reasons which ones are important to you in your choice to include this medicine in the basic insurance:

Multiple answers possible

1. The medicine is effective.
2. There is a chance that this medicine is life-saving.
3. The medicine has a reasonable price considering the health benefits it provides to the patient.
4. There is no alternative treatment available for these patients.
5. The duration of treatment is relatively short, which limits the costs.
6. Other reason: *Open *Fixed

Q009 - B1b:

Which of the reasons you selected is the most important to you?

1. The medicine is effective.
2. There is a chance that this medicine is life-saving.
3. The medicine has a reasonable price considering the health benefits it provides to the patient.
4. There is no alternative treatment available for these patients.
5. The duration of treatment is relatively short, which limits the costs.
6. Other reason: *Open *Fixed

Ask only if Q007 was no

Q010 - B1c:

Choose from the following reasons which ones are important to you in your choice not to include this medicine in the basic insurance

Multiple answers are possible

1. The medicine only provides a chance of life extension but no certainty.
2. The medicine is too expensive considering the health benefits it provides to the patient.
3. The government should prioritize cheaper treatments that benefit a larger group of patients.
4. Healthcare becomes unaffordable if treatments at this price are reimbursed.
5. Drug manufacturers need to receive a signal that high prices are not accepted.
6. Other reason: *Open *Fixed

Q011 - B1d:

Which of the reasons you selected is the most important to you?

1. The medicine only provides a chance of life extension but no certainty.

2. The medicine is too expensive considering the health benefits it provides to the patient.
3. The government should prioritize cheaper treatments that benefit a larger group of patients.
4. Healthcare becomes unaffordable if treatments at this price are reimbursed
5. Drug manufacturers need to receive a signal that high prices are not accepted.
6. Other reason: *Open *Fixed

Q012 - B2:

Medicine B

This is a medicine for the treatment of a chronic intestinal disease. The disease primarily affects patients between the ages of 25 and 60 and has a significant impact on their quality of life. The medicine does not cure the disease but helps suppress the symptoms. Other treatments are available, but they are less effective. Patients need to continue the treatment for several years. The costs are approximately €20,000 per patient per year. It is estimated that around 800 patients are eligible for this treatment each year. If all patients are treated, it would cost the government approximately 16 million euros annually.

Would you reimburse this drug from the basic health insurance?

1. Yes
2. No

Ask only if Q012 was yes

Q013 - B2a:

Choose from the following reasons which ones are important to you in your choice to include this medicine in the basic insurance:

Multiple answers are possible

1. The medicine is effective
2. The medicine has a reasonable price considering the health benefits it provides to the patient.
3. The medicine prevents a great deal of suffering because it is for patients who have to live with this disease for a long time
4. The medicine improves people's quality of life.
5. Other reason: *Open *Fixed

Q014 - B2b:

Which of the reasons you selected is the most important to you?

1. The medicine is effective
2. The medicine has a reasonable price considering the health benefits it provides to the patient.
3. The medicine saves a lot of suffering as it is for patients with a disease they have to live with for a long time.
4. The medicine improves people's quality of life.
5. Other reason: *Open *Fixed

Ask only if Q012 was no

Q015 - B2c:

Choose from the following reasons which ones are important to you in your choice not to include this medicine in the basic insurance

Multiple answers possible

1. The disease this medication helps with is not life-threatening.
2. The medicine is too expensive considering the health benefits it provides to the patient.
3. There is a less expensive treatment available for these patients.
4. The treatment duration is long, which makes the costs even higher.
5. The government should prioritize cheaper treatments that benefit a larger group of patients.
6. Healthcare becomes unaffordable if treatments at this price are reimbursed.
7. Drug manufacturers need to receive a signal that high prices are not accepted.
8. Other reason: *Open *Fixed

Q016 - B2d:

Which of the reasons you selected is the most important to you?

1. The disease this medication helps with is not life-threatening.
2. The medicine is too expensive considering the health benefits it provides to the patient.
3. There is a less expensive treatment available for these patients.
4. The treatment duration is long, which makes the costs even higher.
5. The government should prioritize cheaper treatments that benefit a larger group of patients.
6. Healthcare becomes unaffordable if treatments at this price are reimbursed.
7. Drug manufacturers need to receive a signal that high prices are not accepted.
8. Other reason: *Open *Fixed

Q017 - B3:

Medicine C

This is a medicine for the treatment of patients with Alzheimer's dementia. This disease primarily affects older individuals (>65 years) and patients experience memory complaints, behavioral problems, and changes in character. The medicine is intended to slow down the progression of the disease, but its effectiveness is uncertain. Other treatments are available, but they also have limited effects. Patients need to continue the treatment for several years. The costs are €50,000 per patient per year. It is estimated that approximately 5,000 patients are eligible for this treatment each year. If all patients are treated, it would cost the government a total of over 240 million euros per year.

Would you reimburse this drug from the basic health insurance?

1. Yes
2. No

Ask only if Q017 was yes

Q018 - B3a:

Choose from the following reasons which ones are important to you in your choice to include this medicine in the basic insurance:

Multiple answers possible

1. The medicine offers a chance of improvement, even though it is uncertain.
2. The medicine has a reasonable price considering the health benefits it provides to the patient.
3. The medicine is intended for patients with a disease that causes increasing disabilities.
4. Other reason: *Open *Fixed

Q019 - B3b:

Which of the reasons you selected is the most important to you?

1. The medicine offers a chance of improvement, even though it is uncertain.
2. The medicine has a reasonable price considering the health benefits it provides to the patient.
3. The medicine is intended for patients with a disease that causes increasing disabilities.
4. Other reason: *Open *Fixed

Ask only if Q017 was no

Q020 - B3c:

Choose from the following reasons which ones are important to you in your choice not to include this medicine in the basic insurance

Multiple answers possible

1. The medicine only offers a chance of slowing down the disease, but there is no certainty.
2. The disease this medicine helps with is not life-threatening.
3. The medicine is too expensive considering the health benefits it provides to the patient.
4. There is a less expensive treatment available for these patients.
5. The government should prioritize cheaper treatments that benefit a larger group of patients.
6. Healthcare becomes unaffordable if treatments at this price are reimbursed.
7. Drug manufacturers need to receive a signal that high prices are not accepted.
8. Other reason: *Open *Fixed

Q021 - B3d:

Which of the reasons you selected is the most important to you?

1. The medicine only offers a chance of slowing down the disease, but there is no certainty.

2. The disease this medicine helps with is not life-threatening.
3. The medicine is too expensive considering the health benefits it provides to the patient.
4. There is a less expensive treatment available for these patients.
5. The government should prioritize cheaper treatments that benefit a larger group of patients.
6. Healthcare becomes unaffordable if treatments at this price are reimbursed.
7. Drug manufacturers need to receive a signal that high prices are not accepted.
8. Other reason: *Open *Fixed

Q022 - B4:

Medicine D

This is a medicine for the treatment of patients with an inherited muscle disease. Patients with this disease experience symptoms from a young age, and the disease leads to severe physical disabilities and can be fatal in some cases. The medicine helps a majority of children have better development and fewer disabilities. However, its effect on adults is unknown. There are no other treatment options available. Patients need to continue the treatment for several years. The costs are €350,000 per patient per year. It is estimated that approximately 85 patients are eligible for this treatment each year. If all patients are treated, it would cost the government a total of 30 million euros per year.

Would you reimburse this drug from the basic health insurance?

1. Yes
2. No

Ask only if Q022 was yes

Q023 - B4a:

Choose from the following reasons which ones are important to you in your choice to include this medicine in the basic insurance:

Multiple answers possible

1. The medicine is effective.
2. The medicine has a reasonable price considering the health benefits it provides to the patient.
3. There is no alternative treatment available for these patients.
4. The medicine is intended for patients with a disease that causes increasing disabilities.
5. The medicine treats patients with a disease for which no other treatments are available.
6. The medicine is also suitable for children.
7. Other reason: *Open *Fixed

Q024 - B4b:

Which of the reasons you selected is the most important to you?

1. The medicine is effective.
2. The medicine has a reasonable price considering the health benefits it provides to the patient.

3. There is no alternative treatment available for these patients.
4. The medicine is intended for patients with a disease that causes increasing disabilities.
5. The medicine treats patients with a disease for which no other treatments are available.
6. The medicine is also suitable for children.
7. Other reason: *Open *Fixed

Ask only if Q022 was no

Q025 - B4c:

Choose from the following reasons which ones are important to you in your choice not to include this medicine in the basic insurance

Multiple answers possible

1. The medicine offers a chance of improvement, but no certainty.
2. The medicine is too expensive considering the health benefits it provides to the patient.
3. The government should prioritize cheaper treatments that benefit a larger group of patients.
4. Healthcare becomes unaffordable if treatments at this price are reimbursed.
5. Drug manufacturers need to receive a signal that high prices are not accepted.
6. Other reason: *Open *Fixed

Q026 - B4d:

Which of the reasons you selected is the most important to you?

1. The medicine offers a chance of improvement, but no certainty.
2. The medicine is too expensive considering the health benefits it provides to the patient.
3. The government should prioritize cheaper treatments that benefit a larger group of patients.
4. Healthcare becomes unaffordable if treatments at this price are reimbursed.
5. Drug manufacturers need to receive a signal that high prices are not accepted.
6. Other reason: *Open *Fixed

Section C

Q029 - C2:

If a medication is in the Coverage Lock, an additional assessment is conducted on the scientific evidence of its effectiveness, and the minister negotiates with the manufacturer to lower the price of the medication. This process takes time, averaging around 11 months.

In the following overview, please indicate when you believe a medication in the Coverage Lock period should still be made available and who should bear the costs:

A medication in the Coverage Lock should be made available...

	No	Yes: the government should bear the costs	Yes: the manufacturer should bear the costs
... for all eligible patients	0	0	0
...if the medication is intended for patients with a life-threatening disease	0	0	0
...if the medication is intended for patients for whom there is no alternative treatment available	0	0	0
...if delaying the treatment causes irreversible worsening of symptoms or disabilities in patients	0	0	0
...if the patients are children	0	0	0

Q027 - C1:

If a medicine is placed in the Coverage Lock, the scientific evidence of its effectiveness and the price are evaluated by specially established committees. Their recommendations are then sent to the minister, who ultimately decides whether to reimburse the medicine or not.

If you were to assemble these committees, which of the following people would you include?

Multiple answers possible

1. Patients
2. Citizens
3. Doctors
4. Economists
5. People from pharmaceutical companies
6. Scientific researches
7. Ethicists
8. Lawyers
9. Hospital administrators

Q028 - C1a:

Who's vote should be decisive when parties don't agree on the assessment of an expensive medicine.

1. Patients
2. Citizens
3. Doctors
4. Economists
5. People from pharmaceutical companies
6. Scientific researches
7. Ethicists
8. Lawyers
9. Patients
10. The majority should then have the final say.

Section D**Q031 - D1:**

Could you please indicate the extent to which you agree or disagree with the following statements?

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I support expensive medicine not being reimbursed, even if it means I would not have access to the medicine myself in the future.	☐	☐	☐	☐	☐
I support expensive medicine not being reimbursed, but patients who choose to pay for the medicine themselves should still be able to receive the treatment.	☐	☐	☐	☐	☐

Q032 - D3:

Please imagine the following situation:

Your neighbor's 1.5-year-old boy is diagnosed with a rare disease. If left untreated, he will never learn to walk, might require ventilation support, and could even pass away at a young age. There is an expensive medicine available that offers your neighbor's son a chance at a normal life expectancy and a life with fewer disabilities.

However, in the Netherlands, this medicine is under Coverage Lock. The costs of €1.9 million per patient are not covered. In the Netherlands, patients cannot access the medicine even if they pay for it themselves. Your neighbors, the parents of the boy, start a crowdfunding campaign to afford the treatment with the expensive medicine in another European country.

Would you be willing to financially contribute to this crowdfunding campaign so that your neighbor's son can receive the treatment?

1. Yes
2. No

Ask only if Q032 was yes

Q033 - D3a:

What is the main reason you would like to financially contribute to this crowdfunding campaign?

1. That I can afford it financially.
2. That I feel compelled to help others when they reach out to me.
3. That I can imagine myself being in this situation myself.
4. Other reason... *Open *Fixed

Ask only if Q032 was no

Q034 - D3b:

What is the main reason you do not want to contribute financially to this crowdfunding campaign?

1. That I don't have the money for it.
2. That I don't feel compelled to financially support the treatment of my neighbor's child.
3. That this crowdfunding campaign increases inequality among patients because there are parents who cannot raise the amount.
4. That, in my opinion, this treatment is excessively expensive.
5. That I prefer to spend my money on a cheaper treatment that can benefit a larger group of patients.
6. Other reason... *Open *Fixed

Q035 - D4:

Imagine the following situation:

If the healthcare premium for everyone in the Netherlands is increased, not only your neighbor's child can be treated, but also all other children in the Netherlands with the same disease.

Would you support raising the premium of the mandatory health insurance so that all children with this disease in the Netherlands can receive treatment?

1. Yes
2. No

Ask only if Q035 was yes

Q036 - D4a:

The average price of a basic health insurance is 1498 euros per year (which is €124.80 per month). Can you indicate from the list below the maximum premium increase that you find acceptable?

