Critical Paediatric Bioethics and the Treatment of Short Stature

- an interdisciplinary study -

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To my family

ABSTRACT

Several studies have argued that there is a correlation between short stature and negative experiences and characteristics, such as social discrimination, economic disadvantage, health problems (especially for men). The idea that short men have a disadvantage in social interactions and in partner choices is also widespread in popular culture and common knowledge. It is now possible to use recombinant human growth hormone (hGH) to treat children with idiopathic short stature (ISS), namely children who are shorter than average for unknown medical reasons. Critics argue that there is a lack of evidence of both psychological distress caused by short stature and the efficacy of the treatment in increasing children's well-being. This controversy is reflected in international drug evaluations: while the Food and Drug Administration (FDA) in the US granted marketing authorisation for hGH for children with ISS in 2003, the European Medicines Agency (EMA) refused it in 2007.

The research presented here had two aims: first, to identify and analyse the norms, values and assumptions about short stature and the use of hGH treatment for children with ISS, found within sociocultural, philosophical and regulatory discussions of these, and within narrated lived experiences of short stature. Second, to critically and reflectively discuss how these analyses contribute to bioethical debates on the use of hGH treatment for children with ISS. It employs what it calls a critical paediatric bioethics theoretical approach, which deems as important to carefully analyse different reasoning, conceptualisations and arguments around the object of study, through a self-reflective analysis that is also sceptical about other forms of problematisation, and that combines philosophical analyses while being open to social implications and drawing upon empirical methods.

The first article proposes a critical understanding of medicalisation as both a concept and a phenomenon, and explores what insights such critical understanding brings to ethical discussions about hGH for ISS. It argues that three main ethical issues concern the medicalisation of short stature: the downplayed role of the qualitative dimension of short stature, the justification of the treatment (as sometimes based on uncritically assumed social beliefs and unrealistic parental expectations), and possible misconduct of stakeholders.

The second article examines the arguments for and against granting marketing authorisation of hGH treatment for the indication of ISS presented in selected FDA and EMA documents. It combines argumentative analysis with an approach to policy analysis called 'what's the problem represented to be' and focuses on underlying assumptions and presuppositions about short stature and hGH treatment for ISS. It then discusses these arguments through the relational, experiential

and cultural understandings of disability, and argues that the choice about whether to give hGH is not merely a choice based on efficacy and safety, but requires an examination of the values that we transmit by that choice.

The third article examines how and why attendance to lived experiences of height is needed in bioethical and biomedical discussions of hGH treatment for children with ISS. It first describes what it defines as the ‘problem-oriented’ approach to the debate about hGH treatment for children with ISS. It then offers a sociophenomenological analysis of whether and, if so, when and how, height matters to the interviewed people in the Netherlands who are shorter than average without any known medical reasons. The sociophenomenological analysis shows the richness of meanings of lived experiences of short stature that cannot be captured by the problem-oriented approach, and suggests complementing clinical practices with narrative approaches.

This research contributes to the ethical debate about using hGH for children with ISS, setting a critical gaze onto the social perception of short stature, highlighting some ethical challenges met by stakeholders involved at different levels (such as families, medical professionals and policy makers), and providing new insights into how to address these ethical issues. It is, therefore, of interest to stakeholders, bioethicists and lay people willing to explore alternative ways to address such bioethical dilemmas, and other paediatric interventions that aim to normalise children’s bodily characteristics.

Keywords: critical paediatric bioethics – growth hormone treatment – medicalisation – phenomenology of the body – critical disability studies – short stature – drug regulations

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Maria Cristina Murano

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LIST OF ABBREVIATIONS

BVKM - Belangenvereniging Van Kleine Mensen¹
CHMP - Committee for Medicinal Product for Human Use
CJD - Creutzfeldt-Jakob disease
EHESP - School of Advanced Studies in the Social Sciences Paris
EMA - European Agency for the Evaluation of Medicinal Products²
EMA - European Medicines Agency
FDA - Food and Drug Administration
GH - Growth Hormone (with this, I refer to the hormone naturally released in the human body)
GHD - Growth Hormone Deficiency
HES - Department of Health Ethics and Society, Maastricht University, the Netherlands
hGH - Human Growth Hormone (with this, I refer to the recombinant hormone used for treatment)
HrQoL - Health-related Quality of Life
ICPED - International Classification of Pediatric Endocrine Diagnoses
ICF - Informed Consent Form
IGHD - Isolated GHD
ISS - Idiopathic Short Stature
LiU - Linköping University
NVGG - Nederlandse Vereniging voor Groeihormoondeficiëntie en Groeihormoonbehandeling³
QoL - Quality of Life
QoLISSY - Quality of life in short-stature youth
REA - Research Ethics Assembly, Maastricht University, the Netherlands
SAG - Scientific Advisory Group
SGA - Small for Gestational Age
SDS - Standard Deviations Score
STS - Science and Technology Studies
WPR - what's the problem representation to be

¹ In English: Association of little people.

² This is the name of EMA, see in the list above, from 1995 until 2004.

³ In English: Dutch Society for Growth Hormone Deficiency and Growth Hormone Treatment.

LIST OF ARTICLES

This thesis is based on three articles. In what follows, they are referred to by roman numerals.

- I. Murano, M.C. 2018. Medicalising short children with growth hormone? Ethical considerations of the underlying sociocultural aspects. *Medicine Health Care and Philosophy* 21(2), 243-253.
- II. Murano, M.C. (submitted to *Health Care Analysis*). A disability bioethics reading of the FDA and EMA assessments on marketing authorisation of growth hormone for idiopathic short stature.
- III. Murano M.C., J. Slatman, K. Zeiler. 2018. How sociophenomenology of the body problematises the ‘problem-oriented approach’ to growth hormone treatment. *BMJ Medical Humanities* Online First: 26 November 2018 DOI:10.1136/medhum-2018-011548.

FOREWORD

My interest in the topic of this study has its roots in my childhood. My parents gradually realized that I was worryingly shorter than other children in my age. When I was 7 years old, we went to the doctor to find out *why* I had stopped growing three years earlier. It turned out that I had a medical condition, called growth hormone deficiency. That is how my journey into regular medical check-ups and daily injections for 6 years began. It was initially predicted that I would become 140 cm as an adult, but I am now 157 cm.

Deciding whether I should undergo the treatment was a very hard choice for my parents. They were doubtful, uncertain, worried. They knew that a few years before my diagnosis, the same drug had been involved in a terrible scandal. It was discovered that it transmitted Creutzfeldt-Jakob disease, an incurable and neurodegenerative disease, to some children. The endocrinologist assured my parents that this had happened only because at that time the drug was extracted from cadavers. By the time I was diagnosed, growth hormone was instead produced in a laboratory and this technique was “perfectly safe”, the doctor said. My parents thought they did not have much of a choice: I had a “deficiency” even though it was hard for them to understand what exactly that meant. The only “symptom” they could see was my (short) height. They asked themselves: what if they did not do anything and I developed problems later in life? Would they have regretted the choice not to intervene when they presumably had the means to do so? What if they gave me the treatment, and I experienced side effects later in life? This has not been the case so far.

I was diagnosed in the mid 1990s, when both the use of recombinant growth hormone treatment and the academic debate on bioethics were in their early stages (if we consider that bioethics as a field emerged in the 1970s). I believe that my parents’ questions and dilemmas, my own experience as a treated child, the uncertainties and problems related to the development of growth hormone as a medical technology, and my studies in philosophy all contributed to nourish and strengthen my interest in the ethical debates about this treatment and my exploration of cultural understandings about short stature.

While I am disclosing my personal experience to the reader for the sake of transparency, this research should not be read as an autobiographical work. Thanks to my academic interest in paediatric bioethics and medicine, I realized that the history and practice of hGH treatment are complex, and generate several philosophical and ethical discussions. I considered the fact that hGH is not a mainstream topic in the bioethics debate as an opportunity to investigate unexplored dimensions and offer fresh perspectives. I thought that, having been a patient myself, and having experienced the complexities and nuances at stake in communication with medical practitioners and

loved ones, I could, as a researcher approach the field with a more accurate perception of the multifaceted aspects involved.

Please note that, while I was diagnosed with growth hormone deficiency, which is a dysfunction of the gland that produces the hormone, in this study I focus on the condition of idiopathic short stature. Children with this diagnosis are short, but all pathological conditions, among them growth hormone deficiency, are excluded. Focusing on this indication gave me some distance to the object of study. I did not approach this research with any *a priori* standpoint: I was rather driven by a genuine curiosity to know more about the treatment and explore different sociocultural understandings and lines of reasoning.

INTRODUCTION

“With the possible exception of gender and skin color, our physical size is probably the first thing other people notice about us, especially if we vary significantly in any direction from the mean, whether short or tall, thick or thin.”

Hall, S.S. p. 7

Over the years, growth hormone treatment (hGH) has been used on both adults and children for different purposes. Its primary clinical application is as a hormone replacement therapy for children and adults with growth hormone deficiency (GHD) – a medical condition due to the dysfunction of the pituitary gland, which controls growth hormone secretion. This is an approved indication worldwide (e.g. in the US, EU, Egypt, Gulf Cooperation Council countries, China; Grimberg et al. 2016a, EMA 2012, Nouf Albalawi et al. 2018, Al Herbish et al. 2016, Xue 2016). Some athletes and bodybuilders use hGH illicitly to improve their performances, and some private clinics use it as an anti-ageing drug (Morrison 2008). These are not approved uses of hGH, and its efficacy in these uses has not been fully documented. With respect to paediatric indications, hGH is commonly accepted and used in endocrinology clinics to increase the height of children with some non-GHD conditions (e.g. chronic renal insufficiency, small for gestational age, Turner syndrome). While the only effect of hGH is to increase height in these conditions, hGH also provides some metabolic benefits in at least one other condition – Prader-Willi syndrome (Hardin et al. 2007, Wit 2002). The use of hGH for idiopathic short stature (ISS), which is a non-GHD condition, is controversial (e.g. Allen 2017, Gill 2006). Children with ISS are shorter than average for currently unknown medical reasons.

The research presented here critically and reflectively examines norms, values and assumptions about short stature and hGH treatment for children with ISS. It engages with aspects of sociocultural, experiential and regulatory discussions about short stature and hGH treatment, and it contributes to the body of bioethical research that examines whether, and if so, why and under what circumstances, hGH treatment should be considered as an option for children with ISS. As will be explained later in the thesis, I adopt an approach to bioethics that I call ‘critical paediatric bioethics’, which combines philosophical with empirical methods and sees bioethical discussions as a continuous “dialogical learning process” (Árnason 2015, p. 162).

Some scholars have defined children with ISS as “small normal children”, “normal variant short stature” (Gill 2006, p. 270) or “short, otherwise healthy children” (Allen 2017, p. 146). The

diagnosis of ISS is possible only by exclusion of any medical causes of short stature. Short stature is nowadays understood to be caused by either endocrine dysfunction (as in the case of growth hormone deficiency) or genetic variation (e.g. Turner syndrome, Prader-Willi syndrome, achondroplasia and other skeletal dysplasias), or to be a symptom of a chronic medical condition, such as chronic renal insufficiency.

The indication of ISS is unique not only because of the lack of explanations for its aetiology, but also in the ways it manifests. Other conditions that result in short stature might present other atypical bodily characteristics than height. For example, the U.S. National Institutes of Health (NIH) writes that some children with Turner syndrome present some somatic features, such as “extra folds of skin on the neck (webbed neck), a low hairline at the back of the neck, puffiness or swelling (lymphedema) of the hands and feet, skeletal abnormalities” (NIH 2019a). The diagnosis of ISS, instead, requires the exclusion of any such differences in bodily traits. It also excludes “disproportionate” short stature (FDA 2003, p. 26). While children with achondroplasia and other skeletal dysplasias present what is defined as an imbalance in body proportions (namely, the arms and legs are disproportionately shorter relative to the size of the trunk, when compared with what is understood to be proportionate), children with ISS, like children with GHD, have balanced body proportions (FDA 2003). Moreover, while most other diagnoses of short stature present health problems unrelated to height (some people and children with achondroplasia have medical symptoms such as otitis, hearing impairment, or vertebral problems (NIH 2019b), for example), the diagnosis of ISS excludes any medical symptoms.

The thesis presents first a brief historical and descriptive approach to hGH treatment. This provides some context and makes the reader familiar with the historical development of hGH treatment, and the ways in which the definition of ISS and the clinical practice of hGH for this indication are presented in medical literature. The following section describes briefly current debates about short stature and the use of hGH treatment for ISS, and then presents the aims and research questions, theory and methods adopted. The three articles are then summarised, and a section discusses how the analyses of these articles contribute to the overarching aims and research questions. Finally, the relevance of this study is considered.

BACKGROUND

Brief History of hGH Treatment

The pituitary gland is an endocrine gland with the size of a pea located at the base of the brain. It is responsible for the regulation of growth hormone (GH) in the body. The understanding of its functioning and its relevance for human growth was possible thanks to the conjunction of a series of scientific, technological, social, and political events that took place during the 20th century in Europe and North America. At the beginning of the century, laboratory experiments on animals (among them dogs, bovines and rats) in the United States showed that the pituitary gland is somehow related to growth. At first, it was not clear what hormone or hormones were involved. It was not until 1944 that GH was isolated and purified from animals (cows) in the US (Morrison 2008). Also during the 20th century, endocrinology emerged as a discipline, and public health movements increasingly focused on child healthcare and paediatrics, which had emerged as a discipline during the 19th century as a growing area of medical specialization (Morrison 2008, Roberts 2016).

