1 Introduction

1.1 Purpose of the Report

Assessment of health related quality of life in children and adolescents is moving forward. Measures to assess quality of life in young persons have been developed for both populations: studies covering all facets of health states and for clinical studies of children with acute or chronic health conditions. Some measures have been made available both nationally as well as internationally, the latter with an eye towards cross-cultural applicability. Recent reviews of the literature show that there is a wide range of generic measures which can be used in cross-cultural epidemiological and clinical studies in adults, but increasingly also in children (Payot & Barrington, 2011; Matza, Swensen, Flood, Secnik, & Leidy, 2004). With regard to condition specific measures, tools have been developed for highly prevalent paediatric conditions such as asthma and diabetes, but fewer have been developed for conditions related to impairments of the physical and mental development of children. One condition relating to the physical development of children is short-stature and its associated impairments, which can severely compromise the health related quality of life of children, their parents and families.

The aetiology of short stature is associated with genetic, endocrinological and psycho-social factors. Height and growth-velocity can fall below normal if growth hormone secretion is insufficient, through endocrine factors, chronic disease, chromosomal abnormalities and malnutrition (Ross et al., 2004; Voss, Mulligan, Betts, & Wilkin, 1992). Also psychosocial, and economic causes have been identified (Peck & Lundberg, 1995). If causes are unknown, the term idiopathic is used.

Among the endocrine factors, growth hormone deficiency (GHD) is most prevalent. However, short stature can also be present without a growth hormone deficit (idiopathic short stature – ISS). Children and adolescents who have GHD or ISS have been described as suffering from behavioural and emotional problems that suggest that being of short stature is a challenge to both children and their families. This challenge relates to potential impairments in wellbeing and functioning, i.e. health related quality of life. In order to measure the impact of the condition on quality of life, condition specific instruments have to be developed.

1.2 Outline of Chapters

The Quality of Life in Short Stature Youth (QoLISSY) project aimed at developing such an instrument simultaneously in five countries. After an introduction (Chapter 1) into the

QoLISSY project, Chapter 2 gives an overview of short stature followed by health-related quality of life assessment in children and adolescents (Chapter 3). After outlining the development of the QoLISSY instrument (Chapter 4), the report proceeds to the three main developmental steps of the instrument, namely focus groups (Chapter 5), pilot test with cognitive debriefing (Chapter 6) and field test (Chapter 7). The last chapter presents a short description of the development and testing of the QoLISSY instrument, its scoring and use, thus serving as a manual (Chapter 8).

1.3 The QoLISSY Project

Since paediatric growth disorders such as Growth Hormone Deficiency (GHD) and Idiopathic Short Stature (ISS) might affect subjective wellbeing and functioning, treatment outcomes should include assessment of health related quality of life (HrQoL). The multinational QoLISSY project aims at developing simultaneously in several European countries, a targeted instrument to measure outcomes in short stature children.

The QoLISSY instrument has been developed in five languages (English, Swedish, Spanish, French and German) and can be applied by clinicians, researchers, pharmaceutical companies, health care providers, and government agencies to:

- give children and their parents a voice in health care,
- document the HrQoL of children and adolescents with short stature,
- describe the impact of short stature and its treatment on the child's well-being from the patient and parent perspective,
- assess pediatric HrQoL outcomes for clinical use and in health economic research.

The QoLISSY instrument is available as a patient reported and a parent reported instrument as a pencil and paper version (an electronic version is under development). It includes the following versions:

- QoLISSY questionnaire for children and adolescents (8-12, 13-18 yrs), with three core QoL domains (physical, emotional and social) and three additional domains (coping, beliefs and treatment).
- QoLISSY questionnaire for parents of children with short stature (4-7, 8-12 and 13-18 yrs), with three core QoL domains (physical, emotional and social), three additional domains (coping, beliefs, treatment) and two specific domains for parents (future and effects on parents).