1. 2%: This is approximately €30 per year and €2.40 per month.
2. 5%: This is approximately €75 per year and €6.25 per month
3. 10%: This is approximately €150 per year and €12.48 per month
4. 25%: This is approximately €375 per year and €31.20 per month
5. More than 25%

Ask only if Q035 was no

Q037 - D4b:

What is the main reason why you are not willing to pay higher healthcare premiums?

1. That I don't have the money for it.
2. That I don't feel compelled to financially support the treatment of children with this rare disease.

3. That only children with this disease would benefit from it, while other patients needing expensive medications would not.
4. That, in my opinion, this treatment is too expensive.
5. That the money could be better spent on a cheaper treatment for a larger group of patients.
6. Other reason... *Open *Fixed



Chapter 6

Differences in access to nusersen in Europe; are moral reasons taken into account in reimbursement decisions?

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Abstract

Introduction: In 2017, the first treatment for spinal muscular atrophy (SMA) became available. Nusinersen is a lifesaving treatment, and enables children not only to survive, but also to gain new motor skills that were previously unattainable. However, nusinersen is an expensive treatment and together with many other expensive medicines, it puts a strain on solidarity-based healthcare systems. Due to differences between reimbursement policies, access to nusinersen among patients in Europe varied greatly even among countries with similar socio-economic circumstances. This raises the question which arguments or principles underpin these policies for reimbursement of expensive treatments.

Methods: We compared the reimbursement policies of four neighboring European countries with comparable economies. We searched scientific and grey literature on the reimbursement systems for expensive drugs and their reimbursement decisions on nusinersen. The search was initially performed between July 2021 and June 2022, and updated in February 2025.

Results: Belgium and Germany have special regulations for orphan drugs. Germany and The Netherlands have financial thresholds for requiring a health technology assessment (HTA) on new medicines. Aside from cost-effectiveness calculations, two moral reasons were found in the reimbursement decisions. The disease severity was mentioned in Germany as an argument to reimburse nusinersen also in patient groups with limited proven efficacy. Solidarity was mentioned in France and in The Netherlands as an argument to not reimburse nusinersen.

Conclusion: We identified two moral arguments explicitly mentioned in reimbursement decisions for expensive medicines in European countries. The exceptions made for orphan medicine by Germany and Belgium reflect the unmet medical need in patients with orphan diseases. However, moral reasoning as part of the decision making remains informal.

Introduction

New drugs for rare diseases (so called orphan medicines) fulfill important unmet medical needs, but their high prices are one of the challenges for the sustainability of health care systems (1). Between 2017 and 2021 the European Medicines Agency (EMA) approved three medicines (nusinersen, onasemnogene abeparvovec and risdiplam) for hereditary proximal spinal muscular atrophy (SMA), a rare autosomal recessive neuromuscular disorder with an incidence of 1:6000-1:10,000 new-borns caused by the loss-of-function of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q (2). SMA is one of the more common genetic causes of premature death and severe disability of infants and young children. The most severe, infantile onset variant (SMA type 1) is also the most common in approximately 50% of patients. It leads to respiratory failure in the first year of life in the majority of patients if left untreated (3). The chronic childhood forms, i.e. SMA types 2 and 3, are characterized by stalled gross motor development followed by gradual deterioration in muscle strength and severe levels of disability from an early age and a life expectancy into middle age or beyond (4). Adult onset SMA (type 4) causes weakness and slowly progressive deterioration of motor function (3-6). The three drugs for SMA significantly altered the prognosis of SMA, but their high prices caused a societal debate on the desirability of reimbursement in the Netherlands and other countries (7, 8).

The EMA assesses the benefit-risk ratio of orphan medicines prior to the decision of market access in the European Union, but each individual member state decides whether new drugs will be reimbursed. Nusinersen, an antisense oligonucleotide (ASO), was the first treatment for SMA that obtained market access from the EMA, based on two randomized clinical trials (RCT) in infants with SMA type 1 and young children with SMA type 2 (9, 10). The price of nusinersen is approximately €500,000 for the first year (for six injections) followed by a yearly and lifelong €250,000 (for three injections per year as maintenance) per patient. The level of pricing forced health authorities in EU member states to consider reimbursement conditions in their jurisdictions, which led to significant differences in access to nusinersen between EU member states. In Germany, Italy and France patients had access to nusinersen relatively shortly after EMA approval, while patients in the Netherlands, the United Kingdom and Scandinavia had to wait longer for the decision on reimbursement, which was often confined to subgroups.

A comparison of health technology assessments reports from several European countries on nusinersen has already been published (11). The authors specifically analyzed how the economic evaluation and budget impact of nusinersen influenced the reimbursement decisions in 12 European and North-American countries. An important conclusion was that

all countries adopted a reimbursement arrangement despite the lack of cost-effectiveness in all reports and a clear shortage of arguments in favor of the reimbursement decision. However, the authors did not analyze the impact of moral reasoning in the decision-making process. We therefore aimed to clarify the contribution of moral reasoning to reimbursement of nusinersen as an example of an orphan drug, by comparing health technology assessment (HTA) reports from the Netherlands, Belgium, Germany and France.

Methods

Countries and nusinersen

We selected EU member states Germany, Belgium, France and The Netherlands, countries with comparable levels of affluency but with differences in timing and inclusiveness of access to nusinersen. Following market approval of nusinersen by EMA on May 30th 2017, Germany arranged early access (from December 2017) for all individuals with SMA. Belgium, granted reimbursed access for all patients from July 2018, The Netherlands followed in August 2018 with limited reimbursed access (i.e. nusinersen was available for patients with SMA type 1, 2 and 3, younger than 9.5 years at the start of treatment). France arranged earlier access to nusinersen for children with SMA type 1 and 2 through a post Autorisation Temporaire d'Utilisation (ATU) agreement. The ATU is a temporary authorization for use at the French market for drugs with the intend to provide early access to drugs for patients with a severe or rare disease with a high unmet need and no therapeutic alternatives are available. Reimbursed, although limited access followed in April 2019 (only for patients with SMA type 1, 2 and in selected cases for patients with SMA type 3).

Search strategy

To investigate if countries had a specific policy for expensive drugs we used a combination of search terms per country of “reimbursement”, “expensive drug”, “policy”, “drug pricing” “orphan drug”. We searched in Pubmed and Google Scholar. The literature found with this search was then used to find governmental documents in which policies and reimbursement decisions are described. These policy documents were used for this paper. We retrieved the official reimbursement decisions and their supporting explanations on nusinersen from Germany, Belgium, France and The Netherlands.

The original search was conducted between July 2021 and June 2022. In February 2025 we updated our search on both the policies for expensive drugs and the current reimbursement of nusinersen.

Data extraction

We extracted the arguments used to support the reimbursement decision, which are summarized in **appendix table 1**. We used English versions of reports if available. We used Google Translate to help translate reports and relevant publications when they were only available in French or German if necessary.

Results

We first analyzed reimbursement policies of expensive or orphan medicines in the four selected countries.

Policies for reimbursement of expensive (orphan) medicine

The four countries differed in policies, ranging from no policy, generic policy for expensive medicines and specific policies for orphan medicines.

1. The Netherlands uses a special policy for all expensive medicines (including orphan medicines) called the Coverage Lock (CL). The CL applies to medicines exceeding a financial limit; a budget impact of more than 20 M€ in total or more than 50 k€ per patient resulting in total costs exceeding 10 M€ per year (12). New medicines are placed in the Coverage Lock after EMA approval for the European market. In practice, the Dutch Healthcare Institute (DHI) assesses expensive drugs based on four criteria by, i.e. efficacy, cost-effectiveness, necessity and (financial) feasibility. While this assessment takes place, the (orphan) medicine is not available for patients, unless the pharmaceutical company provides the medicine free of charge. The assessment duration is 14-26 months. In case the conclusion of the assessment is that medicines are of added value but do not meet the criteria for cost-efficacy, the ministry of health starts price negotiations with the manufacturer. If price negotiations are successful, the minister of Health may decide on reimbursement.
2. Belgium and Germany have special policies for orphan medicines. In Belgium an orphan medicine is considered of added therapeutic value by its orphan label rather than by the outcome of a pharmaco-economic assessment (13-16). The timeline from EMA approval to reimbursement and access for patients is on average 18 months (17). Germany uses a similar initial approach to orphan medicines, i.e., they are considered a priori of therapeutic value, without an additional assessment of added clinical benefit. Unlike in other countries, (orphan) medicines become available for patients directly after EMA approval. It is immediately reimbursed for the list price in the first year, but if the annual expenditure of the specific orphan medicine by the statutory health insurance (SHI)

exceeds the threshold of 30 M€ per year, an assessment of additional clinical benefit is required and price negotiations follow based on the established additional clinical benefit (18-22).

- 3. There is no French policy for expensive or orphan medicine. All types of drugs follow the same assessment and reimbursement procedure and are usually available after a reimbursement decision is made. This process takes on average about 9-12 months (17, 23).

Arguments used in reimbursement decisions for nusinersen

Table 1 provides a comprehensive overview of the arguments that surfaced in our document analysis (with a more detailed overview in **appendix table 1**).

Table 1. Schematic overview of reimbursement arguments used per country				
Reimbursement argument	The Netherlands	Belgium	France	Germany
Efficacy	X	X	X	X
Cost-effectiveness	X			
Additional benefit or clinical benefit			X	X
Solidarity	X		X	
Disease severity				X
Legend table 1. Efficacy = treatment has proven efficacy by clinical trials. Cost-effectiveness = the price per QALY.				

Efficacy

All four countries evaluated the efficacy of nusinersen, either in comparison with standard supportive treatment (France and Germany), or as reported in relevant clinical trials (the Netherlands and Belgium) (9, 10). The health authorities of Belgium and The Netherlands used the same (joint) assessment but approached uncertainties differently. The Dutch authorities concluded that the clinical trials did not provide data of efficacy beyond a specific disease duration with SMA and decided that this precluded reimbursement, while the Belgian Drug Reimbursement Committee (DRC) decided to reimburse Nusinersen treatment for all SMA patients irrespective of disease duration.

The French and German authorities assessed efficacy in terms of (added) clinical value or benefit in the current treatment strategy for SMA based on the available clinical trials (9, 10). In both countries the authorities considered efficacy and clinical benefit for SMA type 1 and 2 evident, but dealt with the uncertainties of efficacy for SMA type 3 and 4 in various ways. The German authorities acknowledged the lack of relevant data for these patient categories, but nevertheless supported reimbursement based on considerations of disease severity and advice from the medical society for all SMA patients. The French authorities considered that the clinical benefit of nusinersen for patients with SMA type 3 was potentially high, but at the same time acknowledged that data to support added therapeutic value compared to the standard treatment (best supportive care) was lacking. For SMA type 4, the French authorities thought that there was insufficient (evidence of) clinical benefit. This resulted in a reimbursement arrangement for patients with SMA type 3 based on a case-by-case assessment through multidisciplinary team meetings and the exclusion of patients with SMA type 4 (24).

In summary, the four countries used the same set of data but came to very different reimbursement decisions for Nusinersen.

Cost-effectiveness and price negotiations

Cost-effectiveness was only mentioned by the Dutch Health Institute (DHI). The DHI employs thresholds per Quality Adjusted Life Year (QALY) and uses a threshold of 80k €/QALY that would be exceeded by the treatment with nusinersen for all types of SMA. The DHI argued that negative cost-effectiveness ratios may result in crowding out of other care. The DHI advised the Dutch government to negotiate a price reduction of at least 85% to stay below this threshold. The Belgian DRC did not use the argument of cost-effectiveness in their advice for a non-specified price reduction. Germany and France did not mention cost-effectiveness or a price reduction in their reimbursement statements.

Unmet need and disease severity as reflection of moral considerations

The severity of SMA and the unmet medical need was explicitly acknowledged by Germany in the reimbursement decision. The disease severity and unmet medical need overruled the uncertainties around efficacy in patients with SMA type 3 and 4.

In The Netherlands and France disease severity and unmet need were arguments to facilitate access to treatment via different routes, but were not included arguments in the reimbursement decisions. Access to treatment in France was initially arranged through a temporary market authorization (ATU). ATU is a special arrangement between the French government and the manufacturer to ensure early access to treatments for patients with a

severe disease and unmet medical need. The unmet need did not play a role in the final reimbursement agreement in France.

In The Netherlands the DHI advised the ministry of Health not only to start price negotiations in order to allow treatment of children younger than 9.5 years, but also to facilitate a conditional reimbursement arrangement for older patients. The conditional reimbursement program is designed to create access for patients to new innovative treatments that fulfill an unmet medical need, but have an uncertain efficacy. Belgium did not mention the disease severity or an unmet medical need in their reimbursement decision.

Solidarity as reflection of moral considerations

Solidarity was not a consideration in favor of reimbursement in any of the countries, but mentioned twice as a reason *not* to reimburse treatment with nusinersen in subgroups of patients. The Dutch and French authorities considered that there was no convincing evidence for the efficacy of nusinersen in patient subgroups defined by either age (Netherlands) or SMA type (France). The Dutch and French health authorities specifically argued that a decision not to reimburse treatment would help to preserve solidarity within healthcare systems, since reimbursement of unproven treatments would significantly strain already limited budgets. The Dutch DHI went one step further by stating in their report that solidarity cannot only be asked from citizens but that manufacturers also carry responsibility.