Children's growth and development have been studied since the mid-18th century, when auxology emerged as "an interdisciplinary scientific study of growth" (Robert 2016, p. 329). A century later, the Belgian scientist Adolphe Quetelet (1796-1874) applied for the first time a mathematical approach to empirical data, obtained by measuring his own children (Robert 2016). Starting at the end of the 19th century and continuing into the first half of the 20th century, researchers in Europe and the US conducted studies on children living in orphanages to collect measurements and information on human growth and development (Roberts 2016). Growth thus came to be understood as an "indicator of proper development and wellbeing" (Morrison 2008, p. 207), and school-based height surveys spread through Europe and the US. In addition, international collaborations were promoted and allowed the observation of different growth paths on which national growth charts to predict adult height are based. Among other things, the introduction of X-ray technology showed the association between the maturation of bones (which does not always coincide with chronological age) and physical growth and development.

Cohen and Cosgrove (2009) write that starting from the late 1940s, there was a diffuse enthusiasm about the idea of treating short stature. Once bovine hormone had been extracted, it was experimentally injected into children with the aim of making them taller. This technique did not produce satisfactory results: it became clear that GH is species-specific, and the bovine hormone is not effective in humans. In order to produce a physiological response, the hormone must be derived from other humans (Cohen and Cosgrove 2009; Morrison 2015). While GH was still studied in the

laboratory, in the clinic some children in the early 1950s were treated with gender-aligned sex steroids (among them testosterone) in order to promote development. However, steroids make children reach puberty earlier, and therefore interrupt the growth process. The result is thus not necessarily greater height in adulthood. The first successful use of GH from humans (hGH) was in 1958, when an American physician and researcher, Dr. Raben, extracted it from cadavers. Consequently, experiments started to treat short children with hGH.

The main targets of these experiments were children who had a growth hormone deficiency (GHD), i.e. their pituitary gland did not produce the amount of GH needed for regular and steady growth. However, it was not possible to measure GH levels in the children until 1963 (Morrison 2015). This meant that it was not possible to identify with biochemical certainty children who had GHD. In order to select possible patients, physicians mainly observed visible features, such as facial proportions and body fat distribution, and an appearance that was younger than that of other children of that age (Cohen and Cosgrove 2009). This observational approach led to hGH being used for conditions that today have been identified as having different causes and explanations, such as a deficiency due to damage of the pituitary (e.g. tumours), conditions with genetic causes (e.g. Turner syndrome, Prader-Willi syndrome), being small for gestational age, having idiopathic short stature (ISS, i.e. those short due to an unknown medical cause), achondroplasia, and familial short stature (Cohen and Cosgrove 2009, Morrison 2015).

As interest in conducting clinical investigations on hGH grew, and in 1960 the first pituitary bank in the world was established in the University of California Medical Center, San Francisco. Three years later, the US National Institutes of Health established a national collection project, the National Pituitary Agency, with the aim to collect pituitaries and distribute hormones for research purposes on children (Cohen and Cosgrove 2009). Experimental pituitary programmes soon spread to the rest of the world. For instance, the Medical Research Council in the UK established a committee of physicians to control clinical experimentation to test GH (Morrison 2015). It was soon discovered that the treatment resulted in greater adult height if the children had a deficiency of the pituitary gland (namely, GHD), and treatment was primarily used for this indication.

In 1973, British scientists discovered that the procedure used to purify the hormone after extraction from cadavers did not eliminate viruses, and concerns about safety arose. Even though no case of an affected child had been reported, scholars from different countries, such as South Africa, Sweden, the UK and the US, started to develop better procedures to purify the hormone (Cohen and Cosgrove 2009). It was not until 1985 that it was discovered that several patients around the world had been infected during hGH treatment by the prions of Creutzfeld-Jakob disease (CJD), an incurable neurodegenerative medical condition (Hall 2006). It is difficult to assess accurately how

many children eventually died, because physicians kept poor records of patients after treatment, and because the incubation period can be longer than 20 years (Cohen and Cosgrove 2009). However, in 2012 it was reported that 226 cases of CJD associated with hGH treatment had been identified: 119 cases in France, 65 cases in the UK, 29 cases in the US, 6 in New Zealand, 2 each in Brazil and the Netherlands, and 1 each in Austria, Ireland and Qatar (Brown et al. 2012). This was a huge scandal: families were informed of the risk of infection and the service was eventually shut down in all countries (Cohen and Cosgrove 2009).

A recombinant version of hGH, produced by the American pharmaceutical companies Eli Lilly and Co. and Genetech, was approved in 1985 by the Food and Drug Administration (FDA) and other national regulatory agencies to treat the indication of GHD in children (Morrison 2015). Recombinant hGH was proved to be efficient and safe, and the supply was potentially unlimited. Over the years, the efficacy and safety of hGH was assessed for other conditions, and the FDA approved its use for some adult indications (such as GHD, HIV/AIDS-associated wasting), and some paediatric ones, among them chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, small for gestational age, and idiopathic short stature (ISS). ISS is the most controversial paediatric indication of hGH, and its treatment has not been approved by the European Medicines Agency (EMA 2007a). This is the only case in which children do not have any recognized pathology, and the EMA has questioned whether the benefits of the treatment outweigh its risks.

The Definition of Idiopathic Short Stature

ISS has been defined as:

a condition in which the height of an individual is more than 2 SD score (SDs) below the corresponding mean height for a given age, sex and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities. Specifically, children with ISS have normal birth weight and are GH sufficient. ISS describes a heterogeneous group of children consisting of many presently unidentified causes of short stature (Cohen et al. 2008, p. 4211).

This is a “statistical (auxologic)” definition (Noeker 2009, p. 75), and it is only possible to reach a diagnosis of ISS by exclusion, after ruling out other pathological conditions such as GHD, dysmorphic syndrome, skeletal dysplasia, and small for gestational age (Wit 2011).

In medical studies, the definition of ISS has been described as controversial for two main reasons⁴. Firstly, there is disagreement about which diagnoses to include in the ISS definition: some include familial short stature (FSS) and constitutional delay in growth and puberty (CDGP; Wit et al. 2008), while others do not (Kelnar et al. 1999, Rosenbloom 2009). If these two diagnoses are included, “it is estimated that approximately 60-80% of all short children at or below -2 SDs fit the definition of ISS” (Cohen 2008, p. 4211)⁵. Secondly, some conditions, such as isolated partial GHD, are difficult to exclude (Cohen et al. 2008). For this reason, the definition of GHD has also been described as controversial, elusive (Allen & Fost 2004), and arbitrary (Rosenbloom 2009).

In recent years, various attempts have been made to shed light on the aetiology of ISS. Some genome-wide association studies (GWASs) have shown that multiple genes determine height variation within a population (Wit 2011, Wit & Oostdijk 2015, Kang 2017). A more recent study speculates on the prevalence of one gene over the others to determine one’s height (Pennisi 2018). At present, “genetic disorders, including genetic mutations affecting the growth plate such as SHOX and NPR2 defects, must be excluded” from the definition of ISS (Grimberg et al. 2016a, p. 194).

The term ‘idiopathic’ is commonly used to indicate conditions for which “we have not discovered a cause but expect one to exist” (Beaney 2013, p. 128). Future results of studies that aim to discover the “genetic cause (or causes)” of short stature might change the way ISS or short stature in general are perceived and described. For instance, while the definition of ISS is currently controversial due to an uncertainty about whether it should be considered a medical condition, a (physical or psychosocial) disability, or a physical difference (see, for instance, Wheeler 2004, Grimberg et al. 2016a, Sandberg and Colsman 2005, Gill 2006), genetic studies might reveal variations at the genetic level that will determine whether ISS should be classified as a ‘disease’ or not. Further, such studies may provide more information about the response that an individual child will show to hGH treatment, as Grimberg et al. (2016a) say: “Genetic testing is expected to expand and offer additional insights, and elucidation of markers for therapeutic responsiveness may help guide clinical decisions” (Grimberg et al. 2016a, p. 388).

The journal *Nature* has recently published a study that downplays the relevance of GH for growth, suggesting that growth should be better understood as depending on “multiple hormones,

⁴ Allen (2017) writes that also the condition known as “isolated GHD” (IGHD) is ethically controversial. He writes: “Isolated GHD (IGHD) refers to short, otherwise healthy children who have low stimulated GH levels but normal MRI scans, no other pituitary hormone deficiencies, and no other reason for GHD. Idiopathic short stature (ISS) refers to short, otherwise healthy children distinguished from IGHG only by higher GH testing results” (Allen 2017, p. 146).

⁵ According to the International Classification of Pediatric Endocrine Diagnoses (ICPED), ISS includes familial ISS and non-familial ISS, both with and without pubertal delay (Grimberg et al. 2016a).

paracrine factors, extracellular matrix molecules and intracellular proteins that regulate the activity of growth plate chondrocytes” (Baron et al. 2015, p. 735). In other words, growth disorders are due “to a dysfunction of the skeletal growth plate—the structure responsible for bone elongation and, therefore, overall body size” (Baron et al. 2015, p. 743). Baron et al. (2015) therefore define the idea that GH is a central factor in making children with ISS grow taller as an “historical paradigm” (p. 735), which is soon to be overtaken by a “broader conceptual framework” in the understanding of short stature (p. 740). Baron et al. (2015) base their study on both underlying biological mechanisms and genome-wide association studies, and they claim that:

We can, therefore, anticipate that the number of children who receive the unhelpful diagnosis of idiopathic short stature will continue to diminish. With these advances, we can look forward to treatment approaches that are tailored to the specific genetic cause of the disorder (Baron et al. 2015, p. 743).

In the work presented here, I take these debates in the medical literature as a starting point for a critical and reflective analysis. I do not position myself as advocate or critic of any of these definitions and understandings *a priori*, but I consider them as part of the investigation.

hGH Treatment for Children with ISS: how does it work?

In order to maximize height gain, hGH treatment should be started before puberty. However, the adult height reached by an individual patient is highly variable and depends on the dosage and individual response. It ranges from 3.5 to 7.5 cm for a treatment of 4 to 7 years (Cohen et al. 2008). The treatment regimen requires daily injections, regular visits to the clinic (Wit 2002), and considerable cost. The estimated cost of hGH is € 50,000–75,000 for a gain of 5–7 cm, where the final cost depends on dose, frequency and the “proprietary preparation used” (Gill 2006, p. 271)⁶. The use of hGH for children with ISS presents the same short-term safety profile as other conditions treated with hGH (e.g. chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, small for gestational age), but it does not bring any health benefits to these children that are unrelated to height gain. Metabolic benefits, at least, have been reported for children with other conditions, such as GHD and Prader-Willi syndrome (Hardin et al. 2007, Wit 2002). Studies of long-term side effects of hGH for children with ISS have not been conclusive. Surveillance is recommended for the risk of cancer, metabolic side effects (Cohen et al. 2008, Carel et al. 2012, Swerdlow et al. 2017), for a possible increase in mortality, and the risk of stroke (Carel et al. 2012, Poidvin et al. 2014).

⁶ According to Grimberg et al. (2016a), the cost of hGH therapy is USD 35,000–50,000 per inch of height gained (p. 387).

Concerns about the impact of short stature on children's psychosocial adjustment play a crucial role in medical decision-making on hGH treatment for both families and physicians (Silvers et al. 2010, Grimberg et al. 2015). Some studies have shown an association between short stature and developmental, social and educational problems (Siegel et al. 1991, Underwood 1991), but these have been highly criticised for methodological flaws and the lack of control groups (Kranzler et al. 2000, Sandberg 2011, Gardner et al. 2016). Moreover, other studies have not found a significant difference in psychological adaptation between children with ISS and those with average height (Voss and Sandberg 2004, Cohen et al. 2008). There is also no evidence that hGH treatment improves psychological functioning (Visser-van Balen et al. 2006, Bullinger et al. 2013). The scarcity of empirical data confirming an improvement in the quality of life after hGH treatment (Theunissen et al. 2002, Allen & Fost 2004, Cohen et al. 2008) may be explained by the fact that little attention has been paid to the long-term monitoring of children's psychological wellbeing and quality of life (Grimberg et al. 2016a).

Various quality of life (QoL) assessment tools have been used in clinics and research throughout the years. Recently, a short stature-specific quality of life measurement (QoLISSY) has been developed by the pharmaceutical company Pfizer Limited and the University Medical Centre Hamburg-Eppendorf. The QoLISSY questionnaire aims to assess the possible effects of hGH treatment and psychological interventions in short children referred to endocrinology clinics (Bullinger et al. 2013). Researchers involved in the development of the QoLISSY questionnaire write that "short stature as an isolated characteristic may constitute a risk factor for behavioural and emotional problems" not only because of "barriers in everyday life" but "also because short stature can be regarded as a social stigma, which in turn may affect self-perception and the social integration of persons with short stature" (Bullinger et al. 2013, p. 2). The project to develop QoLISSY has involved collaboration between several clinics and research centres in Europe (France, Germany, the UK, Spain, Sweden, and the Netherlands; Bullinger et al. 2013, Rohenkohl et al. 2016) and in the US (Bullinger et al. 2015).

CURRENT BIOETHICAL DISCUSSIONS

The use of hGH treatment for children with ISS has caught the interest of scholars working in several disciplines, such as medicine and psychology (e.g. Gill 2006, Sandberg 2011, Allen 2017), social sciences (Conrad and Potter 2004), science and technology studies (Morrison 2008, Morrison 2015), and philosophy and bioethics (Verweij et al. 1997, Sandel 2007, Harris 1992). While children with ISS are treated with hGH mainly because of the concern that short stature might causes psychosocial problems (e.g. Visser-van Balen et al. 2006), many scholars have described the use of hGH for children with ISS as controversial both because of the contingent characteristics of the treatment, and because it raises some fundamental philosophical and bioethical concerns.

hGH Treatment for Children with ISS: Why? Why not?