The QoLISSY instrument can be used to assess the health-related quality of life in short stature youth regardless of its cause; however it was specifically developed for patients with GHD and ISS and their parents. It is usable for children and adolescents between the ages of 8 to 18 years and for parents of children with short stature between the ages of 4 to 18 years. The process of instrument development followed international guidelines including literature review, focus groups with children and parents to identify relevant domains, items

and a conceptual model of QoL, pilot testing with cognitive debriefing of a preliminary questionnaire as well as field and re-testing of the instrument in patients and families across five countries.

This process resulted in a cross-culturally usable instrument, which fills a gap in HrQoL assessment in children with short stature. It respected in its development the experience of patients and parents as well as the cultural backgrounds of their lives. Noteworthy is the simultaneous cross-cultural development and the fact that it elicits information directly from the children and adolescents, as well as their parents.

In sum, the QoLISSY instrument:
- covers a wide range of application possibilities,
- is developmentally appropriate,
- is reliable, valid and sensitive in terms of psychometric criteria,
- is available in multiple languages,
- is quick to complete and easy to score as well as to interpret.

Its psychometric properties in terms of reliability and validity are very good, but need to be examined in future clinical studies. Specifically, responsiveness to treatment related change in HrQoL needs to be tested in a longitudinal study or in a randomized clinical trial (RCT).

2 Short Stature

2.1 Epidemiology and Definition

Normal height in a population is by definition within ± 2 standard deviations (SD) from the mean height for age and sex. Short-stature (SS) can be defined as a body height, which in relation to age and gender is more than two SD below the average for the population and less than 1.5 SD of the mid-parental height (Cohen et al., 2008; GH Research Society, 2000). Each year, 125,000 children are born in the EU with a height that, by definition, falls below the 2.5th percentile and thereby are considered to have SS.

Short stature is defined relative to the genetic composition of the individual by comparison to a large population of children with an a priori similar genetic background. Reference data are usually collected on a country level. The expected height (target height) is based on the average heights of the biological mother and father. Therefore a person with a specific height in cm may be considered to have short stature in one country but not in another.

Short stature and growth failure are often confused. Growth failure is by definition a pathologic state of abnormally low growth rate over time and a growth deviation from a previously defined growth percentile, whereas short stature can also be due to a normal variation in human height. Thus, evaluation of the growth pattern over a period of time and calculation of the mid-parental target height are important when assessing growth.

2.2 Clinical Aspects of Short Stature

2.2.1 Aetiology

Regardless of the genetic background, Short Stature (SS) may be a sign of a wide variety of pathologic conditions or inherited disorders. The Utah growth study (Lindsay, Feldkamp, Harris, Robertson & Rallison, 1994) found that growth failure can be explained by non-endocrine diseases in 90% of children and by endocrine disease in 5% only (with 5% not to be determined). Within endocrine aetiology a growth hormone deficit (GHD) is most frequent.

In fact, while analysis of the prior growth pattern helps distinguish normal growth from pathologic variants of short stature, deviation from a prior growth pattern appropriate for the genetic background often heralds new pathology.

SS in children may have different causes, including normal variation, genetic defects, malnutrition, post-natal consequences of intra uterine growth retardation in children born

short for gestational age (SGA), chronic systemic disease, endocrine disorders or psychosocial deprivation (see Table 1). Growth hormone deficiency (GHD) represents a relatively rare cause for short stature, which is due to insufficient secretion of growth hormone (GH). Most youths with short stature are GH sufficient based on laboratory tests (Lindsay et al., 1994). The heterogeneous group whose short stature is not attributable to underlying pathology is classified as idiopathic short stature (ISS).