Discussion

With this study we aimed to gain more insight in the arguments and reasons that explain differences in reimbursement policies of orphan drugs between neighboring European countries. We used nusinersen, of which an analysis of the HTA including economic evaluations and budget impact in 12 affluent countries had already been published, as a case study (11). We extensively searched policy documents to see which moral arguments were given to support reimbursement decisions. We found that reimbursement decisions made by health authorities in neighboring countries with comparable levels of wealth, using the same limited set of efficacy data from two clinical trials were significantly different and led to marked differences in patient access to a treatment for which there was, at the time, no alternative. Moral arguments, underlying special policies for orphan medicine, and included in the final reimbursement decisions do explain these differences.

Policies

The four countries use different policies for orphan medicines. Germany and Belgium have specific policies for this drug category, assuming that the orphan medicine label from the EMA reflects a high unmet medical need. Under these policies, the decision on reimbursement is less influenced by the limitations of clinical trials with small sample size and the consequential lack of data of efficacy in the full spectrum of a rare disease (25-28). One could argue that unmet medical need is part of the moral foundation of these policies. In contrast, The Netherlands and France have reimbursement policies that do not prioritize unmet medical need based on the EMA orphan label. The assessments reflected the struggle with small sample sizes and the more general lack of efficacy data for older patients or those with SMA type 3 and 4. Nevertheless, initial reimbursement restrictions were more significant in the Netherlands (i.e., all patients older than 9.5 years) than in France (i.e., very rare SMA type 4). Despite their policies, both The Netherlands and France seemed to acknowledge the importance of unmet medical need in more practical ways. The ATU in France allowed access to nusinersen for patients prior to the reimbursement arrangement in 2019, while early access for young children with SMA type 2 and 3 in The Netherlands was improvised by the ministry of Health in the first months of 2018 after publicized demands by patient representatives. After the relatively restricted reimbursement arrangement (i.e. start of treatment before the age of 9.5 years), a conditional reimbursement agreement enabled access to treatment for older patients from January 2020 onwards.

The Netherlands and Germany use a financial threshold to subject a new medicine to cost-effectiveness assessments, albeit with different timelines. In Germany, an orphan medicine is almost directly available after EMA approval and is reimbursed at its list price. The first year is then used for further assessment and price-negotiations in order to agree on new price arrangements if a specific financial threshold is exceeded. Most of the assessed medicines remain on the German market after the additional analysis (29). In the Netherlands, the coverage lock policy prioritizes cost-effectiveness analysis and price negotiations over early access, which is delayed with an average of 14 months, as was the case with nusinersen (30).

Moral reasoning

We found two explicit moral reasons in the documents of reimbursement decisions, i.e. solidarity and disease severity.

Solidarity is a fundamental value underlying the healthcare system in many countries, including the countries included in this study. Citizens contribute to accessible healthcare by paying taxes and healthcare premiums. This solidarity-based system ensures healthcare for all citizens within society, independently from their social-economic status. However, solidarity was primarily an argument to limit access to nusinersen treatment. Both the French and Dutch health authorities argued that solidarity is an argument *not* to reimburse nusinersen. Both countries use the pharmacoeconomic analysis, in which the efficacy of nusinersen is assessed, to support their solidarity argument.

Analyses of importance of solidarity in the reimbursement of expensive medicines are few. Two articles refer to solidarity and the reimbursement of expensive medicine at the theoretical level (31, 32). Fleck argues that justice can overrule solidarity-based considerations: “(...) acts of health care compassion are not necessarily above or beyond critical consideration from the perspective of health care justice. In other words, acts of compassion are not intrinsically self-justifying, especially when social or public resources are the means through which those compassionate acts are carried out.” (32). Seen from this point, it might be possible to overrule solidarity with justice-based arguments and limit access to care. Nunes remains on a more general level and argues that treatments with unproven efficacy should not be included in the basic insurance package. He states “This package, financed by the solidarity of taxpayers, must truly contribute to the global improvement of health both at an individual as at a social level.” (31).

However, it is interesting that the two other countries (Belgium and Germany), with a similar healthcare system and similar findings on the efficacy of nusinersen did not put forward solidarity as a reason to limit the reimbursement of nusinersen.

Even if justice-based arguments overrule this interpretation of solidarity, the more general question remains whether it is reasonable to use solidarity as an argument to limit reimbursement. Solidarity in healthcare means we all pay taxes and healthcare premiums, to support those who were unlucky, including those with a disabling or lethal diseases like SMA, which result from bad luck in the gene lottery. Withholding available treatment to preserve the money and treat other, often unspecified, illnesses and health problems cannot be justified by solidarity. If we agree that choices have to be made because of limited budgets, we must also acknowledge that a just allocation of the healthcare budget does not

equal solidarity. Justice based arguments for a fair allocation of limited healthcare budgets have been described previously and specifically for expensive medicines (27, 28, 31, 33-41). Although these could be used by policymakers to support such decisions, solidarity-based systems also require governments to develop or use means that would promote fair pricing rather than price levels set at previously experienced willingness to pay (1). After all, if prices are unreasonable, governments may feel a duty to regulate the market of drug prices with policies that do not stifle the development of innovative treatments.

The German Federal Joint Committee used disease severity as a moral reason in their decision to reimburse treatment for all SMA patients, arguing that "...taking into account the available evidence on the medical benefit of nusinersen, the severity of the disease and the statements of the medical societies on the current reality of care, nusinersen may represent a relevant therapeutic option for patients with 5q SMA type 3 / 4...". Arguably, disease severity reflects the unmet medical need criterion that supports the orphan drug policy in Germany, but it seems markedly different from the approach in other countries. The Netherlands, Sweden and the UK are examples of countries where disease severity is not put forward as a moral reason in reimbursement decision making, but is rather incorporated in the cost-efficacy analysis based on QALY methodology (42-44). The German choice to attribute a high relative weight to disease severity in the decision process of nusinersen reimbursement therefore represents the only moral reason that we found supporting broad access to treatment.

Disease severity is indeed mentioned in literature as one of the characteristics of unmet medical need (45, 46). An unmet medical need has many definitions, this is the reason why Vreman proposed it is related to one or more elements, i.e. impact of available treatments, patient population size or disease severity (46). SMA is a severe neuromuscular disease, for which no treatment was available at the time of reimbursement assessments. Patients are usually very young and experience continuous deterioration of their muscle strength leading to severe disability and death (3-5). Nusinersen provided improvement of motor function or at least stabilization of the motor function in SMA patients. With no other treatment available except best supportive care, one can say that nusinersen fulfilled the proposed criteria of unmet medical need in various ways. The fact that unmet medical need is used as an argument for accelerated market access in Europe (47), supports a similar approach for reimbursement decisions as well. Unmet medical need would also honor the Rawlsian difference principle, that advocates compensation for severe disadvantage beyond the choice or control of individuals such as genetic diseases (36).

Strengths and limitations

Our study contributes to the knowledge on moral reasoning in the reimbursement of expensive medicine like nusinersen. By comparing four neighboring countries with similarities in healthcare systems and affluency, we were able to compare the moral reasoning in the respective reimbursement decisions. By choosing four northern European countries with similar economies and healthcare systems, our study is less applicable to countries with different economies and healthcare systems which is a limitation of our study. A general lack of transparency affected our analysis. Transparency is regarded as an important value in reimbursement decision processes that even could help to improve support in societies (27, 38), but is not reflected by the completeness and accessibility of reimbursement decision reports. Reimbursement of nusinersen in Belgium was an example of a relatively under documented procedure (48, 49), while the procedures in the Netherlands required a high level of insider knowledge.

Conclusion

Our findings suggest that countries take moral arguments such as solidarity and disease severity into account in reimbursement decisions. However, moral reasoning as part of the decision-making process appears limited and rather informal, and it remains unclear how these arguments are exactly weighed. Orphan drug policies that acknowledge unmet medical need probably implicitly promote moral reasoning as part of the reimbursement decision process.

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Supplementary files chapter 6

Appendix table 1. More detailed overview of arguments mentioned in reimbursement policies

Mentioned arguments in policy documents		Moment of reimbursed access to treatment
The Netherlands (50, 51)	<ol style="list-style-type: none"> Efficacy is proven in only a small patient cohort with limited disease duration, age and genetic background: <ul style="list-style-type: none"> 1. SMA type 1 and a disease duration no longer than 26 weeks 2. SMA type 2 or 3 and a disease duration no longer than 94 months 3. Presymptomatic infants with a maximum of 3 <i>SMN2</i> copies. <p>By reimbursing only proven effective treatments we remain solidarity within the healthcare system.</p> Cost-effectiveness of nusinersen; exceeds the limit of 80.000€/QALY. Reimbursement only possible after price negotiations. Otherwise, the risk of crowding out of other care. The DHI urged that nusinersen was the first available treatment for SMA and should be available soon DHI stated that solidarity can not only be asked from citizens; pharmaceutical companies have to take their responsibility too Conditional reimbursement is possible when there is an unmet need for the treatment of a disease. 	<p>August 2018</p> <ul style="list-style-type: none"> - SMA type 1 with a disease duration no longer than 26 weeks - SMA type 2 or 3 with a disease duration no longer than 94 months - Presymptomatic children with 2 or 3 <i>SMN2</i> copies <p>January 2020</p> <ul style="list-style-type: none"> - Conditional reimbursement for all SMA patients not considered in the definite reimbursement program.
Belgium (52)	<ol style="list-style-type: none"> The DRC used the joint Dutch-Belgian assessment of nusinersen and advised to create a convention to: <ol style="list-style-type: none"> Treat SMA patients for which added value has been proven (see DHI report) The costs of nusinersen have to be reduced drastically by: <ol style="list-style-type: none"> Reducing the unitary costs in the function of proven efficacy in several subpopulations 	<p>July 2018</p> <ul style="list-style-type: none"> - Reimbursement for all SMA patients

	<p>ii. The costs for the first year of treatment and the costs for non-responders are not recovered from the health insurance</p> <p>iii. There should be a solution for the uncertainty on the final group size of the treated population.</p> <p>c. During the convention, the manufacturer has to collect data on efficacy and safety in subpopulations as well in the real-world clinical practice.</p> <p>2. After price negotiation it was announced treatment was reimbursed for all SMA patients, and efficacy of treatment will be individually assessed after 14 months prior to extending the reimbursed treatment.</p>	
Germany (53-57)	<p>The Federal Joint Committee (FJC) published their first assessment of nusinersen in December 2017 together with the reimbursement decision.</p> <p>They stated that the therapeutic value for:</p> <ul style="list-style-type: none"> - SMA type 1 was substantial - SMA type 2 was considerable - SMA type 3 and 4 not quantifiable, based on the available data (55, 56). <p>The FJC assessed the additional benefit of nusinersen in 2020 after crossing the annual expenditure threshold.</p> <ul style="list-style-type: none"> - SMA type 1 (based on the ENDEAR) it was found that nusinersen gives a major additional benefit - SMA type 2 (based on the CHERISH) it was found to be a considerable additional benefit - SMA type 3 and 4 it was found that additional benefit was not proven, but nusinersen might be a relevant therapeutic option for these patients. "Taking into account the available evidence on the medical benefit of nusinersen, the severity of the disease and the statements of the medical societies on the current reality of care, nusinersen may represent a relevant therapeutic option for patients with 5q SMA type 3 / 4.". (53, 54) 	<p>December 2017: reimbursed treatment for all SMA types, for two years</p> <p>May 2019: manufacturer requested postponement of re-evaluation. More time was needed to evaluate the long-term efficacy and safety due to small patient cohorts.</p> <p>FJC agreed and re-evaluation was postponed till July 2024 (57).</p> <p>June 2020: the Statutory Health Insurance (SHI) noticed that the annual expenditure on nusinersen crossed the threshold of 50 million euros per year. The manufacturer was asked by the GBA to deliver data to assess the additional clinical benefit as part of the AMNOG law.</p>

		May 2021: reimbursed treatment for all SMA patients continued.
France (58-60)	<p>The Transparency Committee of the High Health Authority reported in January 2018:</p> <ul style="list-style-type: none"> - A high clinical benefit for patients with SMA type 1 and 2 and a moderate clinical added value for the therapeutic strategy in these patients. - A high clinical benefit was also considered for patients with SMA type 3, but no proven clinical added value for the therapeutic strategy was found. - Insufficient clinical benefit to justify reimbursement of treatment for SMA type 4 patients based on solidarity grounds. - Furthermore, they suggest to assess efficacy and safety of treatment via a national cohort. 	<p>Treatment was available in a post-ATU agreement until final reimbursement was set in April 2019 for patients with SMA type 1, 2. For patients with SMA type 3 reimbursed treatment was available based on a case-by-case assessment, taking the walking ability into account, through multidisciplinary team meetings. (60)</p>

Legend table 1:

Post-ATU = post Autorisation Temporaire d'Utilisation (ATU). The ATU is a temporary authorization for use at the French market for drugs with the intend to provide early access to drugs for patients with a severe or rare disease with a high unmet need and no therapeutic alternatives are available. This means patients can get access to treatment prior to EMA approval. When the EMA approves market authorization, reimbursement arrangements still have to take place. To ensure ongoing access for patients, the French government can set a post-ATU agreement to continue treatment for patients.