Short stature has been described by paediatricians and endocrinologists as an indicator of health problems (Cohen 2008). Short stature, among other things, might be an indicator of some health conditions (such as Turner syndrome, Prader-Willi syndrome), or of malnutrition (Nouf Albalawi et al. 2018). Some studies show that small height is associated with health problems later in life (albeit without a causal relationship), such as mortality (Engeland et al. 2003), chronic disease (Perelman 2014), and greater risks for psychosis and suicide (Magnusson et al. 2005). While parents seek medical care for their children's height because they are concerned about their health and wellbeing, once all known medical diagnoses are excluded, one of the main reasons to opt for hGH is that they are concerned about the impact that short stature has on "psychosocial functioning", especially for boys (e.g. Grimberg et al. 2016b, p. 345). Visser-van Balen et al. (2006) argue that parents worry that their children might "have lower social competence and show more social problems" than their peers of average height (Visser-van Balen et al. 2006, p. 433). The concern that short stature is associated with psychosocial distress can be found in the medical literature, even though there is no clear evidence that short stature causes such problems:

With currently available data, it is difficult to generalize on the impact of short stature on psychosocial adaptation. Short stature may be a risk factor for psychosocial problems, such as social immaturity, infantilization, low self-esteem, and being bullied, especially for those referred for evaluation. The large interindividual differences in adaptation to short stature and on the impact of being short may be a function of several risk and protective factors, including parental attitudes and prevailing cultural opinions. Stress experiences may be frequent, but true psychopathology is rare. Overall, both clinical and population studies indicate that most short individuals are functioning within the broad range of normalcy;

however, it is of note that extremely short children (< -2.5 SDs) have not been adequately studied (Cohen et al. 2008, p. 4212).

Verweij and Kortmann (1997) maintain that the prevention of psychological and social problems is an ethical justification for hGH because of “societal prejudices concerning short stature” (Verweij and Kortmann 1997, p. 308), and argue:

Short people are easily overlooked – in the literal and figurative sense. They may be stigmatised as abnormal and unimportant. Adults of 150 cm height are constantly confronted with the fact that the physical and social world in which they live is not adapted to people of their length (Verweij and Kortmann 1997, p. 308).

They justify this argument with three main reasons: first, short people might benefit from medical and psychological care; second, parents who decide for the treatment cannot be blamed if they do not heroically resist social beliefs; third, doctors should focus on the wellbeing of the patients and not on the fight against social beliefs (Verweij and Kortmann 1997). Thus, they justify hGH, despite acknowledging that it might both reinforce “cultural stigma” (p. 308) and induce psychological problems in children, leading them to focus too much on height.

Contingent characteristics of the treatment, however, have been described as problematic. Some scholars have pointed out that current state of knowledge on the use of hGH for the indication of ISS is insufficient (in particular regarding efficacy, safety, and realistic expectations), while some raise concerns for economic considerations and stakeholder involvement. It has been argued that there are too many uncertainties to make a risk/benefit assessment for the following reasons: some scholars claim that hGH does not provide substantial height gain for children with ISS, and highlight the fact that individual response (in height gain) is highly subjective (Rosenbloom 2010, Rogol 2018); some argue that there is limited evidence that hGH treatment brings psychosocial or quality-of-life improvements to children with ISS; and some argue that there are uncertainties in long-term safety (see, for example, Voss and Sandberg 2004, Rosenbloom 2009, Grimberg et al. 2016a, Allen 2017). Given the high cost of hGH, questions of justice in access have been raised, and the issue of resource allocation (Gill 2006, Cuttler et al. 2009, Durand-Zaleski 2011). Moreover, some have raised concerns about stakeholder influence and interests. Since ISS represents the largest group of paediatric conditions treatable with hGH, both the industry involvement in post-marketing studies and the possible misconduct of physicians (e.g. prescribing hGH in exchange for benefits from the industry) have been described as problematic (Finkelstein et al. 2002, Cohen and Cosgrove 2009, Hordijk 2017, Allen 2017).

While the concerns described above focus on contingent characteristics of the treatment, some scholars have raised a fundamental philosophical and bioethical issue. According to them, if hGH

treatment is used for children with ISS, it crosses the much-debated boundary between the medical and non-medical realms.

Bioethics Debates on Non-Therapeutic Treatments

The use of hGH for ISS has been defined as cosmetic endocrinology (e.g. Allen 2017, Rosenbloom 2011), enhancement (e.g. Conrad and Potter 2004, Allen 2017), medicalisation (e.g. Verweij et al. 1997), and pharmaceuticalisation (Morrison 2015). I see these concepts as having different focuses and hint at different aspects of the use of hGH treatment for children with ISS, but all highlight that hGH treatment goes beyond what is commonly understood as therapy, because it treats a condition that is not considered to be a disease (e.g. Allen 2017). Using the term ‘cosmetic endocrinology’ highlights the fact that hGH only modifies the height of children with ISS (e.g. Allen 2017, Gill 2006). The concept of ‘enhancement’ refers to the fact that hGH aims to ameliorate – according to a certain preference – a physical characteristic (Harris 1992, Sandel 2007). Talking in terms of ‘medicalisation’ points out that what is assumed to be a non-medical condition (namely, ISS) is treated by medical means (i.e. hGH; Verweij et al. 1997). The term ‘pharmaceuticalisation’, in contrast, has been used to highlight the role played by pharmaceutical companies in the development of the drug and its commercial availability (Morrison 2015). While these concepts highlight different aspects and ways in which the presumed medical/non-medical boundary is crossed, many scholars refer to them because they consider ISS to be a non-medical condition and the use of hGH treatment to be problematic. Such scholars question whether hGH is necessary and/or ethically acceptable for children with ISS (e.g. Sandel 2007, Rosenbloom 2010, Allen 2017).

In bioethics literature, the concepts of enhancement and medicalisation have sparked lively debates, dividing scholars into three camps: those who advocate non-therapeutic interventions (Harris 1992, Bostrom and Savulescu 2009), those who are against such interventions (Sandel 2007, Kass 2002), and those who do not oppose such interventions in principle, but propose some restrictions (Hofmann 2017). While a broad understanding of the concept of enhancement refers to any kind of intervention that goes beyond therapy (medical or not; Bostrom and Savulescu 2009), debates on medicalisation centre on the role of medicine. The aspects and understandings of medicine referred to by scholars using the concept of medicalisation are varied. Examples are those who refer to medicine as an institution (e.g. Zola 1972, Illich 1974), those who refer to the sociological aspects of medicine (e.g. Conrad 1992, Halfmann 2011), and those who refer to “medical practice” or the “art, or craft, of medicine” (Nordin 1999, p. 106). In recent years, particular attention has been given to the role of technological improvements in medicine (e.g. Hofmann 2001, Clarke et al. 2003). Clarke et al. (2003), for example, suggest that the concept of

biomedicalisation is useful to highlight not only technoscientific innovation, but also a cultural transformation that this implies. They define medicalisation as “the processes through which aspects of life previously outside the jurisdiction of medicine come to be construed as medical problems” (Clarke et al. 2003, p. 161), and maintain that this notion has until now focused on illness and disease. Biomedicalisation, instead, they argue, aims to treat potential risks, and modify health and lifestyles. They suggest that biomedical interventions not only provide increasing means of intervention, but also shape a cultural tendency towards transforming and tailoring one’s own condition. They picture biomedicalisation not as a substitute for medicalisation, but as new cultural understandings of medical interventions, which may overlap, co-exist with, or accompany previous ones (Clarke et al. 2003).

Clarke et al. (2003) based their study on US medicine, and the degree and extent of this cultural shift may differ from country to country. However, an increasing number of medical interventions that go beyond therapy is available to modify children’s non-conforming bodily characteristics. For example, girls who are considered to be too tall may be given oestrogen treatment to reduce their growth (Rayner et al. 2010, Pyett et al. 2005); children with achondroplasia may undergo limb-lengthening surgery to become taller (Sullivan Sanford 2006); children with cleft palates may undergo surgery to minimize the difference in facial appearance (Mouradian et al. 2006); children born with a non-binary sexual anatomy may have surgery to conform to prevailing binary gender norms (Zeiler and Malmqvist 2010); and children may wear orthodontic braces to achieve “movie-star teeth” (Wickström 2016). These kinds of intervention are, in most cases, justified by the assumption that it would be hard for children to grow up surrounded by negative sociocultural norms, and that an attempt of normalization constitutes a way of preventing psychosocial distress and/or enhancing the children’s possibilities of well-being. These “appearance-normalizing” interventions (Parens 2006, p. 3) have been the subject of ethical controversy. For example, Sandel (2007) maintains that it would not be socially desirable if all parents unhappy with their children’s appearance (one of which is a deviation from expected height) recur to medical interventions. They should, instead, be “open to the unbidden”, and should accept and love their children as they are. His view contrasts with that of Harris, who argues that height is a morally neutral physical trait and, for this reason, the choice to intervene to satisfy personal preferences (in this case, parents preferring taller children) cannot be considered morally wrong (Harris 1992).

Two themes in these ongoing bioethical and philosophical discussions are relevant for my study on hGH for children with ISS. The *first* is ethical and philosophical concerns about the use of medical interventions for conditions that are commonly not considered disease, while the *second* is

how medical interventions can be informed by sociocultural norms and beliefs, and how this might be perceived differently from an ethical viewpoint.

Sociocultural Norms and Beliefs about Short Stature

In 1975, Saul D. Feldman introduced the neologism ‘heightism’ to refer to the stigmatization of short people in the US. He compared it with racism and sexism and stressed the idea that people “react strongly” (Feldman 1975, p. 441) when confronted with shorter people. He then identified several aspects of life in which heightism is apparent: he writes that in common language we frequently use shortness to refer to negative characteristics (such as ‘short-sighted’ or ‘put someone down’); in romantic relationships, courtship is harder for shorter men; in politics, American presidents are normally taller; in terms of economic inequalities, taller men usually have a higher income, and are more likely to be hired in employment processes than shorter ones; in popular culture, most sports are such that they favour taller people, and romantic roles in films are generally intended for tall actors. More recently, Hall (2006) coined the term “altocracy” to describe the uncritical public belief that associates tall people with “positive traits” (Hall 2006, p. 15), such as intelligence, success, sexual desirability and leadership skills.

Studies of a wide variety have argued that there is a correlation between short stature and negative experiences and characteristics, such as social discrimination, economic disadvantage, and decreased attractiveness (especially for men). For instance, short stature has been described as a “burden” that carries social stigma and disadvantage (Downie et al. 1997, Kranzler et al. 2000), short people described as having lower social status (Herpin 2006, Lasco 2017), lower intelligence, or lower academic achievement scores (Wheeler et al. 2004, Case and Paxon 2008), and shorter men as having a lower probability of being married (Manfredini et al. 2013). However, most of the studies quoted above were conducted in Western countries, and it has been pointed out that they have some cultural bias. Studies on partner preference, for example, have focused mainly on Western countries and on heterosexual individuals, whereas different preferences have been revealed in at least one traditional ethnic group in Tanzania (Sorokowskia and Butovskayab 2012), and in people with non-heterosexual orientations in Brazil and the Czech Republic (Valentova et al. 2016). Moreover, some studies have shown that shorter people live longer than taller ones (Samaras 2009, Allen 2017).

Negative cultural representations of short stature are also widespread, and present some recurring themes. One of these is the supposed disadvantage in partner choices (especially for short men). The cult movie “Freaks” (1932), for example, tells the story of a company of sideshow performers, in which most of the characters have atypical bodies, such as the living torso (a person

without arms and legs), the half boy (a person with no legs), and the living skeleton (a very tiny man). These people are called “freaks” in the movie, and the main characters are a couple of “midgets”. The story is about Hans, the short man, falling in love with a “normal-statured” woman, called Cleopatra. She makes fun of him and infantilises him on several occasions, without taking seriously his romantic and sexual feelings. This movie has generated reflections on cultural representations of disabled people and atypical bodies (Garland-Thomson 1996), and it reinforces stereotypes about shortness and taller-man preference. This theme is still widespread (even if we do not talk in terms of ‘freaks’ or ‘midgets’). A more recent cinematic reference is the 2016 French film “Un homme à la hauteur” (English Title: “Up for Love”), which recounts the love story of a short man and the dilemmas of the “normal-size” girl in maintaining a relationship with him, despite his (short) height.

The possible implications of widespread negative sociocultural norms and beliefs about short stature are expressed and discussed on, for example, websites dedicated to short people, with the stated aim to “support” short people (www.shortsupport.org) or “help” short people to fight heightism (www.supportfortheshort.org). There are even some dating sites dedicated specifically to short people, for example, “Single little people near you” (www.littlepeoplemeet.com) and “Short Passions” (shortpassions.com).

AIMS AND RESEARCH QUESTIONS

Overall Aims

The aim of the work presented here was two-fold. The first aim was to identify and analyse norms, values and assumptions about short stature and the use of hGH treatment for children with ISS, found within a sociocultural, philosophical and regulatory discussions of these, and within narrated lived experiences of short stature. This led to the two-part research question:

- What kinds of norms, values, and assumptions on short stature and hGH treatment are explicitly and implicitly used within sociocultural, philosophical, and regulatory discussions of these, and within narrated lived experiences of short stature?
- How are these norms, values and assumptions expressed, and how do they contribute to different understandings of short stature and problematisations of the use of hGH treatment for children with ISS in the analysed discussions?

This first aim included an aspiration to show how the analysis contributes to bioethical debates on the use of hGH treatment for children with ISS. This led to the second aim: to discuss how the analyses in the first aim contribute to bioethical debates on the use of hGH treatment for children with ISS. This led to the research question:

- Should the analysis of norms, values and assumptions about short stature and hGH identified in the first aim be understood as relevant for bioethical discussions on the use of hGH treatment for children with ISS? If so, how and why?

Specific Aims of the Articles

Each of the articles of this research engages with the three research questions stated above from different perspectives, with different focuses, methods and approaches. While the first article engages with aspects of the philosophical and sociocultural discussions, and the second engages with regulatory discussions of the use of hGH treatment for children with ISS, the third article explores narrated lived experiences of short stature. The three articles first identify the norms, values and assumptions that are implicitly and explicitly used in the considered discussions. They then examine them, critically and reflectively. Finally, each of them provides insights into the ethical discussions on the use of hGH treatment for children with ISS. The concluding discussion, presented here, will explore how these three different articles are related, and how they contribute to the overarching aims of this study.