Table 1: Causes of Short Stature

The non-endocrine causes of short stature can be divided into major categories:

- **Constitutional delay** of growth and puberty
- **Familial short stature (or constitutive short stature).** The hallmarks include bone age appropriate for chronologic age, normal growth velocity, and predicted adult height appropriate to the familial pattern (using the Bayley-Pinneau or Tanner-Goldstein-Whitehouse tables). In familial SS, height can successfully be increased with GH treatment; however as there is no medical deficiency or illness, treatment is generally not implemented. Although height is increased, it does not affect the genetic predisposition of future generations. By contrast, constitutional growth delay is characterized by delayed bone age, normal growth velocity, and predicted adult height appropriate to the familial pattern.
- **Genetic syndromes** such as Downs, Silver-Russell, Turner, Prader-Willi and Noonan.
- **Bone diseases** such as Achondroplasia, Hypochondroplasia, Dyschondrosteosis and many others.
- **Chronic diseases:** impaired respiratory conditions, cardiac conditions such as congestive heart failure and renal problems such as chronic renal insufficiency. Among the chronic diseases of childhood, malnutrition remains the leading cause of SS worldwide. In addition, any poorly controlled chronic condition can lead to growth failure (diabetes mellitus, celiac disease etc.).
- **Psychosocial dwarfism** due to chronic neglect.
- Many short children evaluated by clinicians in developed countries have familial short stature, constitutional growth delay, or both.

The endocrine causes of short stature can be:

- **Growth hormone deficiency** (GHD) or hypopituitarism: complete absence or insufficiency (partial absence). The GHD can be isolated or combined with other hormonal deficits and can draw its origin from organic, genetic or acquired causes.
- **Hypothyroidism**
- **Hypercorticism**
- **GH resistance** encompassing all the different pathways of GH transduction effect.

2.2.2 Diagnosis

Short stature can be the symptom of many illnesses, since growth is also influenced by many physiological factors, such as gastrointestinal processes. Also psychological stress, e.g. generated through family conflicts, can influence the growth of a child (Gelander, Hagenas, & Albertsson-Wikland, 2002).

Once a child has been found to have short stature (see definition above), the clinician performs a medical interview and examination searching for symptoms of all possible causes of this condition (see Table 1).

In general, endocrine related short stature will result in reduced height, but will also have other consequences for the growing child, such as poorly developing bone structure, lower bone density, lower muscle strength and impaired cognitive development.

The difference between GHD and ISS is based on a GH threshold, below which it is classified as GHD and above which it is classified as ISS. The accepted threshold has changed historically and is also dependent on the method of assessment. Normal GH production differs between individuals and varies over a 24 hour period with the greatest production level being during the sleeping hours. The variation has also been reported to occur seasonally.

2.2.2.1 Growth Hormone Treatment

Growth hormone, also called somatotropin, is a polypeptide hormone which stimulates growth and cell reproduction. Growth hormone deficiency (GHD) is a medical condition in which the body does not produce enough growth hormone (GH). Growth hormone deficit may be congenital or acquired. The diagnosis is clinical, confirmed by low response to GH provocation tests with peak values < 10 μg/l (GH Research Society, 2000). The prevalence of growth hormone deficiency (GHD) in American and European children is about 1:3480 and 1/5600 respectively (Lindsay et al., 1994; Thomas et al., 2004).

For children with complete GHD or very low production of GH there can be a number of medical consequences. Children with GHD deviate in their skeletal maturity (bone age), they have body proportions similar to a younger age child; low muscle mass and increased fat. GHD children can therefore be mistaken for being younger than they are, not only due to height but also body shape. There are also effects upon the nervous system so that a GHD child can be slow in movement and considered to lack initiative. This may mean that they do not tend to play with other children their age which in turn effects their social development as well as body development (Gelander et al., 2002). Therefore, growth hormone deficiency has different effects at different ages. In newborn infants the primary manifestations may be hypoglycemia or micropenis, while in later infancy and childhood, growth failure is more likely. Deficiency in adults is rare, but may feature diminished lean body mass,

poor bone density, and a number of physical and psychological symptoms. Psychological symptoms include poor memory, social withdrawal, and depression, while physical symptoms may include loss of strength, stamina, and musculature. Other hormonal or glandular disorders frequently coincide with diminished growth hormone production.

2.2.2.2 Idiopathic Short Stature

Idiopathic short stature (ISS) is a diagnosis of exclusion and thus refers to children in whom no medical cause could be found with current diagnostic tools. The term has been in use since at least 1975 without a precise percentile or statistical definition of "extreme". It is defined as normal size at birth (> –2 SDS), significant short stature (< –2 SDS), normal or low growth velocity, with no significant abnormalities in laboratory studies, and no evidence of systemic disease, malnutrition, hypothyroidism, or GHD (Ranke, 1996).