Chapter 7

General discussion

Spinal muscular atrophy (SMA) is a rare, hereditary and severe disease. The quest for therapeutic options exemplifies both biotechnological progress that allowed the development of specific medicine as well as the societal dilemma concerning the reimbursement of such highly expensive medicine. The orphan drug act passed by the United State Congress in 1983 (and similar legislation in the European Union in 1999) (1, 2) facilitated the development of treatments for rare diseases by pharmaceutical companies, but its success also introduced new challenges. While pharmaceutical companies view the development and marketing of orphan medicine as a viable business model, their high pricing in combination with uncertainty regarding efficacy challenge the sustainability of public healthcare systems (3-8).

In this thesis I explored the efficacy and safety of nusinersen, an orphan drug, as well as the dilemmas that surfaced around its reimbursement in the Netherlands. Nusinersen was the first treatment for SMA that became available in 2017. The European Medicines Agency (EMA) granted market access for this drug, based on the results of two pivotal trials. The group of around 250 participants in these trials were all children up to the age of 13 years (9, 10). The medical need of patients with SMA older than 13 year was however as unmet as for the younger patients. Moreover, the available data limited a comprehensive evaluation of treatment effects. The first aim of this thesis was therefore to investigate the efficacy and safety of nusinersen in the cohort of Dutch patients (up to the age of 9.5 years at the start of treatment). This was the group for whom reimbursement of the treatment became available in August of 2018. Other patients remained untreated, and this caused a public and political debate in the Netherlands that, although relatively short lived, seemed to indicate an important form of dissent towards reimbursement policies. The Coverage Lock, the policy instrument of the Dutch government to contain costs of expensive drugs that limited access for patients older than 9.5 years, has never been systemically investigated. The second aim was therefore to evaluate the justification of this policy, especially from the perspective of health care and society's basic principles of justice and solidarity.

7.1 Treatment effects of nusinersen for SMA patients

7.1.1 Treating children with SMA with nusinersen is effective

In **chapter 2** I report the effects of treatment with nusinersen on motor function in a population-based cohort of children with SMA over a period of three years. This cohort is relatively unbiased and encompasses all Dutch children eligible for treatment. We show that treatment with nusinersen is effective and that the majority of children (72%) experienced improvement of motor function as documented by an SMA-specific motor function scale. Importantly, children whose motor function did not improve, often experienced no further

loss of motor function during treatment, which is different from the natural history of SMA that is characterized by deterioration of muscle strength over time (11-16). Patients and caretakers view not only improvement but also stabilization as significant treatment success. We observed that motor function improvement correlated with shorter disease duration, but modelling of the data shows that there is no specific age limit that would predict treatment success.

Improvements in motor function after the start of treatment is not linear but flattens to a new 'plateau' after the first one to two years. We think that this pattern can be explained by the maturation or activation of a fixed pool of 'hibernating' motor units (17) while the flattening of the treatment effect reflects the limitation in the number of these motor units that can be revived. The outcome measures used to document treatment effect are motor function scales (i.e., CHOP-INTEND, HFMSE, MFM, RULM etc.). Using only motor function scales may lead to underestimation of treatment effects. Patients report a wider range of experiences to describe effects of nusinersen treatment, but the use of patient reported outcome measures is still more the exception than the rule in trials and post-marketing studies. An additional drawback of the current approach is that motor function scales are relatively insensitive to document (subtle) changes over time. No studies have been published with a longer follow-up period than the 3 years in our study. The real long-term effects of nusinersen are thus still unknown.

7.1.2 Window of opportunity for treatment efficacy of nusinersen

Pivotal trials in rare diseases are usually performed with limited numbers of selected patients. The two trials that led to market access in the EU contained fewer than 300 patients with SMA type 1 and 2, up to the age of 13 years. What we have learned is that treatment efficacy is best before the onset of symptoms (18-20). This finding has led to the inclusion of SMA in the neonatal screening programs in a growing number of countries. The inclusion of SMA screening in the newborn screening program in the Netherlands in July 2022 was a major step forward in the effort to improve the health perspective of SMA patients. Nevertheless, the question remains if we can define patient subgroups that are likely to respond to treatment in a meaningful way, or in other words: if we can define the *window of opportunity* of treatment efficacy.

Our results on the efficacy of nusinersen in an unselected cohort of pediatric patients have been confirmed by other studies (9, 10, 21-26). In addition to proven efficacy in children up to the age of 13 years, a growing body of evidence shows efficacy in adolescents or even adult patients with SMA, i.e., patients who started treatment after the age of 9.5 years (27-38). A systematic literature review and three meta-analyses of the available data show improvements of motor function in most participating adults (34, 39-41). Minimal clinically

important differences (MCID, an improvement beyond day-to-day variation and with clear clinical impact on daily functioning) of motor function scores were reported in varying percentages of adults ranging from 34% up to 78% (39-41). It should be mentioned that ambulant patients were clearly overrepresented in these studies. The window of opportunity for treatment (i.e. the disease duration that would still be compatible with motor function improvement after the start of treatment) may be longer in milder variants of SMA.

Irrespective of SMA severity, short disease duration is a determinant of treatment success, as shown in two meta-analyses (34, 39). Hagenacker and colleagues also showed that the improvement in motor function was larger in ambulatory patients than non-ambulatory patients (41). This may reflect a larger number and/or longer preservation of hibernating motor units.

Taken together the available meta-analyses and post-marketing studies indicate that improvement of motor function after the start of treatment is not confined to young children. A first conclusion is that the window of opportunity for successful treatment extends beyond the current upper limit for reimbursed treatment in the Netherlands (i.e., 9.5 years) and that this is particularly relevant for patients with milder variants of SMA. Unfortunately, there are no other clinical characteristics or biomarkers that would help to predict treatment efficacy.

7.1.3 Safety and side effects: does intrathecal administration of Nusinersen treatment trigger unwanted inflammatory reactions?

When the EMA granted market access to nusinersen, the data regarding safety were limited. The serious adverse events that had been reported were communicating hydrocephalus and sterile meningitis. A possible explanation for both side-effects could be either the pro-inflammatory properties of nusinersen, or the repeated trauma of the meninges due to the lumbar punctions for administering nusinersen. However, the subcutaneous administration of antisense oligonucleotide (ASO) can cause skin changes with inflammatory properties (42, 43). Similar side effects could lead to inflammation and changes of meningeal tissues.

We therefore investigated the presence of pleiocytosis and inflammatory markers in the cerebral spinal fluid of treated children during the first year of treatment (**chapter 3**). Three children (out of 69 in the whole nusinersen cohort) showed a one-time elevation of their leukocytes. In these three samples with slightly elevated leukocyte counts we found an increase in Interleukin-10 (IL-10) levels, which returned to normal by the following injection. Monocyte chemoattractive protein-1 (MCP-1), a protein with an uncertain role slightly increased over time in the CSF of patients with SMA type 2 and 3. Our conclusion was that

nusinersen administration did not trigger an increase in cytokines that could indicate or sustain inflammatory processes.

Only a few other studies analyzed changes in cytokines during nusinersen treatment as biomarkers for disease activity, inflammation or treatment efficacy (**table 1**) (44-48). In contrast to our study, none of these reports documented CSF leukocyte counts in relation to cytokine levels.

Table 1. Short overview of cytokine changes over time in CSF of pediatric patients treated with nusinersen

Study	N of pediatric patients	Median follow-up time	Elevated cytokines at baseline in CSF	Changes over time in CSF
Nuzzo et al. (45)	SMA type 1: 18	10 months	IL-2*, IL-4*, IL-6*, IL-8*, IL-12*, IL-17A*, IFN- γ *, TNF- α *, MIP-1 α *, MCP-1*, eotaxin*, PDGF-BB*, VEGF* were elevated	Decrease of IL-2*, IL-4*, IL-7*, IL-9*, IL-12*, IL-17*, VEGF*, eotaxin* and TNF- α *
	SMA type 2: 19		None	Increase of G-CSF*, IL-8*, MCP-1*, MIP-1 α *, MIP-1 β *
	SMA type 3: 11		None	Decrease of IL-1ra*
Bonanno et al. (46)	SMA type 1: 4	6 months	None	None
	SMA type 2: 12		None	None
	SMA type 3: 5		None	None
Zhang et al. (44)	SMA type 1: 16	6 months	MCP-1*, IL-7*, IL-8* were elevated	Decrease of eotaxin*, MIP-1 β * Increase of IL-2*, IL-4*, VEGF*
	SMA type 2: 4		None	None
Cheng et al. (47)	SMA type 2: 9	6 months	None	Increase of MCP-1* when SMA type 2 and 3 are pooled Decrease of TNF-a* when SMA type 2 and 3 are pooled

	SMA type 3: unclear		None	Increase of MCP-1 * when SMA type 2 and 3 are pooled Decrease of TNF- α * when SMA type 2 and 3 are pooled
Verma et al. (48)	Unknown	Unknown	None	Decrease of sAPP α *, sAPP β *, MCP-1
Our cohort (chapter 3)	SMA type 1: 4	10 months	C5a and MCP1 were elevated	Decrease of MCP1
	SMA type 2: 22		None	Increase in MCP1
	SMA type 3: 12		None	Increase of MCP1*

Legend table 1: IL-1 β = Interleukine-1 bêta, IL-2 = Interleukine-2, IL-4 = Interleukine-4, IL-6 = Interleukine-6, IL-7 = Interleukine-7, IL-8 = Interleukine-8, IL-10 = Interleukine-10, IL-12 = Interleukine-12, IL-17 = Interleukine-17, IL-22 = Interleukine-22, IL-23 = Interleukine-23, IL-31 = Interleukine-31, IL-33 = Interleukine-33, IL-1ra = Interleukine-1 receptor antagonist, TNF- α = Tumornecrosefactor-alfa, IFN- γ = Interferon-gamma, MCP-1 = Monocyte chemoattractant protein-1 (also: CCL2), MIP-1 α = Macrophage inflammatory protein-1 alfa, MIP-1 β = Macrophage inflammatory protein-1 bêta, VEGF-A = Vascular endothelial growth factor A, Eotaxin = Eotaxine, G-CSF = Granulocyte colony-stimulating factor, C5a = Complement component 5a, PDGF-BB = Platelet-Derived Growth Factor-B, sAPP α and β : Soluble amyloid precursor protein α and β

* Were significant differences or changes

MCP-1 and IL-10 were the common denominator in these five studies; I will therefore discuss these proteins in more detail.

The studies reported different levels of MCP-1 in CSF prior to treatment in patients with SMA. MCP-1 levels at baseline were higher in young SMA type 1 patients in our cohort and in two other studies (44, 45) than in (older) patients with SMA type 2 and 3. In contrast, one other study reported higher levels of MCP-1 at baseline in patients with 3 SMN2 copies compared to those with 2 or 4 copies (47). This study was restricted in its scope in the sense that it only reported on patients with SMA type 2 and 3 (and not SMA type 1).

MCP-1 levels changed differently during treatment: in young patients with SMA type 1 a short increase during the nusinersen loading phase was followed by a return to baseline (chapter 3 and (44)), while there was a gradual increase of MCP-1 in patients with SMA type 2 and 3 (chapter 3 and (45, 47)). One study found a non-significant decline of MCP-1 during nusinersen treatment (SMA types not specified), which significantly correlated with motor function improvement after six months (48).

MCP-1 has both pro-inflammatory and neuro-protective properties (49-51). Zhang et al., and Nuzzo et al., both suggest that the high levels of MCP-1 in SMA type 1 patients at baseline reflect a pro-inflammatory state related to a severe disease type. Nuzzo et al., even conclude that nusinersen administration does not fully reverse the pathophysiology of SMA, and that an increase of MCP1 over time in SMA type 2 is a sign of therapy failure (45). Zhang and colleagues suggest the increase of MCP-1 in SMA type 2 patients is not related to SMA or nusinersen treatment, but age related (44, 52, 53). We and Cheng et al., suggested that nusinersen elevates MCP-1 levels with neuro-protective function, and thus may exert beneficial effects through more pathways than just elevating SMN-protein levels in patients with SMA type 2 and 3 (chapter 3 and (47)). To Zhang et al. MCP-1 looked like a probable biomarker for disease severity (44), but this was, as discussed, not corroborated by other studies.

At this moment we can conclude that MCP-1 is consistently present in CSF of patients with SMA, but that the reason of its presence and the exact (pro-inflammatory, neuroprotective, or a bit of both) role of MCP-1 is unclear. Only one study found a correlation between MCP-1 and motor function improvement, which makes a straightforward correlation unlikely. MCP-1 is not a biomarker for disease severity or treatment response.

The second consistent finding was IL-10, again mentioned by Zhang et al.(44), and Bonnano et al.(46) as a possible biomarker for treatment response. Zhang et al., found that higher levels of IL-10 at baseline in the CSF were associated with motor function improvement after six months of treatment (44) and Bonnano et al., found a similar association with *serum* levels of IL-10 (46). Rather confusingly, Cheng et al., found an inverse correlation of IL-10 CSF levels and motor function improvement during treatment. We did not find any relation between IL-10 and motor function, but in CSF samples with slightly elevated leukocyte counts we did find a short-term increase of IL-10. IL-10 has a dual anti-inflammatory and B-cell activating role. IL-10 delayed motor neuron loss and muscular atrophy after intramuscular injection in mouse models for amyotrophic lateral sclerosis (54-56). Higher levels of IL-10 thus might have a (neuro)protective function. As for MCP-1, IL-10 is not a consistent biomarker for SMA or its treatment. Important drawbacks of all studies are the limited sample size, the limited follow-up time and the incomplete description of patient characteristics.