The first article proposes a critical understanding of medicalisation as both a concept and a phenomenon, and explores what insights such critical understanding brings to ethical discussions about hGH for ISS. To do so, it first applies my understanding of medicalisation as both a concept and a phenomenon to short stature and hGH treatment. Second, it identifies what sociocultural aspects are explicitly and implicitly involved, and then analyses them through the lenses of philosophical discussions on the medical/non-medical distinction and the goals of medicine. Finally, it reflects on the ethical implications of such analysis.

The second article examines the ethical implications of the understandings of short stature, and the justification for treatment with hGH that the FDA and EMA conveyed with their arguments *pro* and *contra* the marketing authorisations of hGH for the indication of ISS. To do that, it first analyses the documents, focusing on underlying assumptions and presuppositions. It then discusses the ethical implications of the concepts and themes, analysed from the perspective of disability studies.

The third and final manuscript examines how and why consideration of lived experiences of height is needed in bioethical and biomedical discussions of hGH treatment for children with ISS. It first describes what it defines as the ‘problem-oriented’ approach to the debate on hGH treatment for children with ISS. It then offers a sociophenomenological analysis of whether and, if so, when and how, height matters to the interviewed people in the Netherlands who are shorter than average without any known medical reasons. It finally shows how this sociophenomenological analysis of the interviews contributes to biomedical and bioethical discussions about hGH for children with ISS.

THEORETICAL FRAMEWORK AND CONCEPTS

Bioethics has been a multifaceted and complex field of inquiry since its origins. According to Engelhardt (2012), the term ‘bioethics’ was coined in 1927 by Fritz Jahr, and reused by Van Rensselaer Potter in 1949. However, most literature traces its origins back to Van Rensselaer Potter’s publications of 1970 and 1971 (Engelhardt 2012). He used the term in a broad sense to refer to a new discipline that combines “biological knowledge and human values” (Potter 1970, p. 127). Still in the 1970s, André Hellegers (Reich 1999) and Sargent Shriver (Engelhardt 2012) restricted the meaning of the term to the study of moral questions posed by biological knowledge and its application to medicine. Lecaldano (2002) suggests that bioethics can now be understood broadly as a critical field of inquiry that studies ethical dilemmas concerning life (in the human, animal, and environmental sense). The term may be used in a narrower sense to refer to studies that focus on human life (Lecaldano 2002). Several subfields have emerged over the years that fit the latter understanding of bioethics, such as clinical ethics, medical ethics, and nursing ethics, according to the main areas of investigation involved. These different areas overlap and intertwine. The work presented here centres on ethical debates about the use of hGH treatment for children. This is the reason that I refer to it as ‘paediatric bioethics’.

Several theoretical and methodological approaches have been proposed and used in studies that contribute to bioethics research. Examples of these approaches: principlism (Beauchamp and Childress 2009 [1979]), utilitarianism (e.g. Singer 2011 [1979]), virtue ethics (e.g. Pellegrino and Thomasma 1993), personalism (Schotsmans 1999), narrative ethics (e.g. Montello 2014), phenomenological approaches to bioethics (Svenaeus 2018; see also Zeiler and Käll 2014), and disability bioethics (e.g. Scully 2008, Garland-Thomson 2017). I will first describe the theoretical framework and methods used in the work presented here.

Critical Paediatric Bioethics

Ethical concerns about children’s medical care have always been discussed in bioethics literature, but the need for a specialised reflection has emerged in recent years, reaching its maturation at the beginning of the 21st century, when paediatric bioethics centres started to be established in the US, such as the ones in Seattle and Kansas City (Lantos 2010). Some of the specific themes of discussion are: parental authority and family interest, informed assent, the best interest standard, children’s rights, and research involving children (e.g. Groll 2014, Diekema et al. 2011, Kopelmann 1997, Goldhager 2016, Lantos 2010). A major focus of debate in paediatric bioethics is on clinical ethics, and explores issues such as end-of-life care, neonatal care, organ donation, decision-making,

and the use of new technologies (e.g. Miller 2009, Diekema et al. 2011, Hendriks and Lantos 2018). Childhood is generally described as a complex and multifaceted phenomenon that encompasses several phases of development, and the main reasons given for a research focus on paediatric care is the understanding of children as vulnerable, in need of special protection, which requires the involvement of parents and families as decision-makers (e.g. Lantos 2010, Garrett 2018). An ongoing debate concerns whether, and if so, when and how, children/adolescents should take part in decisions concerning their own healthcare (e.g. Piker 2011, Casula 2013). Many studies have focused on the ethics of children and adolescents' medical care without necessarily using the term 'paediatric bioethics'. For example, some studies have focused on children's mental health and the ethical challenges posed by stimulant drug treatments for children with ADHD (Singh 2013), or early interventions in psychosis (Corsico et al. 2018).

I have adopted an approach to paediatric bioethics that I call 'critical paediatric bioethics'. This approach was inspired by studies in bioethics that suggest combining philosophical with empirical methods (e.g. Hedgecoe 2004, Zeiler 2005, Borry et al. 2005, Leget et al. 2009). In particular, I agree with the suggestion put forward by Hedgecoe (2014) and by Árnason (2015) of what critical bioethics should be. Hedgecoe (2004) writes that critical bioethics should be empirically rooted, theory-challenging, reflexive and politely sceptical. Árnason (2015) lists four main characteristics of critical bioethics. First, it requires a careful attempt to understand others' arguments and reasoning around the object of study and the context of their positions. Second, it should engage in a self-reflective work of analysing one's own assumptions and presuppositions. Third, it should look at the broader social implications, and philosophy should be open to the social sciences. Finally, it should engage in a "dialogical learning process" (Árnason 2015, p. 162). This last point highlights the idea that ethical inquiry should be seen as an engagement in dialogue, as an attempt to make sense of different viewpoints and actors' interactions, while being aware of one's own biases and assumptions, and being receptive to the different values at stake (Árnason 2015).

As a bioethicist who aspires to develop a critical approach, I engaged in this study in a reflective and self-reflective exploration of the norms, values and assumptions at stake in discussions about the paediatric use of hGH for ISS and about short stature in general. I have sought to engage in a dialogical learning process that has led me to consult literature from several disciplines (such as philosophy, sociology, and medicine), and to explore various dimensions of the discussion (such as sociocultural, philosophical and regulatory dimensions). I embraced the challenge of encountering different epistemological perspectives and applying different knowledge and skills as a way to develop and increase my "hermeneutic sensitivity and awareness" (Árnason 2015, p. 162).

Medicalisation

While the use of hGH for children with ISS has been described in many ways, in this study I focus on the concept of ‘medicalisation’⁷. I see medicalisation as a framework of analysis that allows an engagement with philosophical/conceptual debates on the use of hGH for children with ISS, while still being attentive to sociocultural discussions. In this study, I adopt Conrad’s (1992) definition of medicalisation as a

process by which nonmedical problems become defined and treated as medical problems, usually in terms of illness and disorder (Conrad 1992, p. 209).

This concept aptly brings out two main themes that I see as central to discussions and analysis of the use of hGH for ISS, namely: the idea that this concept refers to a “sociocultural process” (Conrad 1992, p. 211), and the idea that the process is described as crossing the boundaries between the medical and non-medical realms that are much debated in philosophy and bioethics literature⁸.

In this study, therefore, I consider the concept of medicalisation as a concept in need of investigation, which provides theoretical tools to explore the norms, values and assumptions about the practice and ethical debates about hGH treatment for children with ISS within sociocultural discussions. I adopt medicalisation as a framework to broaden the ethical debate over the reasons

⁷ I prefer the concept of ‘medicalisation’ to the concept of ‘enhancement’ because I see the latter as implying that an intervention that crosses the boundaries of therapy is a form of improvement. However, I consider it to be a matter of inquiry whether hGH treatment improves the lives of children with ISS. A similar reason formed my decision to avoid referring to ‘cosmetic endocrinology’. I do not consider that height affects beauty, and I do not want the reader to believe that I have taken a stand on whether being tall is aesthetically better than being short. The concept of ‘pharmaceuticalisation’, in turn, has been defined as a “conceptual apparatus” that aims to understand pharmaceutical aspects of medicalization (Bell & Figert 2012). Talking about pharmaceuticalisation would, therefore, draw attention to pharmaceutical aspects, which is not the main interest of this research. Even though I analyse the documents of drug regulatory agencies, I focus on their arguments and final decision, and not on the practical implications of the industry’s involvement, or the way in which marketing approvals for drugs function. Lastly, I exclude also the concept of ‘biomedicalisation’ because, while it is important to acknowledge technoscientific developments in medicine, I consider medicine to be necessarily tied to new technologies, and possible cultural implications of technosciences.

⁸ The debate about medical/non-medical problems has sometimes been discussed in terms of health/disease (e.g. Purdy 2011, Parens 2013). Several explorations of the definitions and meanings of ‘health’ and ‘disease’ have been offered (e.g. Canguilhem 1966, Wakefield 1992, Mordacci 1995). To mention two classic (and opposite) examples: Boorse (1977) advances a biostatistical definition of health, to be assessed on the basis of statistical normality for an individual’s organism according to the normal species design. Nordenflet (2007) instead suggests a definition of health based on a general evaluation of the person’s bodily and mental state, focusing on the quality of life of the person (Nordenflet 2007). In the debate about the goals of medicine, Pellegrino (1999) distinguishes between the approaches of ‘essentialists’ and ‘constructionists’: while constructionists negotiate the goals of medicine, essentialists (among them Pellegrino) argue that – what they define to be – the essence of medicine should delimit medicine. Medicine came to existence, Pellegrino argues, because of the human experience of illness, and thus medicine should limit itself to the care, cure and healing of patients. Interpretations of what ‘care’ means may differ, of course, according to one’s understanding of health/disease.

for and against hGH treatment for children with ISS, not only taking into account the complexity of the sociocultural phenomenon, but also critically investigating the conceptual aspects of medicalisation.

The complexity of the sociocultural phenomenon of medicalisation became apparent to me through reading its descriptions in medical sociology literature, in particular the characterisations of Conrad (1992) and Halfmann (2011). Conrad states that the process of medicalisation should be understood in terms of degrees, and not as an either/or situation. He describes it as a two-way process that may be paired with demedicalization (which describes the opposite phenomenon: a problem is no longer medically defined or treated), and suggests that it occurs at three levels: the conceptual, institutional and interactional (Conrad 1992). Halfmann (2011) goes further, and draws a distinction between levels (macro: e.g. legislations; meso: e.g. local clinics; and micro: e.g. doctor-patient interaction) and dimensions (discourse, practices, identities) of medicalisation. He exemplifies this, referring to, among other things, the evolution of the definition, laws and practices of abortion in the US in the 1960s and 1970s. He argues that abortion, at that time, could be seen as medicalised because the incidence of abortions increased (macro-level), but demedicalised because there was increasing involvement of non-medical personnel (meso-level), while the use of local anesthesia allowed outpatient abortions in clinics (micro-level). While reading about the history and development of both hGH treatment and the definition of ISS, I came to recognise the complexity described by Halfmann. In the analysis presented here, I suspend any *a priori* judgment on hGH treatment and the sociocultural process implied. I seek not to consider short stature as medicalised or demedicalised at any given time, but rather look for levels and dimensions in the decrease and increase of medicalization or demedicalization of short stature.

Disability

In previous literature, and in the analysed documents of the Food and Drug Administration and the European Medicines Agency, short stature has been described in terms of handicap, impairment and disability (e.g. Kranzler et al. 2000, Wheeler et al. 2004, Grimberg et al. 2016; EMA 2007b, FDA 2003). These concepts, however, have not been critically discussed or questioned when used to refer to short stature, whereas extensive research has been conducted within the critical and interdisciplinary field known as ‘critical disability studies’ on aspects such as lived experience, definitions, policies on disability and cultural understandings of atypical bodies (e.g. Scully 2008, Oliver and Barnes 2012, Shakespeare 2012, Garland-Thomson 1996). Disability has also been the subject of bioethics research into the ethical acceptability of medical interventions on people with disabilities (e.g. Parens 2006, Sandel 2007, Garland-Thomson 2012). Some recent studies have used

the concept of ‘disability bioethics’ and have focussed on, for example, disability rights (Ouellette 2011), embodied experience (Scully 2008), and cultural understandings (Garland-Thomson 2017). It has been suggested that theorisations of disability have revealed underlying assumptions and commonly held understandings of disability and of people with atypical bodies (e.g. Oliver and Barnes 2012, Garland-Thomson 2017). I have here used the concept of ‘disability’ as a theoretical framework to explore implicit assumptions and presuppositions in the understanding of short stature and the use of hGH for children with ISS.

An intense debate among disability activists and researchers has been in progress in the UK, the US and Scandinavia since the 1960s, in an effort to re-theorise disability, and develop a “disability culture” (Oliver and Barnes 2012, p. 15). People with disability have increasingly started to identify as a minority group, in the same way as groups of women, racial minorities and homosexuals have done since the 1950s (Oliver and Barnes 2012). The disability movement was motivated by the idea that there are widespread negative sociocultural understandings about disability, and that disabled people are disadvantaged by discriminatory policies (Oliver and Barnes 2012). Therefore, an intense work to reshape common understandings of disability and political activism started, for example, to claim human rights and fair treatment, such as access to services and non-discriminatory policies. In particular, disability scholars and activists have been vocal in protesting and trying to dismantle the so-called medical (or also called individual) model of disability adopted by “policy makers, professionals and mainstream scholars” (Oliver and Barnes 2012, p. 11). According to Oliver and Barnes (2012), this model pictures disability as a “personal tragedy” (p. 11) and primarily as a health issue. It “explains disability in terms of medical diagnoses of individual pathology, associated functional limitations and culturally determined deficits” (Oliver and Barnes 2012, p. 11).