In general, the available studies do not report consistent changes in cytokines pointing towards a persistent pro-inflammatory state in children with SMA treated with nusinersen.

The exact roles of detected MCP-1 and IL-10 remain unclear and probably requires larger longitudinal studies.

7.2 Reimbursement of treatment

Nusinersen appears to be a safe and an effective drug for larger patient groups than included in the pivotal trials. However, the lifelong yearly costs of treatment with nusinersen (in the first year is €499.800 per patient, the following years are €249.900 per patient) are a significant burden for health care budgets. The two genetic treatments for SMA that followed after market approval of nusinersen have comparable price tags (onasemnogene abeparvovec (gene replacement therapy) currently costs €1.900.000 euro per patient (57). Treatment with risdiplam (a daily administered oral antisense oligonucleotide) costs on average €274.505 per year) (58).

Healthcare systems are confronted with the rising, and from a societal and health-economic perspective excessive, costs. This is ironically at least partially the result of policies that were implemented decades ago to stimulate the development of drugs for rare diseases.

The American orphan drug act and its European equivalent were important policies to stimulate the development of orphan medicine by pharmaceutical companies in order to address the unmet medical need caused by rare diseases. It was thought that there was a risk of limited (if any) return on investment due to the small numbers of affected patients and with these policies the USA and EU authorities aimed to take care of people with orphan diseases. In the EU this means pharmaceutical companies receive protocol assistance, direct access to the EMA centralized procedure for registration, ten-year market exclusivity and some financial incentives (59). The orphan drug policies, especially the market-exclusivity, are thought to contribute to the excessive pricing (6, 60-62). It is clear that these policies need to be re-evaluated and adapted, since orphan drugs create a business model with larger profit for pharmaceutical companies than previously thought and profit maximization is becoming a reason to manufacture orphan drugs or takeover businesses (63-66).

Controlling prices of drugs is complicated by the tandem involvement of European and national health authorities. After safety and efficacy assessment of new drugs, EMA grants medicine access to the EU market but the decision to reimbursement is left to individual member states. This has led to variation in policies and the speed at which patients have access to orphan medicines. The Orphanet website classifies member states policies according to the time-to-treatment, ranging from 'slow' (Belgium, UK), 'classic' (the Netherlands and a large number of other countries) to 'rapid' (France, Germany) (67).

The Dutch government employs a unique policy instrument since 2015, called the Coverage Lock (CL). This policy is meant for expensive medicines, i.e., those exceeding the threshold of €20M in total expenditure per year, or €50K per patient resulting in total costs exceeding

€10M per year. It is worth noting that this policy does not cover all expensive orphan drugs; if the cumulative costs of a new drug for an ultra-rare disorder would not exceed forementioned threshold, the coverage policy would not apply. Drugs placed in the coverage lock will, upon request of the producer, undergo an assessment based on four criteria: efficacy, cost-effectiveness, necessity and feasibility. Based on the assessment, the Dutch Health Institute (Zorginstituut Nederland (68)) advises the Minister of Health about the desirability of reimbursement. This advice could be positive for reimbursement, positive for reimbursement but with an advice for price negotiations or negative for reimbursement. The procedures take time; on average 26 months from EMA approval to reimbursement (69).

This policy delayed patient access to nusinersen with 14 months. Looking back - and with the current knowledge of the beneficial effects of the treatment – significant gains in health for a large group of SMA patients in the Netherlands has probably been delayed or possibly even missed. In addition, patients, their families and involved healthcare professionals had to endure the situation in which the first SMA treatment was on the market but they did not have access to it. Is this justifiable? This and other questions led us to take a closer look at the reasons for and arguments behind the Dutch CL policy for (extremely) expensive medicines.

7.2.1 Stakeholder perspectives on reimbursement policies for extremely expensive medicines

In **chapter 4**, we present the results of an in-depth qualitative interview study amongst stakeholders of the nusinersen CL procedure, to learn from their experience and provide potential points for improvement of the CL.

We identified six themes as key issues for evaluation of the CL. Especially patients, their families and their care givers reported the emotional strain caused by the CL procedure for nusinersen. The time-consuming process was hard to swallow in the light of the ongoing progression of the disease. Stakeholders agreed that the CL may be less appropriate for orphan medicines like nusinersen: the limited data availability complicated the assessment and contributed to the duration of the CL, counteracting the accelerated market access for orphan medicine. In such uncertain times, most participants thought that transparency of the procedure and the timelines important. However, all, except the stakeholders who actually conducted the procedures of the CL, did not know the exact way in which the policy was applied nor the accompanying timelines. Another element was the arguments that are used for decision making and the absence of patient-centeredness. Currently, the decision making is dominated by a cost-effectiveness analysis, i.e., a calculation of costs in relation to quality adjusted life years (QALY). While this method is also used in other countries, it insufficiently addresses the lived experience of patients, their families and clinicians. More

generally, critique focuses on the limitations of a utilitarian approach, such as the problems with quantifying utility, the fact that utility does not reflect justice and that the approach can lead to counter-intuitive outcomes (70-79). Finally, all stakeholders mentioned the lack of uniformity between European Union member states as a problem as this introduces differences in (time to) access to medicines between patients in neighboring countries like Germany and France and in this case also Belgium.

Although stakeholders reported these six shared points for improvement, they all agreed on the need for fair-pricing to support cost-control in healthcare and shared the opinion that the CL probably helps achieve this aim.

In **chapter 5** we present the results of a survey among a representative sample of Dutch citizens. The Dutch general public demonstrated solidarity with patients in need of expensive medicines: only a small part (2.9%) was against reimbursement of all expensive medicines. On the other hand, a slight majority (51%) was against an increase of healthcare premiums to be able to reimburse these treatments. The CL was seen as unjustifiable by the majority, mainly because patients have no influence on their need for expensive medicine. We presented four cases to our participants of medicines that had previously been placed in the CL and asked them to rate their importance for reimbursement. There was a large degree of consensus for the reimbursement of two medicines, and not to reimburse the two others. This indicates the public's consciousness and critical attitude towards innovative and expensive medicines and their costs. Important reasons to support reimbursement were prevention of suffering, increasing quality of life, their shown efficacy and the lack of equivalent alternatives. Important reasons to reject reimbursement were uncertainty about efficacy and a negative cost-effectiveness ratio coupled with excessively high pricing. The participants also pointed out that access to treatment was important. More than half of the participants opted for one of the two reimbursement systems that ensured swift access to new expensive medication. A large majority of the participants thought that access to new medicines is important during the CL.

In **chapter 6** we performed an analysis of policy documents related to reimbursement decisions of nusinersen in Belgium, Germany and France. We aimed to gain a better understanding if and how moral reasoning underlies reimbursement policies.

We found two moral arguments that seemed to have influenced reimbursement decisions. Documents from France and The Netherlands referred to solidarity as an argument to *deny* reimbursement of nusinersen for specific patient subgroups. In France this was confined to the mildest form of SMA (i.e., type 4), representing a very small minority of patients, while in the Netherlands most patients were excluded from reimbursement. In contrast, German authorities used disease severity as an argument in *favor* of reimbursement for all patients and SMA types. This reflects a policy that aims at facilitating access to orphan drugs,

although an extensive efficacy and cost-effectiveness analysis is required in case a financial threshold is exceeded in the first year of access.

Belgian authorities have adopted similar policies by exempting orphan medicines from an extensive analysis on clinical added value, thus allowing rapid access for patients. None of the documents contained extensive moral reasoning that explained policy choices. However, it seems plausible that moral reasons, for example the acknowledgement of the vulnerability of patients with a rare disease and access to drugs that would meet a high medical need, underlie policies in Germany and Belgium.

The findings of chapters 4 and 5 seem to indicate that a more explicit moral framework – or at least outlining the moral *dilemmas* involved in the reimbursement of expensive drugs – could ultimately improve transparency of policy choices and facilitate societal discussions. Although drafting a moral framework is beyond the scope of this thesis, we think that a detailed exploration of how reimbursement policies could be designed to avoid the felt injustice of denying vulnerable people access to treatments would be in line with the responses of stakeholders and the general public as described in chapters 4 and 5.

7.2.2 Fairness and the Coverage lock policy

The empirical studies in chapter 4 and 5 show that many respondents share the uneasiness regarding orphan drug pricing, but at the same time intuitively question the fairness of the CL. Importantly, the CL has never been evaluated after its introduction. Therefore, we sought to evaluate the *procedural* fairness of the CL. For this purpose, we used the principles of a fair decision-making process known as Accountability for Reasonableness A4R, proposed by Daniels and Sabin (80). The principles can be summarized as follows:

1. **Publicity:** The decision must be publicly accessible and must ensure clarity about reasons underlying the reimbursement decision.
2. **Relevance:** This condition asks for a reasonable explanation of how the organization provides “value for money” in meeting the varied health needs of a defined population under reasonable resource constraints. Specifically, an explanation is reasonable if it appeals to reasons, evidence and principles that are accepted as relevant by the affected (fair-minded) stakeholders.
3. **Revision and appeals:** There should be a mechanism to challenge and dispute the resolution regarding limit-setting decisions; this includes the opportunity for revising decisions in light of further evidence or arguments
4. **Regulative condition:** There should be a voluntary or public regulation of the process to ensure that conditions 1 to 3 are met.

If we apply the A4R approach to the Coverage Lock, it falls short on all of the proposed requirements.

First, although the outcome and rationale of the assessment of drugs placed in the CL is available to the general public (e.g., (81)), we think the CL policy is not in line with publicity principle, since the description of the current methodology is beyond the grasp of the general public or healthcare professionals and therefore lacks clarity. The **publicity** principle therefore requires more transparency in the description of processes. The results from chapter 5 show that the appraisal of new drugs by citizens is not uncritical. The general public can decide against reimbursement of expensive drugs if properly informed. However, methodological transparency is crucial to gain and maintain public support for difficult allocation choices (6, 82, 83).

Second, the **relevance** principle draws attention to the assessment methods, criteria used in the CL and the scope of assessments made by the relevant authorities. At the time nusinersen was introduced, the CL was only applied to expensive drugs. The Healthcare Institute aims to add innovative expensive technological interventions to their future assessments; but this is still in a pilot phase (84). However, the limited use of the CL approach, i.e., only to expensive drugs, would suggest that it is primarily an instrument to control budgets, which is difficult to reconcile with the condition of meeting varied health needs.

Moreover, the cost-effectiveness methodology as applied during the assessment of nusinersen has shortcomings. Its use for a fair decision process has been criticized on ethical, methodological and contextual grounds (70-79). One example is the counter-intuitive conclusion of the assessments made by the Dutch Healthcare Institute that the treatment with nusinersen of children with SMA type 1 would be more cost-effective than those with SMA type 3. Treated children with SMA type 1 will likely experience longer survival at the cost of being completely dependent on the care of others, while treated children with SMA type 3 - who would have a semi-normal life expectancy with and without treatment (11, 14) - would escape the severe disability associated with SMA type 3 later in life. The results described in chapters 4 and 5 indicate that both stakeholders and the general public are aware of this imbalance.

The age limit for reimbursement of 9.5 years at the start of treatment that resulted from the cost-effectiveness analysis was another point of criticism. It is questionable if this outcome carries the necessary moral weight to make a fair distinction between those who have access and those who have not, especially in light of the scarcity of the clinical trial data on which the calculation was based. Here, the relevance principle would require a broadening of

considerations to be weighed in. An example of such a consideration is the necessity argument. Currently necessity in the CL is understood as the disease severity and whether people are able to pay for treatment themselves (85). However, necessity is an umbrella-term and many more interpretations are found in literature including definition of illness, morbidity/severity, need, (no) alternative treatment, societal functioning and the rule of rescue (86). We found (**chapter 5**) two of these necessity-related arguments could be prioritized: prevention of suffering and the lack of alternative and equivalent treatments (unmet medical need). This is supported by previous studies that report societal support to reimburse medicine for diseases with an unmet medical need (87-89).

Finally, we can be brief about the **revision and appeals, and regulative condition** principles. Currently, there are no options to dispute a decision, nor is there a voluntary or public regulatory organ to ensure conditions one to three are met.

In summary, the CL does not meet any of the criteria for a fair decision-making procedure. For future improvements of the CL, I suggest that the A4R principles, with a focus on the forementioned problems, form a firm foundation. Following these principles will address the fairness of the CL and address a large part of the key issues mentioned by stakeholders and the differences between the CL and the public preferences.

7.2.3. Justice and the reimbursement of expensive medicine

Procedural fairness is not the only form of justice possible within policies. Moral theories on justice underlying policies or instruments used in policies form another base of justice. The main goal of the CL is to maintain costs within the basic health package. By using QALY's and focusing on cost-effectiveness, utilitarianism is (implicitly) the main moral theory supporting the CL. The Netherlands is not the only country that chose this approach (72, 79, 90-93). However, an important drawback of utilitarianism is that patients with a rare disease do not have equal chances for reimbursed treatment (72). Other justice-based principles have been proposed to give orphan medicine a fair chance on reimbursement, although their practical use is limited (77).

Theoretical considerations are to weigh QALYs differently, for example by taking disease prevalence into account and thereby weighing rarity more heavily (91). Another approach is to give priority to the worst off in order to give those people an equal opportunity in life (72, 94). Finally, another approach described (and practiced) is the duty to rescue. The rule of rescue entails that we have a presumptive justice-based obligation to rescue from death those who can be rescued (72, 95). The United Kingdom (UK) applies this rule of rescue to

deviate from normal cost-effectiveness practice to provide treatment that prolong life in cancer-care (90).

7.3 Solidarity and the Coverage Lock

The Dutch government used solidarity initially as an argument to not reimburse nusinersen, and later to exclude SMA patients older than 9.5 years from reimbursement because of the risk of crowding out other (unspecified) more effective care. Also in the French policy documents, exclusion of a specific small patient group is justified by referring to the principle of solidarity. Opinions of the Dutch general public compiled in chapter 5 however converge to a wish to implement policies that express solidarity with patients in need of expensive treatment.

Little is written about solidarity and the reimbursement of expensive medicine and what is available remains on a highly theoretical level (96, 97). More is written about solidarity in healthcare in general. An often-used definition comes from Prainsack and Buyx: “An enacted commitment to carry costs (financial, social, emotional or otherwise) to assist others with whom a person or persons recognize similarity in a relevant respect” (98). They describe that solidarity can be practiced at three levels (tiers). Tier 1 remains on an interpersonal level, i.e., someone experiences the willingness to carry costs to assist others with whom they experience sameness or similarity in a relevant respect. This relevant respect is a broad definition encompassing adhering the same religion, sitting on the same airplane etc. Tier 2 is about solidarity within groups of people who identify with each other; it is a collective commitment to carry costs to assist others. Tier 3 is on an institutional level and taxes to create a social safety net for people who are less fortunate are an example of solidarity on tier 3.

The Dutch healthcare and tax system is based on tier 3 solidarity. Taxes and obligatory healthcare insurances enable all members (independent of their contribution and needs) to consume care. The ability-to-pay-principle, by which citizens with a larger income carry more costs, is another social aspect of our healthcare and tax system. Although the level of acceptable taxation is part of the political debate, it is obvious that are limitations to healthcare expenditure. When the decision to not reimburse an expensive treatment is based on the limitations of tier 3 solidarity (as was the case with nusinersen), this conflicts with solidarity on lower tiers, experienced by patients and their caregivers. In fact, patients with rare diseases that could be treated with drugs that are deemed too expensive to reimburse are still obliged to carry costs (paid in the form of their own health or even survival) to sustain the institutional level of solidarity in society. Which is, from a personal point of view, problematic.

A solution to bridge the conflict between the solidarity tiers might be to ensure more timely access or access during the CL. When efficacy and cost-effectiveness are the main concerns, managed entry agreements (MEA) can create a way out to ensure access (99-101). MEA's are not the standard reimbursement agreement with a 'yes' or 'no', they aim for a risk sharing in cost-effectiveness between the pharmaceutical company and the payer (102). Examples of such arrangements are outcome-based reimbursement with a delayed payment model (103). Such delayed payment models are complex and this is often used as an argument against implementation. Operational concerns are the determination of suitable patient-relevant outcome measures or a lack of efficient and confidential registration of outcomes (100, 104-107). The German approach could be another strategy, in which medicines become available directly after market-approval and evaluation and price-negotiations take place in the first year after market approval. Adapted to conditional reimbursement arrangements, as the one implemented for nusinersen in 2020 (i.e., three years after market access and 18 months after the reimbursement arrangement for children aged up to 9,5 years), could be another approach. A model of conditional reimbursement following market approval could ensure early access, while data collection could help the decision on final reimbursement at a later stage.

It is obvious that the excessive pricing of innovative medicines is the root cause of the strains put on societal solidarity. It is furthermore regrettable that there is insufficient concerted action in the European Union to reign in excessive drug costs. We found public support for political action to ensure reasonable prices. Continuing or only amending reimbursement policies will not solve dilemma that the costs will remain high for society while the pharmaceutical industry benefits from successful drug development and is insured against failure.

7.4 Methodological reflection

To come to the results described above, we used both qualitative and quantitative methods. This enabled us to cover a broad range of topics.

An important strength of the dataset used in **chapter 2** and **3**, is that they were collected in a single-center. Since all SMA patients in The Netherlands are treated in Utrecht, these are population-based data with little or no selection bias. Moreover, the interobserver variability of motor function scores, or variation in the analysis of the CSF in our samples is limited.

In **chapter 4** we interviewed stakeholders. The small sample size of fifteen stakeholders is a weakness, but all stakeholder groups were represented. We chose to focus on one CL procedure and not for example of all available SMA therapies (i.e., risdiplam and

onasemnogene abeparvovec). For more insights in the experiences with the CL it would be interesting to interview stakeholders from other CL procedures to see if the same issues arise.

With our survey study described in **chapter 5**, we covered a large number of topics. It appeared the general public was not well informed about the CL prior to the survey. We tried to tackle this hurdle by giving a short description of the CL at the start of the survey. A more profound understanding of the CL and the impact of the CL could have contributed to more a more conscious choice of participants during the survey. However, with our approach we ensured the participants had global knowledge of the CL, and this is probably sufficient to get a good impression of the opinions regarding expensive medicines, attitudes towards people in need of expensive medicine and the CL in general.

7.5 Future directions

In this thesis I focused on nusinersen, its clinical profile and the reimbursement procedure. While writing this thesis, two more treatments became available for nusinersen. No real comparative trial has been done yet. The importance of head-to-head trials is often pointed out in order to get insight in what is the most effective treatment for subgroups of patients, but the execution of such trials is more the exception than the rule. Policies that would support investigator-initiated comparative trials would probably serve the purpose.

I aimed to evaluate if the CL is working from a justice point of view. In this thesis, I conclude that the CL is unjust and the CL procedure of nusinersen is a showcase of this injustice. This is supported by the view of many of participants in our studies. However, it might be hard to convince authorities to completely revise the CL based on the evaluation of one procedure. I suggest therefore, that future research on the CL evaluates more procedures. To come to more detailed improvements it could be valuable to asses: (1) several types of medicine (orphan and non-orphan), (2) with different indications (oncology, non-oncology, cure or life-extension or improving quality of life), (3) focusing on different patient groups (pediatric and adult patients) and (4) conducted at several time frames (current average lead time of the CL is longer compared to the CL procedure of nusinersen in 2018).

I hope that this assessment is an encouragement for Dutch health authorities to critically reappraise the CL, not from a cost saving point of view, but with emphasis on societal views, focusing on justice and solidarity. Engaging with clinicians, caregivers and especially patients who have to wait for medicine is not only important to get a better understanding of the effects of the CL on a personal level, but also to ensure support for allocation policies.

7.6 Conclusion

In this thesis we analysed the efficacy and safety of nusinersen and we used nusinersen as a case-study to investigate the reimbursement trajectory of a new and innovative medicine. Nusinersen is effective in treating SMA and can be used safely. The utilitarian foundation of the CL caused injustice to patients with SMA and this is likely to be repeated for other patient groups in the future. Not only the basic moral principles behind the CL, but also the procedure itself can be criticized, as shown by non-compliance to basically all principles of the A4R framework.

The CL procedure of nusinersen showed room for improvement from a stakeholder, public and international perspective for future procedures of expensive innovative (orphan) medicine. The CL should be more transparent, and the assessment criteria used could be updated and weighed differently to become more relevant for medicine like nusinersen. Preferences of stakeholders and the general public should be taken into account and differences with neighboring countries in access to treatments should be diminished also to sustain support for such important and societally relevant policies. In parallel, EU member states should collaborate in designing frameworks that promote the development of innovative drugs at fair prices.

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Appendices

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Achtergrond

Spinale musculaire atrofie

Spinale musculaire atrofie (SMA; ook wel: spinale spieratrofie), is een erfelijke en progressieve spierziekte.

SMA wordt veroorzaakt door het ontbreken van een normaal survival motor neuron (*SMN*)1-gen in het DNA. Dit *SMN1*-gen is verantwoordelijk voor de aanmaak van voldoende SMN-eiwit, om de functie van zenuwcellen in de motorische voorhoorn (motorneuronen) van het ruggenmerg te waarborgen. Motorneuronen zorgen voor signaaloverdracht vanuit de hersenen naar de spieren. Bij een tekort aan dit SMN-eiwit sterven de motorneuronen af en ontvangen spieren onvoldoende activerende signalen. De spieren worden daarom dunner en ook de structuur verandert in de loop van de ziekte.

Normaal gesproken hebben mensen twee *SMN1*-genen (één op elk chromosoom). Ongeveer één op de 30 tot 50 Nederlanders is drager van SMA en heeft maar één *SMN1*-gen. Draggers hebben geen symptomen en kunnen normaal functioneren. Mensen met SMA hebben vrijwel altijd ouders die beiden drager zijn; zij hebben van beide ouders het stuk DNA ontvangen waarin het *SMN1*-gen ontbreekt. Er worden in Nederland gemiddeld 15-20 kinderen per jaar geboren met aanleg voor het krijgen van SMA.

Als de motorneuronen langzaam afsterven, neemt de spierkracht geleidelijk aan af. Dit betekent dat mensen met SMA meestal afhankelijk worden van een rolstoel en in ernstige gevallen zelfs ondersteunende apparaten nodig hebben voor de ademhaling en de slikfunctie.

Er is echter variatie in de ernst van de ziekte bij mensen met SMA. Deze variatie hangt voor een belangrijk deel samen met de aanwezigheid van een tweede SMN-gen (*SMN2*) in het erfelijk materiaal van mensen. Het *SMN2*-gen codeert ook voor het SMN-eiwit, maar produceert hier minder van dan het *SMN1*-gen. De ernst van SMA vertoont een relatie met het aantal *SMN2*-gen kopieën in het DNA van de patiënt; hoe meer kopieën, des te milder is vaak het ziektebeloop.

De leeftijd waarop de eerste symptomen ontstaan is een voorspeller van de ernst van SMA. De meest ernstige vorm komt ook het meest voor: SMA type 1. Deze kinderen hebben al voor de leeftijd van 6 maanden zichtbare spierzwakte. Zonder behandeling is de gemiddelde overleving 8 maanden. Wanneer de klachten zich pas na de leeftijd van 6 maanden openbaren, maar vóór de leeftijd van 18 maanden spreken we van SMA type 2. Deze

kinderen leren zelfstandig zitten, maar kunnen niet zelfstandig staan of lopen en zijn rolstoel gebonden. Zij hebben ook een verkorte levensverwachting in vergelijking met mensen zonder SMA, maar halen vaak wel de volwassen leeftijd.

Als kinderen zelfstandig leren lopen, spreken we van SMA type 3. Deze kinderen verliezen in de loop van het leven meestal hun loopvermogen en hebben ook andere beperkingen, maar hebben een normale levensverwachting.

In zeldzame gevallen ontstaan de klachten pas op de volwassen leeftijd, dit noemen we SMA type 4.

Er zijn drie medicijnen die de aanmaak van het SMN-eiwit in zenuwcellen kunnen verhogen. Nusinersen (Spinraza®) was het eerste geneesmiddel voor SMA en werd in 2017 in Nederland geïntroduceerd. Nusinersen activeert het *SMN2*-gen zodat er meer SMN-eiwit wordt gemaakt. Het is echter wel een belastende behandeling, nusinersen moet via ruggenprikken worden toegediend. In het eerste behandeljaar gaat het om 6 injecties, gevolgd door een onderhoudsbehandeling van 3 injecties per jaar gedurende de rest van het leven.

In de afgelopen jaren zijn nog twee andere geneesmiddelen beschikbaar gekomen: onasemnogene abeparvovec (Zolgensma®), een vorm van gentherapie waarbij er eenmalig, met een zogenaamde 'virale vector' die bestaat uit virusdeeltjes, het missende *SMN1*-gen in de cellen van het lichaam wordt gebracht. Daarnaast is er risdiplam (Evrysdi®), een medicijn dat je kunt slikken en qua werking erg lijkt op nusinersen. Alle behandelstrategieën zijn erop gericht om de productie van het SMN-eiwit te verhogen.

Alle drie de medicamenteuze behandelingen voor SMA zijn duur. De catalogusprijs van nusinersen is €87.000 per injectie. Dat komt in het eerste jaar neer op €522.000 per patiënt, en elk jaar daarna €267.000. Risdiplam kost gemiddeld €250.000 per jaar per patiënt. Zowel nusinersen als risdiplam moeten het hele leven worden gegeven. Onasemnogene abeparvovec kost €1,9 miljoen per behandeling en is in principe een eenmalige behandeling.

Pakketsluis

In Nederland hebben alle burgers via de verplichte zorgverzekering toegang tot een breed basispakket van gezondheidszorg. Vanwege zorgen over de groeiende cumulatieve kosten van nieuwe geneesmiddelen werd in 2015 de 'Pakketsluis' ingesteld door de Nederlandse regering. Dit is een landelijk beleid dat bepaalt dat geneesmiddelen die boven een financiële drempel komen, niet meer vanzelfsprekend worden opgenomen in het basispakket. Deze

financiële drempel is als volgt gedefinieerd: de kosten op jaarbasis zijn €20 miljoen of meer, of de kosten zijn €10 miljoen per jaar én meer dan €50.000 per patiënt per jaar.