The main reason that this model has been described as problematic is because it considers the cause of disability to be intrinsic to the individual (Oliver and Barnes 2012). The medical model considers sociocultural discrimination to be due to the objective physical or psychological difference of the individual, and medical treatment as a solution to the problem. The social model of disability was, therefore, proposed to counter this view with one in which disability is described to be a “social and structural problem” (Oliver and Barnes 2012). According to this model, disability is not an intrinsic problem of the individual, but contingent to societal circumstances (such as lack of accommodation), which are the source of the problem. This is a political concern and approach to disability (Oliver and Barnes 2012). In this approach, the reason why people with disability have more problems in finding a job than ‘able-bodied’ people are environmental and social barriers rather than an un-ability to carry out the necessary tasks for the job (Oliver and Barnes 2012). With

this critical shift in perspective, disabled activists and scholars have raised awareness of discriminatory discourses and practices, and demanded changes in policies and in the way that societal organisations work.

The social model of disability has been successful in raising awareness of the negative understanding of disability, and improving the lives of people with disabilities under the social and institutional perspectives thanks to its impact on policies and regulations (such as the most recent WHO International Classification of Functioning, Disability and Health-ICF; WHO 2002, Oliver and Barnes 2012). However, it has been criticised because it assumes a fundamental distinction between impairment (understood as physical/mental/intellectual problem) and disability (seen as economic and social disadvantage; Oliver and Barnes 2012, Slatman 2014). Other scholars have highlighted the importance of the relational embodied, experiential and cultural dimensions of disability (e.g. Fougeyrollas and Beauregard 2001, Gustavsson 2004, Martiny 2015, Garland-Thomson 2011). In this study, these models and theorisations are referred to in order to critically and reflectively discuss the norms, values, and assumptions made about short stature and the use of hGH for ISS in the analysed documents of the the Food and Drug Administration and the European Medicines Agency.

Phenomenology of Embodiment

I see phenomenology of embodiment as a tool of analysis that can attend to deep-seated norms, values and assumptions that are often taken for granted. In particular, the work presented here examines such norms, values and assumptions related to short stature held by people interviewed in the Netherlands who are and/or identify themselves as shorter than average. Phenomenological philosophy focuses on subjectivity and lived experiences, from a first-person perspective. I adopt this theoretical framework to explore narrated lived experiences of the interviewees for two main reasons. *First*, (at least certain kinds of) phenomenological philosophy provide(s) a framework for examining the role of embodiment for subjectivity (understood as including self-awareness) and agency (in the sense what someone can do), and how the latter might be co-shaped in relationships with others, things and the world (e.g. Young 2014, Feder 2014, Zeiler 2013, Weiss 2015). *Second*, exploring the first-person perspective and the body (understood as fundamental to one's being-in-the-world) might contribute to the ethical debate (e.g. Weiss 1998, Malmqvist 2014, Slatman 2011). Svenaeus (2018) even coined the term 'phenomenological bioethics', and describes phenomenology as contributing to bioethics in the way that it brings a new perspective "by focusing upon embodied, social, cultural, and existential aspects of human life and medical-technology development" (Svenaeus 2018, p. x). In the work presented here, I consider the contribution of phenomenology to

be a tool, and use it to identify previously taken-for-granted norms and assumptions. Phenomenology also offers grounds on which to questioning these norms and assumptions. Phenomenological inquiry in this sense has been used, for example, in a study of parents' experiences of having a child with ambiguous sex and medical decisions on genital surgery (Zeiler and Wickström 2009).

I adopt the concept of phenomenology of embodiment as first described by Merleau-Ponty (1962) and subsequently enriched by further studies to explore the experiences of different bodies in different social encounters and situations (e.g. Young 2014, Weiss 2015, Zeiler 2010). In particular, I draw on Merleau-Ponty's (1962) understanding of the self or subjectivity as embodied and situated in a world and in relation to others. He describes our basic mode of being as pre-reflective and practical, and any independent agency as intrinsically dependent on the situation in which it is articulated. Merleau-Ponty (1962) understands the embodied self in an ambiguous experience of one's as subject and, at the same time, object. Embodiment is the subject's condition of the possibility of perception and action, and the body that one is and lives, that one experiences as one's own, is also what this person can experience as thing-like. The body as the locus of "being-in-the-world" (Merleau-Ponty 1962, p. xiii) is "ontologically open to a temporality of the body (in habit and perceptual learning), to space (in movement), to language (in expression) and to others (in intersubjectivity)" (Morris 2008, p. 118).

METHODOLOGICAL DISCUSSION

It was my ambition with the research presented here to contribute to the bioethical debate about the use of hGH treatment for children with ISS, engaging in a dialogue with different disciplines (such as medicine, sociology, and philosophy), and adopting empirical qualitative methods (interviews and document analysis), while keeping a philosophical perspective. I agree with the idea that “true philosophy consists in relearning to look at the world” (Merleau-Ponty 1962, p. xx). I adopt empirical qualitative methods not with the aim to derive an ‘ought’ from the ‘is’. Instead, my use of such methods contributes to ethical discussions with explorations of different norms, values and assumptions, and critical and reflective analyses. This is compatible with my understanding of critical paediatric bioethics (as explained in the theory section). I use different methods in the articles that are included in this thesis: philosophical and bioethical analysis of sociocultural discussions (Article 1), a combination of argumentative analysis and a method for policy analysis called ‘what’s the problem representation to be’ for regulatory discussions (Article 2), and phenomenological hermeneutical analysis of narrated lived experience (Article 3).

Philosophical and Bioethical Analysis

I first explored medical literature. I searched for articles that describe the treatment and the definition of ISS. I found it difficult to understand medical information, and the writing style and approaches used in the field. I was at times intimidated and at times discouraged, but I found it helpful to focus on articles in medical journals, written by medical doctors, that discussed the ethical issues of using hGH for children with ISS. I examined how these articles describe and conceptualise the ethical issues at stake, and what the focus and forms of problematisation are. I thought through the different ways in which they describe the expected benefits, potential side-effects of using hGH for children diagnosed with ISS, the different criteria of inclusion and exclusion within this indication, and what priorities doctors give to other considerations (such as economic considerations). I found it helpful to consult paediatric endocrinologists and ask for clarification. In particular, I had the opportunity to talk informally with one doctor in the Netherlands, one in the UK and, more recently, one in the US. I then explored the history of hGH treatment and the diagnosis of ISS, and discovered a critical study with a Sciences and Technology Studies (STS) approach that has been crucial at different stages of this research (Morrison 2008).

In Article 1, I examined my understanding of these medical and historical searches on hGH and ISS through the framework of medicalization, as a concept and phenomenon. While I engaged with different kinds of literature, I did so in the following steps: I searched for descriptions and conceptualizations of medicalisation in both sociological and bioethical literature, and related discussions in the philosophy of medicine. I then analysed different conceptualisations about the use of hGH for children with ISS gathered from different disciplines, and brought them together according to my understanding of medicalisation as both a concept and a phenomenon. I saw the idea of medicalisation as an opportunity to enhance my “sociological imagination” (Hedgecoe 2004, p. 143; Árnason 2015, p. 162) because it pushed me to explore societal implications, beyond the debate over the reasons for and against the treatment. This has also led me to be attentive to sociocultural norms and beliefs about short stature in general, and how these norms and beliefs shape regulatory discussions.

Document Collection and Analysis

In Article 2, I analyse selected FDA and EMA documents on marketing authorisation of hGH for the indication of ISS. I collected FDA and EMA documents using two different strategies, since the two bodies function differently and are governed by different regulations about information to the public. I started to collect documents in the spring of 2015, and I received all the documents requested from the EMA in the summer of 2016.

FDA Documents

It is possible to search the FDA website for documents on specific drugs. Searching for ‘somatropin’⁹ gives a list of 24 drugs. For each of them, it is possible to download pdf files about the approval and label history, which mainly provide scientific data on safety and efficacy. It is also possible to consult “Committees and Meetings Materials”. All New Drugs Applications (NDA) for which market authorisation is evaluated are discussed in such meetings. The decision about Humatrope® (somatropin [rDNA origin] for injection) produced by Eli Lilly and Company was approved for ISS by the Endocrinologic and Metabolic Drugs Advisory Committee on 10 June 2003. Documents accessible online are: Notice of Meeting, Draft Agenda, Draft Questions, Committee Roster, Consultants-Guests Roster, Briefing Information, the PowerPoint presentations made during the meeting (both by the pharmaceutical company and by the scientific advisory group), a brief video of a child’s testimony, index and transcript. The ‘briefing document’ folder contained the briefing

⁹ This is the international nonproprietary name, an official and generic name for a recombinant form of hGH.

document, an addendum to the FDA briefing document, table of contents, clinical review, statistical review and evaluation, and bibliography. Some documents (such as the draft agenda, draft questions, and committee roster) contain mainly brief information about the meeting and details about participants. Some others (such as the clinical review and the statistical review) contain information about efficacy and safety, and these documents use much medical jargon. The briefing document includes general information on the rationale of the treatment, the definition of ISS and understandings of short stature, in addition to considerations on efficacy and safety. These are the reasons why I focused on this last document in my analysis.

EMA Documents

Searching in the EMA website internal Google engine with the search term ‘somatropin’ and the exact phrase ‘idiopathic short stature’ gave 31 documents. Among them, I found the report of the plenary meeting in which extending the use of NutropinAq (somatropin) from Ipsed Ltd. for the indication of ISS had been refused. This document contained very little information about the reasons for the refusal of hGH for ISS, which led me to search for documents that described the procedure of the negative opinion. I found, among others, “Questions and answers on recommendation for the refusal of a change to the marketing authorization for NutropinAq”, 20 September 2007 (EMA 2007a), and “Procedure No. EMEA/H/C/000315/II/24, Withdrawal Assessment Report for NutropinAq”, 28 January 2008 (EMA 2008). These documents published online contain some general information about the EMA decision to refuse the use of hGH for ISS.

In a second step, I requested online the transcript of the plenary meeting in which the discussion on ISS took place, and I received one document with the extract from the minutes of a meeting of the CHMP in September 2007. This document had been redacted according to the EU regulation on the protection of personal data, and no information was available about the decision or the discussion about hGH for ISS. I therefore contacted by email the coordinator of access to the document and I asked for suggestions about how to find the documents in which reasons *pro* and *contra* the approval are reported in more depth. She replied that the actual assessment is not made during the plenary meetings, but when rapporteurs issue their reports and members states comment on them (according to the decentralised procedure on marketing authorisation, that involve a network of 4500 experts throughout the European Union). Thus, as she suggested, I requested the following documents:

- a copy of the rapporteur’s assessment report dated 14 September 2007
- minutes of the meeting of the SAG¹⁰ that took place in March 2007

¹⁰ SAG is acronym for Scientific Advisory Group.

- copies of the rapporteur's and co-rapporteur's assessment reports
- minutes from the SAG meeting in January 2008.

I also requested:

- the request for the extension of NutropinAq to idiopathic short stature children made by Ipsen in 2006
- the recommendation for the refusal of a change of the marketing authorization for NutropinAq.

Given the large number of documents, I was informed that I would receive them in several batches. While some of them contain clinical assessments of efficacy and safety provided by the industry, some contain assessment reports based on the industry data prior to the experts' meeting. I selected the minutes of the meeting in which the experts comment on the rapporteur's reports (SAG Diabetes-Endocrinology Meeting 23.03.07 – Minutes; EMA 2007b) and the document with the experts' negative opinion on marketing authorisation (NutropinAQ II-24 Opinion Negative Final 20.09.07; EMA 2007c).

Document Analysis

I combined argumentative analysis (Van Eemeren & Grootendorst 2004; Hansson and Hirsch Hadorn 2016) with an approach to policy analysis called 'what's the problem represented to be' or WPR (Bacchi 2009, Bacchi and Goldwin 2016) to examine the selected documents.

Argumentative analysis is a philosophical analytic tool that allows for a deep exploration of those utterances and expressions that aim at "achieving a certain goal. For instance, an oral or written expression is a standpoint if it expresses a certain positive or negative position with respect to a proposition, thereby making it plain what the speaker or writer stands for" (Van Eemeren & Grootendorst 2004, p. 3). In Article 2, I aim at "reconstructing a given argumentation as clearly as possible" (Hansson and Hirsch Hadorn 2016, pp. 4-5). However, I do not aim to uncover fallacies (understood as mistakes in the argument) in a strictly logical sense, but rather to explore the norms, values and assumptions of these arguments, and then discuss them critically. I use the WPR method for this, which aims "to dig deeper than usual into the meaning of policies and into the meaning-making that is part of policy formulation" (Bacchi 2009, p. vi). I do not focus on policies in the traditional sense, but on documents that report discussions on the clinical and safety assessments on hGH for marketing authorisation for the indication of ISS. However, WPR can be applied to texts that are not formally recognised as policy, but that belong "to the full range of articulations of 'what to do' by policy-making institutions" (Marshall 2012, p. 64; Bacchi 2009). The documents analysed explicitly recommend or refuse (what to do) concerning the use of hGH for children with ISS. WPR asks six questions and makes one recommendation:

Question 1: What's the problem (e.g., "gender inequality", "drug use/abuse", "economic development", "global warming", "childhood obesity", "irregular migration", etc.) represented to be in a specific policy or policies?

Question 2: What deep-seated presuppositions or assumptions underlie this representation of the "problem" (problem representation)?

Question 3: How has this representation of the "problem" come about?

Question 4: What is left unproblematic in this problem representation? Where are the silences? Can the "problem" be conceptualized differently?

Question 5: What effects (discursive, subjectification, lived) are produced by this representation of the "problem"?

Question 6: How and where has this representation of the "problem" been produced, disseminated and defended? How has it been and/or how can it be disrupted and replaced?

Step 7: Apply this list of questions to your own problem representations (Bacchi and Goldwin 2016, p. 20).

Bacchi and Goldwin (2016) acknowledge that these questions present some overlapping and repetition, and claim that they "serve a heuristic function and ought to be treated accordingly" (p. 19). I was inspired by these questions as a point of departure, and selectively focused on the aspects of the questions that were relevant for my aim. I followed the first three questions, defined as descriptive by Bacchi (2009), for the part of the analysis of the documents in which I attempted to unfold as clearly as possible the agencies' arguments, and the underlying assumptions and presuppositions. In the discussion part, I focused on specific aspects of the last three questions: (4) What is left unproblematic in this problem representation? Can the "problem" be conceptualized differently? (5) What effects are produced by this representation of the "problem"? (6) How can this representation of the "problem" be disrupted and replaced? During the analysis, I realised that many of the themes were recurring in the EMA and FDA documents that are objects of study in the critical disability literature. In the discussion, I therefore draw upon critical disability literature to explore the different ways in which short stature can be understood and how such understanding can justify hGH for children with ISS.

Conducting and Analysing Interviews

When I started this research, I wanted to explore how people who are and/or consider themselves to be shorter than average make sense of their embodied lived experience. However, I was a student on an international PhD programme, and found that feasibility in terms of time and location was a considerable challenge. The Phoenix Doctoral Programme has compulsory mobility – my main

university is LiU, Linköping, and I spent a period at the School of Advanced Studies in the Social Sciences (EHESS) Paris to satisfy the mobility requirement. I was required during this period to take a certain number of ECTS, from a selection of courses and exams. I therefore spent the first year and half exploring my theoretical background and methodological approaches. In the second year, students are required to take an internship. I decided to dedicate this to my fieldwork, and in the spring of 2016 I spent three months as visiting scholar at the Department of Health Ethics and Society (HES) at Maastricht University. I received additional supervision here from Prof. Jenny Slatman, who also combines philosophical with empirical methods in research. It seemed interesting to investigate the narrated lived experiences of people shorter than average in the country with the world's tallest population (Schönbeck et al. 2013).

Recruitment Strategies and Challenges

In a first step, I contacted two associations for short people: the Belangenvereniging Van Kleine Mensen (BVKM) 'Association of Little People' (<http://www.bvkm.nl/english>) and the Nederlandse Vereniging voor Groeihormoondeficiëntie en Groeihormoonbehandeling (NVGG) 'Dutch Society for Growth Hormone Deficiency and Growth Hormone Treatment' (<http://www.nvgg.nl/>), asking whether they would be willing to spread information about my project among their members. The BVKM website states that the association is open to all people below 155 cm (with or without medical conditions), while the aim of the NVGG is to provide information about hGH treatment to everyone who is interested. I sent these organizations a letter about the study, explaining that I would be conducting an interview study with people with 'idiopathic short stature'. The inclusion criteria for this interview study included: being older than 18 years; speaking English; having experienced severe short stature in childhood (even though the participant might be within the average range now); and not having any identifiable medical cause for their short stature (i.e. all relevant pathologies, such as growth hormone deficiency and chronic renal insufficiency were exclusion criteria).

I was eventually contacted by one member of the BVKM who asked for more information about the project, and explained that she was interested in participating. (I received no answer from the NVGG.) This person from BVKM did not fit the inclusion criteria, but we met over Skype to talk about the project, and about how to phrase my information letter to improve clarity. She explained that some members of the association are shorter than average without having any diagnosis. I rewrote the information letter and redefined the inclusion criteria, as in Annex A, based on the following considerations. The average height in the Netherlands is 184 cm for men and 171 cm for women, but there might be differences between regions (Schönbeck et al. 2013). According to the

growth charts provided by Schönbeck et al. (2013), -2 SDs (which is the requirement for the definition of ISS) corresponds to 170 cm for men and 158 cm for women. Schönbeck et al. (2013) suggest that in the Netherlands people are considered short if they are -3 SDs (about 162 cm for men and 152 cm for women), but they do not explain why this should be considered the threshold. The treatment has been approved by the FDA for children in the US who are predicted to achieve - 2.25 SDs (which corresponds to 166 cm for men and 155 cm for women). Finally, perceived height (and not only measured height) is relevant for people's self-perceptions and meaning making. I decided not to make any distinction according to ethnic origins.

Thus, I decided to keep the sample open to the participants' interpretation and opted for the formulation: people who are shorter than average, which is about 184 cm for men and 171 cm for women in the Netherlands. I stated the other recruitment criteria: being older than 18 years, having spent their childhood and adolescence in the Netherlands, feeling comfortable speaking English, not having identifiable medical causes for their short stature (and thus having any growth disorder such as growth hormone deficiency, or achondroplasia was an exclusion criterion). The information letter is given in Annex A.

I adopted three recruitment methods. First, I sent the information letter to both associations again via email; second, I distributed information fliers on paper and via social networks (mainly Facebook); third, I adopted snowball sampling (asking participants if they knew someone who meet the inclusion criteria).

Participants and Interviews

I was eventually contacted by one member of the association BVKM, six people who had seen my information flyers, and three people through snowball sampling. I conducted ten semi-structured interviews of average duration one hour with six women, ranging from 150 cm to 159 cm, and between 18 and 50 years old; and four men ranging from 166 cm to 169 cm, and between 25 and 52 years old. Four participants preferred to do the interview via Skype rather than in person. I conducted the other six in person, five in Maastricht and one in Eindhoven. Participants chose the location of the interview, which was at bars or café in five cases, and the participant's office in one case. There are potential downsides in conducting some face-to-face and some online interviews, but I preferred to let participants choose their arrangement.

Once I met the participants, I spent the first 10-15 minutes introducing myself, explaining my ideas about the interview and asking participants if they had any questions. I also gave them a printed copy of the informed consent form (Annex B), which they read and we then discussed. I tried to make sure that they felt free to ask any questions about it. When satisfied, and after they

stated that they still wanted to be part of this research interview, the participants signed the informed consent form. I kept one signed copy and gave one to them (or sent it via email during the Skype conversations). During the interviews, I followed four key topics of discussion: participants' self-perception, their view on the social significance of height, the relevance of height for them, and their opinion about hGH treatment (Annex C). These themes were used as a supporting checklist during the interviews. However, each interview was structured in an attempt to follow the narrative of the participant being interviewed. In order to make the discussion about hGH treatment easier for participants, I based this discussion on a brief written explanation paper (Annex D). I limited this study to 10 interviews given that saturation was achieved (i.e. the content of the interviews started to be repetitive). All interviews were audio recorded.

Interview Analysis

I transcribed all the interviews verbatim, and included grammatical errors and hesitations (when participants used sounds such as 'hmm'). I also noted emotional expressions such as laughter, and my prompts and small remarks (such as 'Why?', 'Could you explain this further?') in order to keep in mind, during the analysis, variations in tone (e.g. ironic, serious) and the flow of the conversation. After the transcription, I interpreted, together with the co-authors, the data using the phenomenological hermeneutical method (see, for example, Lindseth and Norberg 2004). Inspired by Lindseth and Norberg (2004), I consider the analysis of the interviews to be an interpretative work that engages with an exploration of taken-for-granted assumptions and presuppositions in the narrated lived experience, while being aware of my own taken-for-granted assumptions and presuppositions. All authors read the transcriptions several times and we discussed them. We then attributed open, descriptive codes to excerpts of the interviews that were related to participants' experiences and reflections on height. Examples of these codes include: figurative height, being used to it, other's behaviour, comparison with tall/short people, look up/down, gender discourse. While dialectically reflecting on the themes, the co-authors and I defined our ambition for this article to be to explore how participants make sense of height. While height is normally talked of in terms of centimetres and quantifiable terms, the phenomenology of embodiment allowed us to explore qualitative, more reflective, theoretical and embodied accounts of the *experience* of height.

We refer to the concept of sociophenomenology (Slatman 2014) to emphasise that we take an empirical approach within phenomenological studies. The concept of sociophenomenology stresses the fact that not only the embodied self is considered both as object and subject, but that also the social embedding is taken into account (Slatman 2014). The focus is on the contextualised lived experience, on what people do, and the context of the doing (Slatman 2014). The analysis of the

interviews identifies three themes, and shows that height as a lived phenomenon 1) is active engagement in space, (2) co-shapes habituated ways of behaving, and (3) is shaped by gendered norms and beliefs about height. The analysis of the interviews is eventually used as an alternative critical perspective of the short-stature-specific quality of life questionnaires (QoLISSY), that exemplifies the problem oriented approach to discussions to hGH treatment for children with ISS.

RESEARCH ETHICS

In this section, I discuss some ethical considerations and describe some reflective thinking that guided me in different steps of this research.

Reflectivity

During this study, I was challenged both by frequent changes of environment and theoretical and methodological approaches to research, and by my ambition to combine philosophical thinking with empirical methodology. At LiU, I first worked in the Centre for Applied Ethics and then more closely with a seminar series, P6: Body, Knowledge, Subjectivity, held by the Department of Thematic Studies. At the Centre for Applied Ethics, bioethics is the main field of inquiry and the approach used is rather theoretical, while the approach taken during P6 is open to the encounter of different disciplines to the study of a specific object of study. I was in both cases able to bring my philosophical background into the discussions, but I found it somewhat challenging to shape my writing style and way of thinking such that they fit the expectations and standards of both sides, while shaping and keeping my own emerging identity as a researcher. I encountered a bigger challenge at the School of Advanced Studies for the Social Sciences (EHESS) Paris. There, the approach is mainly sociological, and I was asked several times during my first stay to explain the rationale of my research and why I wanted to use empirical methods. I then started to be reflective about my role as a researcher who is between disciplines, and tried to take advantage of my stay in different departments, consulting the literature suggested and asking for feedback from colleagues. This encouraged me to become aware of different possible ways in which research can be conducted, and to find my own way.

Changing language from one setting to another, and from one document to another, was also rather challenging at first. In France, seminars and bureaucracy were conducted mainly in French, and I forced myself to use French when writing and reading in order to adapt better to the environment, while improving my language knowledge and skills. The struggle encountered by the necessity to translate between two languages, neither of which is my mother tongue, led me to realise that at times I was not able to grasp some meanings, or translate them in my work in the same way as I would have been able to if I remained using English. So, each time I had to ask myself whether it was more appropriate to consult the English version (where available). I realised that I had to compromise between my passion for languages and the demands of time, and make the choice that would allow me to meet the next deadline. This also kept me focussed on English, and has required that I continually strive to improve my writing and communication skills. This brought

me to realise that sometimes clarity concerns not only language, but also a deeper and taken-for-granted understanding of research, relationships with others, and the analysed text that is, in my opinion, co-shaped by the sociocultural background in which one is born and raised, and by encounters with other sociocultural backgrounds.

Research Ethics, Copyright, and Document Analysis

During document collection and analysis, I asked myself how I should and could use the information collected. The FDA documents were public, and the FDA website states that the content of the website may be “republished, reprinted and otherwise used freely by anyone without the need to obtain permission from FDA” (FDA 2018). As regards the EMA, I made two requests for documents through the online request form, explaining that I was conducting research on hGH for ISS. I received the documents that I had requested. However, since some of the documents from the pharmaceuticals industry were previously unpublished, I decided not to use information from these documents (for copyright reasons) and focused on the documents that either had been published online or were unpublished but produced by the EMA. The documents I use are also those that provide more information on the discussions for and against the marketing authorisation of hGH treatment for ISS.

Throughout the analysis, I questioned my own viewpoints, assumptions and presuppositions and asked the WPR questions several times. I discussed drafts of Article 2 with international colleagues. This has helped me to develop an increasingly critical approach. As a way of example, I found myself ‘positioned’ very closely to the EMA argument in the early stages of my work, which made me extra vigilant as regards the importance of critically examining and thinking through various assumptions made, also my own. I found it very important also to discuss drafts of the article with colleagues both from the US and the EU. I noticed that those in the EU had opinions similar to those of the EMA, while those in the US had ways of reasoning similar to those of the FDA. I then tried to challenge my own attitudes, with this in mind.

Research Ethics and Interviews

Since I was conducting a research within a European Doctoral Programme that involved three countries (Portugal, France and Sweden), and was going to conduct my interviews in a fourth country (the Netherlands), each of which has different procedures for formal ethics assessment, I consulted the consortium of the Doctoral Programme to establish how I should deal with this. I also consulted the scientific secretary of the regional research ethics board in Östergötland (Sweden) in 2016, who explained that this research did not need approval from the regional ethics board in Sweden. The scientific secretary explained that I should instead follow the Dutch procedure for

research ethics applications, since the interviews would be performed in the Netherlands. I submitted and discussed my research with the Research Ethics Assembly (REA) at Maastricht University. The REA is an opportunity granted by the Department of Health Ethics and Society to discuss the ethical issues encountered by researchers both in the planning phase and when work has been completed. The aim of the assembly is to help to analyse and clarify any ethical issues presented by the fieldwork. Ethical clearance was obtained on 25 May 2016 (reference number: 201601).

Ethical considerations were taken into account at each step of the research. Each participant was asked to read and sign an informed consent form (ICF, Annex B). Before starting the recording, I discussed the ICF with them, asked them if they had any questions, and made sure they understood that their participation was voluntary and they were free to avoid any sensitive subject, if they wished so, or to withdraw at any time, without stating a reason. They were informed that there was no direct benefit to them, but that their contribution may contribute to a better understanding of people who are shorter than average and to the bioethical debate about using hGH treatment for short stature. At the end of the interviews, most of the participants told me that they appreciated the topic of this research because it is a topic that, they said, is not often discussed. They considered it important to promote wider debate of the topic. Transcribed interviews were anonymized by giving a pseudonym to each participant. The ICF with the real names of participants and the recordings were kept confidential, and locked in a safe at Linköping University. Participants were asked whether they wanted to read the interview, once transcribed. Only two interviewees wished to do so, and did not ask to make any changes to the transcripts.