Dure geneesmiddelen moeten in de Pakketsluis een extra beoordeling ondergaan op vier criteria: effectiviteit, kosteneffectiviteit, noodzakelijkheid en uitvoerbaarheid. Deze beoordeling wordt gedaan door het Zorginstituut Nederland (ZIN), zij geven na de beoordeling een advies aan de Minister van Volksgezondheid, Welzijn en Sport (VWS) over de vergoeding van het nieuwe geneesmiddel. Dit kan een negatief advies zijn (niet vergoeden), een prijsonderhandeling voor een lagere prijs, of een positief advies (wel vergoeden). Gedurende de Pakketsluis-procedure is het geneesmiddel in principe niet beschikbaar voor patiënten. Zij moeten wachten tot er een definitieve vergoedingsregeling is voor zij het kunnen gebruiken.

Samenvatting proefschrift

Toen nusinersen in 2018 uit de Pakketsluis kwam was er nog maar weinig informatie beschikbaar over de effectiviteit op langere termijn en de veiligheid in een brede populatie SMA-patiënten. De geneesmiddel onderzoeken waren bij markttoelating beperkt tot kinderen jonger dan 13 jaar. Om de effectiviteit en veiligheid in een bredere groep van SMA-patiënten te evalueren onderzochten we in het eerste deel van dit proefschrift de effectiviteit en veiligheid bij de kinderen die in 2018 aanmerking kwamen voor een behandeling. Dit waren kinderen met SMA type 1 t/m 3, tot een leeftijd van 9,5 jaar.

De Pakketsluis procedure van nusinersen heeft geleid tot discussies in de media en de politiek. Er was kritiek op het feit dat patiënten door de Pakketsluis niet behandeld konden worden, terwijl er geen alternatief voorhanden was. Ook de leeftijdsgrens van 9,5 jaar leidde tot onrust. Veel mensen hadden er moeite mee dat patiënten die (net) boven deze leeftijdsgrens zaten, de behandeling misliepen. Ook ontstonden er schrijnende situaties, bijvoorbeeld in gezinnen met meer dan één kind met SMA. In een aantal gezinnen kon het jongste kind met SMA wel behandeld worden en het iets oudere kind niet.

Deze discussies en dilemma's vormden de aanleiding om de Pakketsluis procedure van nusinersen te evalueren. Dit is terug te lezen in het tweede deel van dit proefschrift.

Deel 1 – Effectiviteit en veiligheid nusinersen

In **hoofdstuk 2** beschrijven we ons onderzoek naar de effectiviteit van nusinersen. Hiervoor hebben we 71 kinderen gevolgd met een mediane behandelduur van 38 maanden. Daarvan waren 69 kinderen symptomatisch bij de start van de behandeling en twee kinderen waren

presymptomatisch. Bij deze twee kinderen was de diagnose gesteld door erfelijkheidsonderzoek omdat zij een ouder broertje of zusje hadden met SMA. De belangrijkste bevindingen zijn dat 72% van de kinderen een verbetering van hun spierkracht lieten zien. In 23% van de kinderen leidde deze verbetering van spierkracht tot het behalen van een nieuwe motorische mijlpaal (zelfstandig zitten, staan of lopen). Bij 18% van de kinderen zagen we dat de spierkracht niet verbeterde tijdens de behandeling, maar wel stabiliseerde. Daarnaast zagen we dat hoe jonger de patiënt was bij de start van de behandeling, hoe beter de resultaten waren. Deze bevindingen vormen een duidelijk contrast met het natuurlijke beloop van SMA waarbij er alleen maar verlies van spierkracht optreedt. Wat opviel was dat de spierkracht met name in het eerste jaar van de behandeling verbeterde en daarna stabiliseerde op dit nieuwe niveau.

We hebben twee kinderen gevolgd die presymptomatisch zijn behandeld. Een van de twee kinderen behaalde motorische mijlpalen die niet werden verwacht op basis van het aantal *SMN2*-kopieën. De symptomen van SMA zijn nog wel zichtbaar bij dit kind; de motorische mijlpalen werden vertraagd behaald en het bleek noodzakelijk te starten met nachtelijke ademhalingsondersteuning. Het tweede presymptomatische kind ontwikkelde zich volledig normaal.

Het effect van de behandeling lijkt groter op de motorneuronen die armen en benen aansturen dan op de motorneuronen die verantwoordelijk zijn voor de ademhaling en slikfunctie. Waarom dit zo is weten we niet precies. Onze conclusie was dat nusinersen het natuurlijk beloop van SMA verandert, waarbij een grote groep kinderen een verbetering van hun spierkracht laat zien en anderen een stabilisatie van hun spierkracht. Hoe eerder de behandeling kan worden gestart, des te beter de resultaten.

In **hoofdstuk 3** ligt de nadruk op de veiligheid van de behandeling met nusinersen. Wereldwijd, en ook in Nederland, werden enkele patiënten gezien die mogelijk een ernstige bijwerking hadden (zoals waterhoofd of hersenvliesontsteking) ten gevolge van een ontstekingsreactie ontstaan na de toediening van nusinersen. Om die reden hebben we van 38 kinderen gedurende het eerste jaar van de behandeling het hersenvocht onderzocht op aanwijzingen voor een (chronisch) ontstekingsproces. We zagen bij drie kinderen dat er eenmalig in het eerste jaar een lichte verhoging van de witte bloedlichaampjes (leukocyten) was. Tegelijkertijd met deze lichte verhoging was er ook sprake van een lichte verhoging van het anti-ontsteking eiwit IL-10. Zonder aanpassingen of andere medicatie waren de waarden van zowel de witte bloedlichaampjes als het anti-ontsteking eiwit bij een volgende controle normaal in het hersenvocht.

In een groep van 38 kinderen vonden we geen aanwijzingen voor een chronisch ontstekingsproces tijdens een behandelduur van één jaar. Wel zagen we dat het MCP1 eiwit

verschillende patronen liet zien. Wat de exacte rol is van het MCP1 eiwit is nog onduidelijk. Het wordt in de literatuur zowel beschreven als een eiwit dat juist ontstekingsprocessen aanzet, als een eiwit dat belangrijk is voor de overleving van motorneuronen. Bij kinderen met SMA type 1 was dit eiwit bij aanvang van de behandeling hoog, steeg het nog even door, waarna het daalde tijdens de behandeling. Terwijl we juist bij kinderen met SMA type 2 en 3 lagere waarden vonden bij de start van de behandeling en het langzaam steeg in de loop van de behandeling. Wat de exacte functie is van dit eiwit in de ziekte SMA blijft nog onduidelijk. We concludeerden dat de behandeling met nusinersen veilig is en er geen aanwijzingen zijn voor een chronisch ontstekingsbeeld.

Deel 2 – Evaluatie Pakketsluis procedure nusinersen

We zijn de evaluatie van de Pakketsluis begonnen met het interviewen van vijftien betrokkenen bij de Pakketsluis procedure van nusinersen in **hoofdstuk 4**. Deze deelnemers waren patiënten of hun familieleden, vertegenwoordigers van patiëntenvereniging en farmaceutische bedrijven, betrokken zorgverleners en betrokken beleidsmedewerkers. Het doel was om te achterhalen hoe deze mensen vanuit hun perspectief naar de Pakketsluis keken. We kwamen op zes belangrijke thema's. Het eerste is de grote emotionele impact van de procedure op betrokken patiënten, hun naasten en zorgverleners. Gevoelens van onzekerheid, machteloosheid en oneerlijkheid waren de meest gehoorde emoties bij het bespreken van de Pakketsluis. Daarnaast werd de duur van de besluitvorming als (te) lang ervaren. Kinderen hebben, in afwachting van de uitkomst van het Pakketsluis onderzoek, motorische vaardigheden verloren die niet meer terug te winnen zijn. Dit sluit aan op het derde thema, waarbij men aangeeft dat de Pakketsluis niet geschikt is voor elk soort medicijn. Met name medicijnen voor zeldzame aandoeningen werden als minder geschikt gezien omdat de werking lastiger is aan te tonen dan bij geneesmiddelen die door grote groepen mensen worden gebruikt. Hierdoor is de kans op een negatief vergoedingsbesluit groot omdat er nog twijfels zijn over de effectiviteit van het geneesmiddel.

Als vierde thema kwam naar boven dat er behoefte is aan meer transparantie. Zowel transparantie in het proces van besluitvorming als de tijdslijnen van de besluitvorming. Het vijfde thema is de wens om patiënten een grotere rol te geven in het beoordelingsproces van de Pakketsluis. Zij kunnen namelijk aangeven wat effecten zijn van de behandeling die echte invloed hebben op hun leven. Dit is belangrijk omdat meer algemene en veelgebruikte metingen minder geschikt zijn voor mensen met beperkingen. Tot slot (het zesde thema) leidt de Pakketsluis ertoe dat patiënten in Nederland langer moeten wachten op toegang tot een geneesmiddel ten opzichte van vergelijkbare Europese landen. Dit was voor patiënten en hun familie vaak moeilijk te begrijpen.

We concludeerden dat er ruimte is voor verbetering van de Pakketsluis op verschillende fronten. De Pakketsluis procedure kan transparanter, waarbij vooral duidelijkheid over de tijd die het inneemt belangrijk is. Bovendien moeten de beoordelingen in begrijpelijke taal worden toegelicht. De pakketsluis kan daarnaast beter aansluiten op medicijnen voor zeldzame aandoeningen. Voor een geneesmiddel als nusinersen, het eerste waarschijnlijk werkzame middel tegen SMA, leidt die wachttijd tot onomkeerbare verslechtering bij patiënten en wanhoop en zorgen bij hun families en betrokken zorgverleners. Een mogelijkheid om met onzekerheid over de effectiviteit om te gaan en het geneesmiddel toch beschikbaar te maken is bijvoorbeeld een voorwaardelijk vergoedingstraject.

In **hoofdstuk 5** beschrijven we de uitkomsten van een vragenlijstonderzoek onder 1179 burgers in Nederland. We hebben hun mening gevraagd over de Pakketsluis en de vergoeding van dure geneesmiddelen in Nederland. Maar een klein deel (2.9%) vindt dat dure geneesmiddelen in het geheel niet vergoed moeten worden, wat betekent dat het overgrote deel dus wél voor vergoeding van dure geneesmiddelen is. Ook was er een duidelijk besef dat we niet alle dure geneesmiddelen kunnen vergoeden, waarbij de deelnemers in vier scenario's (gebaseerd op geneesmiddelen die in de pakketsluis hebben gezeten) er uiteindelijk voor kozen om twee geneesmiddelen wel te vergoeden en twee niet. Belangrijke argumenten om medicijnen wel te vergoeden waren: het voorkomen van lijden, bewezen werkzaamheid en het gebrek aan alternatieve behandelingen. Belangrijke argumenten om een geneesmiddel niet te vergoeden waren: onzekerheid over de werkzaamheid en een ongunstige kosteneffectiviteit ratio. Daarnaast gaven deelnemers aan dat het niet vergoeden ook een belangrijk signaal is naar farmaceutische bedrijven dat dergelijke hoge prijzen niet worden geaccepteerd. Het merendeel van de deelnemers vond de Pakketsluis een oneerlijke maatregel. De belangrijkste reden hiervoor was dat mensen die dure medicijnen nodig hebben hier vaak zelf niets aan kunnen doen. We hebben verschillende beleidsmaatregelen voorgesteld voor de vergoeding van dure geneesmiddelen. Ongeveer de helft van de deelnemers kiest voor een beleid waarbij het geneesmiddel direct beschikbaar is voor patiënten en eventuele onderhandelingen over de prijs daarna plaats vinden. 40% van de deelnemers zou alsnog voor de Pakketsluis kiezen als beleidsmaatregel voor kostenbeheersing.

We concludeerden dat er steun is voor mensen die dure geneesmiddelen nodig hebben vanuit de Nederlandse bevolking. Ook is er steun voor de Pakketsluis, hoewel er een voorkeur lijkt te zijn voor andere vormen van beleid waarbij geneesmiddelen sneller beschikbaar zijn voor patiënten. Daarnaast is het niet zo dat men vindt dat alle medicijnen vergoed moeten worden, het Nederlandse publiek lijkt zich bewust dat er keuzes gemaakt moeten worden en doet dit ook op basis van een aantal overwegingen. Ons advies zou zijn

dat deze overwegingen van het publiek in de toekomst worden meegenomen in de evaluatie van geneesmiddelen in de pakketsluis.

Tot slot hebben we in **hoofdstuk 6** de introductie van nusinersen in Nederland via de Pakketsluis vergeleken met de vergoedingsprocedures in België, Frankrijk en Duitsland. Duitsland heeft een duidelijk ander vergoedingssysteem dan de andere landen waarbij een geneesmiddel na goedkeuring voor de Europese markt vlot beschikbaar komt voor patiënten. Het eerste jaar dat het geneesmiddel beschikbaar is wordt gebruikt voor een aanvullende beoordeling en eventuele prijsonderhandeling. Het tweede jaar is het medicijn dan beschikbaar voor de nieuwe onderhandelde prijs. Nederland is het enige land met een Pakketsluis voor dure geneesmiddelen. In België en Frankrijk vindt er ook een evaluatie plaats, en zo nodig prijsonderhandelingen voordat een middel wordt opgenomen in een verzekerd pakket. Deze evaluaties vinden vaak sneller plaats dan in Nederland, waardoor er vlotter toegang is tot een nieuw medicijn. Frankrijk heeft bovendien een speciaal traject voor effectieve (wees)geneesmiddelen zodat patiënten versneld toegang hebben tot deze behandeling. België en Duitsland maken in hun evaluatie een opvallende uitzondering voor geneesmiddelen voor zeldzame aandoeningen, waarbij de klinische toegevoegde waarde van de behandeling wordt aangenomen op basis van de erkenning als weesgeneesmiddel. Indien een weesgeneesmiddel erg duur blijkt, moet in Duitsland deze klinische toegevoegde waarde alsnog moet worden aangetoond voor verdere vergoeding.