Interviewing people who are shorter than average poses two difficult questions: not only how to define short stature, but also how to talk to participants about one of their bodily characteristics without causing them to feel judged or uncomfortable. I made a continuous effort to be reflective, in order to communicate with participants at different stages of our interactions without arousing these feelings. I tried to use terminology that was not judgmental, and to be reflective throughout the complete process, from recruitment to interview. I felt that it was important to repeat on several occasions, both before and during the interviews, that there was no intention of judging them, there were no 'right' or 'wrong' answers to my questions, and the only aim of our conversation was to find out more about their experiences and daily life.

Each participant was first given the leaflet with information about the general scope of the research (Annex A). This also gave preliminary information about the interview (such as possible themes of conversation, approximate duration, and the fact that they might express their interest in participating and then change their mind without needing to justify this decision). After they read

this general information, they were invited to ask questions and get in touch with me by email, phone or Skype. I am myself shorter than average (157 cm), as defined by the Dutch statistical mean, and I gained the impression that this was something the participants would be curious about. I decided to mention my height in interviews conducted via Skype. Some participants were taller than me, some almost the same height and a few were shorter. Having a similar height seemed to create empathy between us, and I noticed that participants felt more comfortable talking about height after they knew my height or had commented on it.

I gave the participants who agreed to do interviews in person the option to meet in a place of their choosing. I also told them that I could go to their place, if it was more convenient for them, but most of them preferred to meet in bars or cafés. One participant decided to hold the interview in his office. Participants who decided to do the interview via Skype were living in other cities than Maastricht, and they said that their busy schedule made it more comfortable for them to talk from their place. I thought it was important that their participation should not bring them any burden or inconvenience in time or travel.

During the analysis, I also constantly reflected on their narratives about their experience of being short, and found similarities with my own narrative, where I have myself experienced being shorter than average several times. This came to my attention especially after I started to travel and live in different European countries, as I experienced my height differently in different countries, not only because of the difference in average height but also in the ways people would or would not explicitly talk about it. Moreover, the fact that I was diagnosed with GHD as a child, and I was predicted to be 17 cm shorter than the height I eventually reached, made me curious about the meaning of height. I do not have a strong opinion or preference about my or other people's height, but I have always wondered what is interesting about it, and why people make remarks.

SUMMARY OF ARTICLES

This chapter provides a summary of each article, whereas their contribution to the overarching aim of this study will be discussed in the next chapter. The focus of the first article is on philosophical and sociocultural discussions about the use of hGH treatment for children with ISS, and it considers the sociocultural phenomenon of the medicalisation of short stature; the second focuses on the arguments provided in selected FDA and EMA documents when considering the marketing authorisation of hGH for the indication of ISS; and the third article focuses on narrated lived experiences of people who are shorter than average and on a short-stature-specific quality-of-life measurement questionnaire. The articles are not presented in chronological order, to better reflect their specific contributions to the overall aims of this research.

Article I

Murano, M.C. 2018. Medicalising short children with growth hormone? Ethical considerations of the underlying sociocultural aspects. *Medicine Health Care and Philosophy* 21(2), 243-253.

This article aims to broaden the ethical debate over arguments for and against hGH treatment for children with ISS. In particular, it includes considerations of the sociocultural phenomenon of the medicalisation of short stature, based on a critical understanding of the concept of medicalisation. To do so, it suspends any *a priori* ethical judgment of the treatment and of the sociocultural process in which it takes place (and that contributes to determining). Medicalisation is here understood as a conceptual tool of analysis that, through examination of the medical/non-medical distinction and the goals of medicine, explores the ethical dilemmas posed by the sociocultural phenomenon of the medicalisation of short stature.

The article questions the ethical relevance of the medical/non-medical distinction and argues that what is important from an ethical viewpoint is not merely the infringement of a prohibited territory, but the kind of treatment involved, and the ways in which the medical treatment is involved. It argues that not all medical interventions are equally ethically troubling. For example, the use of X-rays of the hand and wrists to monitor a child's development does not seem to be ethically problematic in the same way as the use of hGH treatment. Moreover, if the diagnosis of ISS is understood to be a statistical definition that does not provide any information about qualitative aspects of the child's life (such as cultural, experiential and social dimensions), it should not be seen as a sufficient criterion for the evaluation of the treatment.

The article then discusses the view that the debate on the goals of medicine should focus on ‘curing’ and ‘healing’. In the case of hGH for ISS, sociocultural aspects, such as beliefs and assumptions about short stature, might play a crucial role in shaping decisions about the treatment. The article suggests that the debate on the goals of medicine should be seen as a point of departure for considerations of both the sociocultural aspects that influence the medical decisions to intervene on short stature, and the ways and means of involvement of minors in such decisions. Discussions about the justification for the treatment, thus, should reflect on the sociocultural beliefs on which such justification is based, and on which values it fosters. The decision should ultimately be based on considerations of the condition of the child and her or his wishes, leaving aside speculations of unknown variables or assumptions based on others’ experiences. Considering the latter risks fostering societal prejudices (if any exist), rather than giving children the tools they need to accept their own body.

To conclude, the ethical implications of the sociocultural medicalisation of short stature should consider the different levels of normativity: at the regulatory level, for instance, the FDA approval to treat children with ISS with hGH does not imply ethical normativity. In the same way, possible misconduct of stakeholders should not be seen as an ethical argument against the treatment. These considerations should, instead, be the object of scrutiny, together with a recognition of the fact that the diagnosis of ISS, being merely quantitative, does not imply that each person with ISS should be treated. Ethical discussions about the justification for the treatment should evaluate carefully assumptions and beliefs about short stature and, for instance, unrealistic parental expectations. Possible misconduct of stakeholders (and economic and political interests) should be considered at each level, but should not be accepted as reasons to consider treatment with hGH to be ethically wrong.

Article II

Murano M.C. A disability bioethics reading of the FDA and EMA assessments on marketing authorisation of growth hormone for idiopathic short stature [submitted to *Health Care Analysis*].

The US Food and Drug Administration and the European Medicines Agency came to different decisions concerning the marketing authorization of hGH treatment for the indication of ISS – the former approving it in 2003 and the latter refusing it in 2007. The second article considers these decisions and has two aims. First, it identifies and examines the FDA and EMA arguments for and against granting marketing authorisation of hGH for the indication of ISS. In this analysis, it focuses on explicit and implicit assumptions and presuppositions on the understanding of short

stature and the use of hGH treatment for the indication of ISS, and it combines argumentative analysis with an approach to policy analysis called ‘what’s the problem represented to be’. Second, it discusses how these arguments can be read through the medical model of disability, and the relational, experiential, and cultural understandings of disability, and how this reading helps shed further light on assumptions made in these documents.

The article argues that the FDA’s documents put forward an argument of equity. The FDA argues that hGH is a treatment to increase children’s height and, given that it has been approved for other non-GHD conditions, it would be unfair to deny it for the indication of ISS. This form of problematisation is based on two main assumptions: short stature is potentially a disadvantage for children with ISS in the same way as it is for other non-GHD conditions, and approving hGH treatment to increase height is a way to provide fair opportunities.

The EMA, on the other hand, refuses marketing authorisation of hGH for the indication of ISS based on an argument of imbalance between risks and benefits. The EMA argues that hGH should provide an increase in quality of life or psychosocial benefit beyond height increase. This form of problematisation is based on two assumptions: that children with ISS are short but otherwise healthy, and that hGH treatment is a cosmetic intervention for which the evidence of benefit is insufficient to justify its use.

In both cases, the final decision was taken with internal disagreements: some FDA members did not believe that hGH would provide clinically meaningful results for those with the indication of ISS, and some EMA experts thought that there was no imbalance between risks and benefits. While the FDA took its decision during a plenary meeting in which representatives from the pharmaceuticals industry took part, the EMA took its decision in a series of meetings and discussions among experts across Europe. More recent guidelines published by the Pediatric Endocrine Society in the US have proposed that the need for treatment be determined by assessing the degree of psychological or physical disability of the individual child due to short stature.

The article argues that both arguments can be read through the medical (or individual) model of disability. The medical (or individual) model of disability considers disability to be a medical problem intrinsic to the individual (e.g. as an impairment or limitation), and this understanding is strictly related to medical intervention: if the individual has a medical problem, the solution is medical intervention. The arguments of the agencies can be read through the medical (or individual) model of disability in different ways. The FDA argument can be read as being based on an assumption that short stature is a personal impairment and underlying reason for psychosocial disadvantage. Therefore, hGH treatment is ethically justifiable as it grants fair opportunities. The EMA argument, in contrast, since it distinguishes between pathological short stature (e.g. other non-

GHD indications) and healthy short stature (i.e. ISS), and it assumes that children with ISS might benefit from hGH under special circumstances, it might be read as considering short stature to be an individual problem for which hGH treatment is justified only under circumstances in which the individual short child might benefit from it. When short stature is considered based on the medical model, arguments presented by both agencies imply that there is a type of short stature that might benefit from hGH treatment.

In contrast to this approach, the article suggests reading the agencies arguments through the relational, experiential, and cultural understandings of disability. These understandings propose a complex, dynamic and multidimensional understanding of disability. While the relational model focuses on the human developmental process that is common to every human being, the experiential understanding of disability highlights any differences that there might be between different kinds of disability and different ways of experiencing them, and to understand medical interventions. The cultural understanding, finally, sees disability as an essential characteristic of being human. The relational, experiential, and cultural approaches to disability all undermine the causal link between disability and the understanding of it as a problem. Similarly, they help problematise the idea that a form of short stature exists that benefits from hGH treatment, and they embrace the uncertainty about the effects of the treatment for the individual child. The FDA and EMA arguments, when read through the inputs of the relational, experiential, and cultural understandings of disability, can be understood as an invitation to be open to exploring the experiences of children with short stature within the complex, dynamic and multidimensional experience of human growth.

Article III

Murano M.C., J. Slatman, K. Zeiler. 2018. How sociophenomenology of the body problematises the 'problem-oriented approach' to growth hormone treatment. *BMJ Medical Humanities* Online First: 26 November 2018 DOI:10.1136/medhum-2018-011548.

The third article focuses on narrated lived experiences of embodiment of people who are shorter than average in the Netherlands. It aims to show how and why attendance to lived experiences of height is needed in bioethical and biomedical discussions of hGH treatment for children with ISS.

It first describes what it calls the 'problem-oriented approach' to the debate on hGH for children with ISS. This approach is based on the idea that short stature might be a psychosocial problem, and it argues that hGH treatment aims to prevent possible psychosocial problems due to short stature (and/or possible negative stereotypes about short stature). According to this approach, hGH treatment might prevent the risk of future disadvantage or increase the quality of life of children

with ISS. This approach focuses on quantifiable height and depicts height measurement as the cause and the solution of the problems of children with ISS.

In a second step, the article offers a sociophenomenological analysis of the lived experiences of short stature. It draws on theoretical phenomenological discussions of lived and objective space, intercorporeality and norms about bodies, and identifies three themes that address the ways in which the participants in the study make sense of height as a lived phenomenon.

First, they narrate height as active engagement in space, in and through relationships with others. Participants assign meaning to height when they do things, when they engage with others and move in space. They describe height as they inhabit it. This involves both a pre-reflective level (i.e. one in which they do not attend reflectively to their own body) and a level in which they attend to their height in and through relationships with others. To explain this idea further, the article coins the term ‘heighting’ to be understood as a verb, drawing from Heidegger’s idea of the ‘bodying-forth’ (Leiben) of the body. This idea was inspired by Aho (2005), who draws a parallel between Merleau-Ponty’s and Heidegger’s understandings of space as dynamic and active, as everyday involvement between the bodying-forth of the body and others and things in the world. In their narratives, participants make sense of their height as always immersed in a sociocultural surrounding, through action and interaction.

Second, participants narrate how lived height acquires meaning in corporeal exchanges. Participants narrate how bodily interactions with others (for instance, ‘looking up’) and things (i.e. tall refrigerators) carry special meanings in terms of shaping how they behave. These meanings are co-shaped by what they want to do, how others/things are positioned in relation to them, and how they experience the situation. This theme combines materiality, sociality, affect and temporal dimension in co-shaping the habituated ‘I can’. Height is narrated in relation to specific things and situations, which at times inhibit and at times enable the participants, and co-shape what they could be and do. This co-shaping is not deterministic, but takes place in a sociocultural context and with the participants’ perceptions of the world, others, themselves, and their specific situations.

Third, participants narrate gendered norms and beliefs in relation to height. On several occasions, participants associate tallness with masculinity and shortness with femininity. In the interviews, the idea recurs that men prefer their female partner to be the same height or shorter than themselves, while women do not find short men attractive. Participants also narrate how they negotiate these norms, and how this negotiation takes different shapes in different contexts. Moreover, this theme shows that sometimes these norms are taken for granted, without being reflected upon (or negotiated). Drawing on recent phenomenological literature, the article shows that this theme highlights how norms can sometimes be incorporated. The idea of incorporation is

inspired by the description of Merleau-Ponty of how objects can be incorporated into one's lived body, through habituation and repeated motor activity. This idea has been used to describe how sometimes norms are taken for granted through repetition of behaviour and practices, and come to be incorporated within the pre-reflective lived bodily existence. This idea helps to explain the ways in which participants narrate gendered norms as "that from which" they make sense of the world (Zeiler and Malmqvist 2010, p. 144).

In conclusion, the article argues that the analysis shows the importance of focusing on the different meanings of the lived experiences when considering short stature, rather than focusing on possible disadvantages, as the 'problem-oriented approach' does. It shows why this is important, and gives the example of the short-stature-specific quality-of-life measurement (QoLISSY) questionnaire. The QoLISSY questionnaire, this article argues, exemplifies the 'problem-oriented approach' because it focuses on the potential problems of short stature and on quantitative measurements on height. In this way, it frames its questions in a way that is not open to explore the richness of meanings that people might give to their height. This approach risks imposing partial sensitivity to the issues at stake and overestimating the role of hGH for children with ISS. The article argues that the rationale for treating children with ISS should, therefore, be the actual lived experience of the child, rather than the prevention of possible risk. Thus, the lived experience of children should be investigated with narrative approaches, in addition to psychological assessments and medical tests.

FINAL DISCUSSION

The first aim of this research was to identify and analyse the norms, values and assumptions about short stature and the use of hGH treatment for children with ISS, found within sociocultural, philosophical and regulatory discussions of these, and within narrated lived experiences of short stature. To this end, the first article identifies the norms, values, and assumptions focusing on sociocultural and philosophical discussions. It examines how these norms, values and assumptions feed into different understandings of short stature and problematisations of the use of hGH treatment for children with ISS by comparing how they are used in different disciplines (sociology, philosophy, bioethics and medical literature).

The first article argues that the medical and non-medical conditions, as well as the debate on the goals of medicine, are described as important in both philosophical and bioethical discussions about medicalisation and in discussions about the use of hGH treatment for children with ISS. The article highlights that – while these debates are central parts of the theoretical discussions – values in the discussions of the practice of hGH treatment are mainly related to parental wishes and expectations, such as aesthetic preferences, the wish to prevent future distress, and the wish to reduce the child's current and/or future limitations in daily life. The article argues that these values are based on assumptions and presuppositions about the relevance of short stature for children with ISS and the potential benefits of hGH treatment. The article highlights two assumptions in particular: the idea that increasing height brings psychological and social advantages to children with ISS, and the idea that short men are disadvantaged in marriage and partner choice. This article does not analyse these assumptions, but points out that careful examinations of uncritically assumed social beliefs and unrealistic parental expectations are needed.

The relevance of assumptions and presuppositions in sociocultural discussions has directed the focus onto assumptions and taken-for-granted knowledge in the other two articles, together with the problematisations of norms. The first article identifies and analyses three kinds of understanding of norms within sociocultural and philosophical discussions on hGH treatment for children with ISS and short stature. First, 'norm' may be understood to be statistical norm, which is at the base of the indication of ISS as statistical deviation from the average height. This norm is based on quantitative measurement and compares an individual's height to the average height of a population. The second understanding proposed by the article contrasts this norm with one that is more attentive to qualitative aspects, drawing upon Canguilhem's (1966) understanding of health. Canguilhem (1966) puts forward an understanding of health as the ability of the whole organism to adapt to its environment. In his view, being healthy means being normative (Canguilhem 1966) and he highlights that it is important to consider the environment and personal experience of the individual.

In this view, while ISS is seen as a deviation from the average, this definition of ISS does not provide any information about the environment and the personal experience of an individual child diagnosed with the condition. Third, this article argues that there are different levels of normativity of medicalisation, inspired by Mordacci's idea (1995) that health is a matter of experience and its definition a matter of interpretation. The interpretations of the various forms and dimensions of the experience of health correspond to different normative levels (such as biological, social, political, moral). This focus on meaning and interpretation has helped me see the relevance of a hermeneutic endeavour in discussions on hGH for children with ISS. The first article brings the example of the regulatory, the pharmaceutical and the individual levels, and the nuances and complexity that it shows paved the way for the focuses of Articles 2 and 3 on the regulatory and the narrated lived experiences.

Although the second article primarily aims at identifying and analysing assumptions and presuppositions in the selected FDA and EMA documents that contain arguments on whether to grant marketing authorisation for hGH for the indication of ISS, it also reveals how norms and values feed into such assumptions. First, it shows two alternative understandings of norms from those presented in Article 1: in the argument presented by the FDA, norms appear as sociocultural ideas and beliefs about the disadvantages of short stature, whereas in the argument presented by the EMA norms are present as the distinction between abnormally short but healthy short stature (ISS) and pathological short stature (other non-GHD conditions). The distinction between normal and abnormal short stature, for the EMA, seems to be the aetiology of the condition (whether the child has, for example, Turner syndrome), rather than the individual's height *per se*. These different understandings of norms shape the arguments presented by the agencies *pro* and *contra* marketing authorisation, because they are used to characterise the category of ISS and the role of hGH treatment for this indication. For the FDA, which follows the sociocultural norms, hGH might help to prevent disadvantage or discrimination based on height, while for the EMA, which defines ISS as healthy short stature, hGH is unnecessary cosmetic intervention.

Furthermore, article 2 shows that the FDA granted marketing authorisation based on the values of equity and fairness, while the EMA based its decision on the value of evidence-based decision making. The values of fairness and evidence-based decisions did not appear in article 1, and they make alternative interpretations and understandings of the use of hGH treatment for children with ISS possible. I see this as one example of how important it is to be aware of different levels of normativity, as it shows that the regulatory level draws on distinct values and norms, and spelling out these values and norms can be seen as a contribution to more theoretico-philosophical evaluations – if we want these to engage with and have an impact on regulations (and in

subsequently practice). This is also why it seemed important to me to explore the first-hand lived experience of short stature, and of short stature as the target of medical intervention with hGH.

Article 3 analyses narrated lived experiences of height, and identifies gendered norms in the meaning making of participants. It shows that participants' narratives consolidate the dualism of two opposite gender identities and the preference of men to be taller than women. The article analyses these norms through the idea of incorporation. Drawing on phenomenological literature, it suggests that these sociocultural norms are sometimes taken-for-granted and lived, rather than reflected upon. Furthermore, the narratives show that participants make sense of their height not merely through these norms, but in active engagement in space and in relation to others and things. The analysis of the interviews shows a richness of meanings within embodied lived experiences of height that cannot be reduced to objective height. This analysis therefore allows us to identify what the article defines as the 'problem-oriented approach' to discussions about hGH treatment for children with ISS. This approach focuses on possible psychosocial disadvantages or problems of short stature and quantifiable height in the ethical evaluation of hGH treatment for children ISS, at the expense of more nuanced understandings of height and its possible relevance for the child.

The second aim of this research was to discuss how the analysis in the first aim contributes to bioethical debates on the use of hGH treatment for children with ISS. The three articles contribute differently to this aim, following my understanding of critical paediatric bioethics, which, as stated in the theory section, deems it to be important to carefully analyse different reasonings, conceptualisations and arguments around the object of study, to make a self-reflective analysis that is also sceptical about others forms of problematisations, and to carry out philosophical analysis, while being open to social implications and drawing upon empirical methods.

The first article does not suggest what ought to be *done*, but it shows some norms, values, and assumptions that should be *considered* in bioethical discussions, and it considers both the philosophical and sociocultural levels. The combination of philosophical discussions with aspects of the practice of hGH treatment and the sociocultural aspects of the phenomenon of the medicalisation of short stature brings into the debate the complexity of the ethical issues and allows more nuanced considerations. Rather than limiting the discussion to considerations for and against of hGH treatment, the article highlights the complexity of the medical definition of ISS, the involvement of various medical (and non-medical) tools of diagnosis, and the range of reasoning underlying the discussion about the use of hGH. It also shows that labelling the use of hGH treatment for ISS as medicalisation requires careful evaluation, as it hints at several ethical questions and dilemmas at different levels of analysis. While the pharmaceutical level might be troubling because of the economic interests of the industry, the marketing authorisation granted by a

regulatory agency requires different kinds of consideration, as well as what ought to be done in the case of the individual child. This complexity allows a more fully fledged theoretical discussion that considers both philosophical dilemmas and practical issues. Given that the object of this study are the norms, values and assumptions found within discussions about a medical treatment that involves several actors and interactions, the first article contributes to bioethical discussions through a critical analysis that bridges the gap between philosophico-theoretical discussions and sociocultural discussions, and information on the practice of hGH treatment.

The second and third articles combine philosophical analyses with empirical methods. The aim is not to derive the “ought” from the “is”, but rather to dig deep into forms of problematisation, viewpoints and understandings, in order to challenge taken-for-granted assumptions and explore possible alternative understandings. My analyses of the documents and the interviews engage critically and reflectively with meaning makings and forms of problematisation, and do not aim to describe phenomena. The articles take a hermeneutical rather than descriptive approach. Both show that different ways of seeing short stature and problematising the use of hGH treatment for children with ISS (the second article through different models of disability, and the third article by comparing the problem-oriented approach with the analysis of the interviews) shape the ways in which hGH treatment is justified for children with ISS.

The second article argues that the assumptions, values and norms analysed in the FDA and EMA documents shape their arguments to justify or withhold hGH treatment for children with ISS. Moreover, it discusses how different interpretations of these arguments are possible. Reading these arguments through the medical (or individual) approach implies that short stature is understood as an impairment, or a potential problem for the individual (under certain circumstances). In contrast, reading these articles inspired by a relational, experiential, and cultural understanding sees height as part of the complex, dynamic and multidimensional experience of human growth. While this interpretation does not, again, give a clear yes/no answer, it allows the dimension of uncertainty that the decision of whether to use hGH treatment for children with ISS entails to be included in the bioethical discussion. This dimension of uncertainty helps highlighting the fact that the evaluation on hGH treatment is not merely an evaluation of, for example, risks/benefits assessment, but an ethical evaluation in the sense that it requires considerations of the values that the choice for or against treatment may express and/or foster.

The third article shows, through an analysis of the narrated lived experiences of height, the richness of meanings and understandings that participants give to height, how height helps to shape participants’ bodily agency, and how bodily agency is shaped in relation with other people and objects. The article then compares the complex understanding of short stature brought out in this

analysis with the problem-oriented approach, using the example of the QoLISSY questionnaire. It argues that the problem-oriented approach risks limiting the understanding of the lived experiences of short stature, and overestimating the role that hGH treatment may play in the lives of children with ISS, because of the one-sided focus on potential problems. Against this background, the article not only suggests a shift in perspective (from problem-oriented to lived experience); it also suggests how this shift in perspective may have implications for hGH treatment in clinical settings. It may, for example, introduce narrative approaches that complement medical and psychological diagnostic tests.

RELEVANCE AND FUTURE RESEARCH

The three articles, in accordance with my understanding of critical paediatric bioethics applied to examine the use of hGH for children with ISS, have engaged in critical and reflective analyses in an attempt to make sense of different viewpoints, lines of reasoning, and understandings of short stature and the use of hGH treatment for children with ISS. It has been my ambition to engage, analytically and critically, with a broad set of discussions (as seen in the stated aims of the research), and by so doing contribute to ethical considerations of and within the practice of hGH treatment for children with ISS.

The choice to combine philosophical and empirical methods was based on the idea that bioethics is an “embedded socio-cultural practice” (Ives and Dunn 2010, p. 256) and that morality (i.e. the way people think what they ought to do) and ethics (i.e. normative theories) inform and *should* inform one another (van der Scheer and Widdershoven 2004). This approach is inspired by Aristotle’s idea that practical wisdom (in ancient Greek *phronèsis*), or “the insight or understanding born from and guiding experience and the capacity of, respectively, acting, judging and living accordingly”, is a requirement for ethics (van der Scheer and Widdershoven 2004, p. 77). This research values qualitative research as a way to ensure that nuances in meanings and interpretation are considered, for instance to understand the role of embodiment, and what one’s specific body (of a particular height, in this case) can mean for the self. Arguably, reaching an understanding of what being shorter than average can *mean* for people is relevant for ethical discussions of whether to offer a certain treatment for it (see, for example, Svenaeus 2018).

This research has sought to engage in a dialogue with ethical analyses and practical experiences, not with the aim to provide guidelines or rules for conduct, but to offer some critical tools to increase sensitivity to the ethical issues at stake. The research suggests that it is important to decide not only whether to go for the treatment or not, but also to reflect on how to do or not to do so, by paying attention to various forms of problematisations, norms, and values involved. It then shows that some forms of problematisation may invite a certain course of action (and/or justification for hGH or not), and that these forms of problematisation should be challenged and thought through. Finally, the research shows the richness and complexity of the lived experience of short stature and suggests that medical and psychological tests should be complemented by narrative approaches when evaluating children’s need for treatment.

One main theme recurs in this research: the idea that children should be at the centre of decisions about hGH treatment. If the ultimate aim of intervention is to improve their situation, no effort should be spared in engaging in a conversation with children in order to look at them for what they are, and not for what they are projected to be by others. The different understandings of short

stature and problematisations of the use of hGH treatment for children with ISS that I have analysed in the articles show that external discussions and viewpoints often do not grasp the complexity, multidimensionality and dynamism of their experiences, as people in becoming. If the adults around them are informed by the perspectives of the children, this would not only be a first step towards understanding whether the treatment will improve their situation, but also a way to open the ethical assessment to children's possible alternative understandings of short stature, and ways of problematising the use of hGH treatment.

The analyses conducted during this research and the findings that arose from them are relevant to ongoing bioethical discussions of other paediatric medical interventions that aim to normalise the physical characteristics of children's bodies. This is because the norms, values and assumptions involved are similar. For example, these interventions are in many cases justified by the assumption that normalisation is a way to protect children from negative sociocultural norms, prevent possible psychosocial distress, and enhance the children's possibilities of well-being. I refer, for example, to oestrogen treatment to reduce the height of tall girls, leg-lengthening surgery for children with achondroplasia, orthodontic braces, aesthetic interventions for cleft palate, and sex-aligning surgery for children with non-binary sexual anatomy. I argue that it is ethically desirable also in these cases to consider the different forms of problematisation, norms, and values before advocating for or against the treatment; to look at the characteristics of the child that the intervention would modify not as static features but as part of the human process of growth; and to make a medical decision with a sensitivity to the richness of experiences rather than one based on a problem-oriented approach.

There are at least three aspects of the research presented here that would benefit from further study: the technical possibilities of the treatment and clinical practice (such as its long-term safety, the experience of extremely short children, and the best ways to involve children in decisions concerning the treatment), common perceptions of short stature (such as critical studies on sociocultural norms about height, possible disadvantage and discrimination, as well as bioethical studies on whether a distinction should be made between ISS and other conditions currently treated with hGH, such as Turner syndrome or small for gestational age), and critical bioethics research that combines philosophical inquiry and empirical methods in other paediatric interventions (to explore, for example, unexamined ways of thinking, to be attentive to lived experiences, and to keep the children's perspectives at the centre of decision making).

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