Hoewel België geen Pakketsluis heeft, hebben Nederland en België de krachten gebundeld en samen met de farmaceutische industrie onderhandeld over de prijs van nusinersen. Opvallend is dat België bij de beoordeling van nusinersen voor de vergoeding, gebruik heeft gemaakt van het ZIN rapport en de conclusies heeft overgenomen. Ondanks dat België en Nederland dezelfde evaluatie hebben van nusinersen en ook gezamenlijke prijsafspraken maakten, werd nusinersen in België wél voor alle SMA-patiënten vergoed en in Nederland niet. Wat de precieze redenen hiervoor zijn geweest, is niet terug te vinden in de Belgische beleidsdocumenten. Ook Duitsland besloot, na de evaluatie in het eerste jaar, nusinersen te vergoeden voor alle SMA-patiënten. Zij erkennen dat er weinig bewijs was voor de effectiviteit in met name oudere patiëntengroepen. Echter de ernst van de ziekte werd voor deze patiënten als dusdanig geacht dat dit opweegt tegen het gebrekkige bewijs over de effectiviteit van nusinersen en nusinersen beschikbaar moet zijn voor alle patiënten. Frankrijk besloot net als Nederland nusinersen niet voor alle SMA-patiënten te vergoeden. In Frankrijk gaat het om een relatief kleine groep patiënten die niet in aanmerking kwamen voor behandeling. Het ging alleen om patiënten die de eerste symptomen pas op volwassen

leeftijd kregen (SMA type 4). In zowel Nederland als Frankrijk werd hiervoor een solidariteits-argument aangevoerd: het vergoeden van dure behandelingen zonder voldoende bewezen effectiviteit zou ten koste gaan van de solidariteit binnen het zorgbudget.

Wij concludeerden dat vier buurlanden op basis van dezelfde beschikbare data over effectiviteit heel verschillende afwegingen maken en tot verschillende vergoedingsregelingen komen. Deze verschillen lijken een meer ethische basis te hebben waarbij ziekte ernst, solidariteit en het wel of niet zijn van een weesgeneesmiddel zorgt voor (belangrijke) verschillen in toegang tot nusinersen en vergelijkbare geneesmiddelen per land.

Ethische reflectie en discussie

De Nederlandse regering streeft naar een rechtvaardige verdeling van middelen en het behoud van solidariteit in het zorgpakket. We hebben ons daarom afgevraagd of de Pakketsluis daadwerkelijk bijdraagt aan een eerlijke verdeling van het zorgbudget en aan de solidariteit binnen ons zorgsysteem.

Als het gaat om een rechtvaardige verdeling kan er op twee manieren worden gekeken naar de Pakketsluis: 1. Is het besluitvormingsproces rechtvaardig? 2. Zijn de (ethische) grondslag en de argumenten waarmee we het zorgbudget verdelen rechtvaardig?

In de literatuur wordt voor een rechtvaardig besluitvormingsproces vaak gerefereerd naar “accountability for reasonableness” (A4R). Dit zijn vier eisen die door auteurs Daniels en Sabin zijn geformuleerd. Deze vier eisen zijn als volgt:

1. Openbaarheid: het besluit moet publiekelijk toegankelijk zijn en de onderliggende redenering van het besluit moet helder zijn.
2. Relevantie: er moet een rationeel te volgen argumentatie zijn voor het besluit. Hier wordt onder verstaan dat het moet aansluiten op redenen, bewijs en principes die worden gezien als relevant door alle betrokken partijen.
3. Revisie en beroep: er moet een manier zijn om de besluitvorming aan te vechten of te reviseren op basis van nieuw bewijs of argumenten.
4. Toezicht: er moet een vrijwillige of publieke vorm van toezicht zijn opdat aan voorwaarde 1 tot en met 3 wordt voldaan.

Onze conclusie op basis van zowel de stakeholder interviews als het vragenlijst onderzoek is dat de Pakketsluis niet voldoet aan de A4R criteria. Er is ruimte voor verbetering op het

criterium openbaarheid. Een deel van de vergaderingen zijn openbaar en de uiteindelijke beslissingen worden kenbaar gemaakt. Toch is voor een deel van de betrokken partijen niet duidelijk waar in het proces een geneesmiddel zich bevindt en zijn de redeneringen niet altijd te volgen. Op het vlak van relevantie is er veel ruimte voor verbetering.

Het werd duidelijk dat er een discrepantie is tussen de huidige beoordelingscriteria (effectiviteit, kosteneffectiviteit, noodzakelijkheid en uitvoerbaarheid) en wat als relevant wordt gezien in de beoordeling van dergelijke medicijnen door stakeholders en het Nederlandse publiek (o.a. effectiviteit, voorkomen van lijden, geen alternatieve behandeling beschikbaar). In het geval van nusinersen werd de onderbouwing voor de ingrijpende leeftijdsgrens als onvoldoende ervaren door patiënten, hun naasten en zorgverleners.

Ten aanzien van principe 3 en 4 kunnen we kort zijn: hier wordt niet aan voldaan. Er is geen mogelijkheid een besluit aan te vechten en er is geen toezicht op het naleven van principe 1 tot en met 3.

Er is een relatie tussen het niet voldoen aan de A4R principes en de ethische grondslag waarmee de Nederlandse overheid het zorgbudget rechtvaardig wil verdelen. In Nederland, en veel andere landen, worden Quality Adjusted Life Years (QALY) als maat gebruikt om te beslissen of een geneesmiddel vergoed wordt. Bij een QALY worden de kosten van een behandeling afgezet tegen de gezondheidswinst. Door dit uit te drukken in een QALY zouden geneesmiddelen met elkaar vergeleken kunnen worden, en er een rechtvaardige keuze worden gemaakt welke behandelingen wel en welke niet in het verzekerde pakket worden opgenomen. In Nederland is de drempelwaarde van een QALY voor het verzekerde pakket €80.000. Als een behandeling meer dan €80.000 per QALY kost, dan gaat dat te veel ten koste van het budget en QALY's van andere patiënten en wordt de behandeling niet opgenomen in het basispakket.

Mensen die afhankelijk zijn van dure geneesmiddelen lopen met deze QALY-drempel een groter risico om geen behandeling te krijgen dan mensen die geen dure geneesmiddelen nodig hebben.

Echter, het gebruik van QALY's is niet een universeel geaccepteerde wijze om te komen tot een rechtvaardige verdeling van een zorgbudget. Er zijn alternatieven als het gaat om het vergoeden van dure geneesmiddelen. Bijvoorbeeld door te streven naar een gelijke mate van ervaren gezondheid. Dit zou inhouden dat mensen die ernstig ziek zijn voorrang krijgen op mensen die minder ernstig ziek zijn, omdat zij een groter stuk gezondheid hebben 'in te halen' om op hetzelfde niveau te komen. Een ander geaccepteerd principe is "the rule of rescue": je bent het moreel verplicht iemand van de dood te redden als dit tot je mogelijkheden behoort. Deze alternatieve en geaccepteerde principes laten zien dat je op verschillende manieren kan kijken naar mensen die dure geneesmiddelen nodig hebben.

Onze conclusie is dat de huidige QALY-benadering te weinig de belangen van mensen die afhankelijk zijn van dure geneesmiddelen in beeld heeft. Ons advies zou zijn dat er wordt gekeken hoe deze belangen meer centraal kunnen worden gesteld, bijvoorbeeld via een van bovenstaande alternatieven.

Tot slot wordt er gesproken over solidariteit binnen het zorgbudget. Zoals we aangaven in hoofdstuk 6 wordt solidariteit door Nederlandse overheid aangehaald om nusinersen voor deel van de SMA-patiënten niet te vergoeden.

De auteurs Prainsack en Buyx beschrijven dat solidariteit een handeling is waarbij je als mens bereid bent om bepaalde kosten of lasten te dragen ten behoeve van een ander, waarbij je enige gelijkenis ervaart (en dat kan op allerlei vlakken zijn) met diegenen waarvoor je de kosten draagt. Dit kan op verschillende niveaus: niveau 1 is een interpersoonlijk niveau, bijvoorbeeld je buurvrouw. Niveau 2 is op groepsniveau: je behoort bijvoorbeeld tot dezelfde religie of sportvereniging. Niveau 3 is op institutioneel niveau: we betalen als Nederlanders belastingen en zorgpremie's om te garanderen dat iedereen in Nederland, onafhankelijk van diens inkomen, toegang heeft tot zorg.

Als een duur geneesmiddel in de Pakketsluis zit en uiteindelijk deels of niet vergoed wordt, wordt de rekening van een solidair zorgsysteem naar ons oordeel te veel bij een kleine, kwetsbare groep mensen in de samenleving gelegd. Dit is op het derde niveau wellicht te verdedigen, maar levert grote spanning op in de lagere niveaus van solidariteit. Dit dilemma is moeilijk op te lossen en huidige theorie en beleidsvoorstellen hebben daar nog geen goede uitweg in gevonden.

Het is duidelijk dat er keuzes moeten worden gemaakt in hoe het zorgbudget verdeeld wordt en dat niet alle behandelingen in het basispakket kunnen worden opgenomen. Alleen kan er bij het maken van deze keuzes, wel met meer nuance worden gekeken naar de gevolgen van de keuzes voor betrokken patiëntengroepen.

Conclusie

De behandeling van SMA met nusinersen is effectief en veilig. Het natuurlijk beloop van de ziekte wordt duidelijk positief beïnvloed door nusinersen en het middel wordt goed verdragen. De evaluatie van de Pakketsluis procedure van nusinersen leert ons dat er ruimte is voor verbetering van de Pakketsluis. Zowel op procesmatig, als op inhoudelijk gebied. De beoordelingscriteria zoals deze nu zijn, sluiten onvoldoende aan op criteria of argumenten die betrokkenen en het Nederlandse publiek belangrijk vinden. Daarnaast kunnen we van

landen om ons heen leren welke alternatieven er zijn om toegang tot geneesmiddelen zoals nusinersen, sneller te organiseren.

Dankwoord

“If you want to go fast, go alone. If you want to go far, go together.” – Afrikaans gezegde

Een proefschrift is nooit het werk van één persoon, maar het resultaat van een samenwerking met patiënten, deelnemers van studies en collega's. Gesteund door familie en vrienden. In de afgelopen zeven jaar heb ik met veel plezier aan dit proefschrift gewerkt en zijn er veel mensen op mijn pad gekomen die op hun eigen manier hebben bijgedragen aan dit werk. In dit dankwoord wil ik graag stilstaan om een aantal van jullie in het bijzonder te bedanken, zonder jullie was ik nooit zo ver gekomen.

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Curriculum Vitae

Féline Eugenie Valerie Scheijmans was born on 30 October 1992 in Utrecht, the Netherlands. In 2010, she obtained her secondary school diploma (VWO) at St.-Odulphus Lyceum in Tilburg. In the same year, she started her medical training at Utrecht University.



During her medical studies, she conducted extracurricular research on the association between body temperature and functional outcome after stroke (2013–2016) under the supervision of Dr. Marjolein Geurts and Prof. Dr. Bart van der Worp. She subsequently completed an elective research internship on nerve excitability and body temperature (2015–2017) under the supervision of Dr. Maria Kovalchuk, Dr. Boudewijn Sleutjes, and Dr. Hessel Fransen. In 2017, she performed a research internship on the ethical foundations of deferred consent in acute stroke research under the supervision of Dr. Rieke van der Graaf. She obtained her medical degree (MD) from Utrecht University in 2017.

In October 2017, she started her residency in Neurology at the University Medical Center Utrecht (UMC Utrecht), under the supervision of the late Prof. Dr. J.H.J. Wokke, Prof. Dr. T. Seute, and Prof. Dr. G.J. Biessels.

In January 2019, she commenced her PhD research at the Department of Neurology and the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht. Her research focused on the treatment of spinal muscular atrophy (SMA) in children, addressing clinical effectiveness, ethical considerations, and reimbursement challenges. The PhD project was supervised by Prof. Dr. Ludo van der Pol, Prof. Dr. Hans van Delden, and Dr. Ghislaine van Thiel. During her PhD trajectory, she presented her work at the SMA Europe conferences (Évry, 2020; Barcelona, 2022) and at the Cure SMA digital meeting (2020). At the SMA Europe conference in Barcelona (2022), she received the Best Clinical Poster Award.

Alongside her research and clinical training, she is a member of the Medical Ethics Committee of the UMC Utrecht. In 2019, she participated in the Nationale DenkTank, contributing to a project on data exchange in healthcare. She currently serves as a board member of Outdoor Medicine and as an instructor in Mountain Medicine and Wilderness Life Support courses for healthcare professionals. In the fall of 2024, she volunteered for the

Himalayan Rescue Association in Pheriche, Nepal, where she provided primary medical care at a high-altitude aid post.

She intends to continue combining clinical neurology with research and initiatives aimed at promoting equitable access to healthcare, both within the Netherlands and internationally.

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