Psychological and medical intervention in children with ISS are currently considered in Europe, however, future studies are needed in this area (Visser-van Balen et al., 2007).

2.2.2.3 Constitutional Delay in Growth and Puberty

Constitutional delay in growth and puberty is characterized by absence of organic or psychological disease, absence of malnutrition, normal clinical examination and normal results of laboratory studies, delayed puberty, delayed bone age consistent with height age and predicted adult height appropriate for genetic height potential. It is the most common cause of short stature referred for evaluation to the paediatric endocrine unit and together with familiar short stature has traditionally been considered as a separate diagnosis from ISS.

2.2.2.4 Small for Gestational Age

Small for gestational age (SGA) is a diagnosis given to a neonate whose birth weight or birth crown-heel length is at least 2 standard deviations (SD) below the mean (–2 SDS) for the infant's gestational age, based on data derived from a reference population.

2.3 Underlying Mechanisms

2.3.1 Growth Hormone

Growth hormone (GH) is a peptide hormone, stimulating growth, cell reproduction and regeneration in humans and other animals. Growth hormone is used to treat children's growth disorders and growth hormone deficiency. Reported effects on GH-deficient pa-

tients include decreased body fat, increased muscle mass, increased bone density, increased energy levels, improved skin tone and texture. GH is a very complex hormone with many functions which are important for the growing child but also throughout the life-span. Many of the effects of GH are still unknown (Power, 2005). However, GH treatment is used primarily in the stimulation of height increase in children.

In Idiopathic Short Stature (ISS), short-stature cannot be attributed to an underlying illness and GH production is normal. It has been proposed that although GH in the body is normal it is still not sufficient to stimulate the GH receptors. In the treatment of ISS additional GH is administered in order to try to stimulate these receptors. Where this has no effect, GH treatment is stopped and there is no other treatment option.

2.3.2 Normal Human Growth Pattern

The growth pattern followed by humans is divided into three periods:

- Infancy, which is the first 18 months of life. Growth rate is highly influenced by nutrition intake. In terms of physical development, this stage witnesses the most growth. The endocrine system in particular goes from barely functioning in the newborn, to being complete and active in the eighteen-month-old.
- Childhood is the second phase and extends from 18 months through to puberty. GH is very important during this phase and ensures that the child has continuous growth at a steady rate usually about 6-9 centimetre per year.
- Puberty includes a growth spurt, which significantly increases height. Puberty occurs at different ages for girls and boys. The growth spurt in girls starts 1-2 years prior to menstruation, usually when the child is 11-13 years of age. In boys the growth spurt does not begin until the boy is 14-15 years old. Oestrogen and testosterone increase during puberty and both stimulate and impede growth. Sex hormones also contribute to the growth spurt. The end of puberty also marks the end of the height increase. The effect of puberty also means that later puberty provides more time for growth which explains why in general boys are taller than girls. Early puberty results in less height gain at final height. Even if height increase ceases after puberty GH is still produced in the body and is necessary in for example bone strength and physical energy (Gelander et al., 2002).

2.3.3 Psychosocial Aspects of Short Stature

Without intervention, or if catch-up growth is slow or GH treatment unsuccessful, the height difference between the slow-growing child and same-aged peers will widen over time and he or she may even be overtaken in height by younger siblings. The possibility that the disparity in height could put the short-stature child at risk of psychosocial stress as a result of negative comparisons with peers, expectations of parents or social labelling has been investigated in many studies (Bullinger et al., 2009).

Independent of its origin, short stature is potentially associated with impairments in wellbeing and functioning. This is not only because of barriers in everyday life due to the built environment, but also because short stature is regarded as a social stigma affecting the self-perception and social integration of persons with short stature. The degree of impairment depends not only on the degree of short stature, but also the way patients perceive their condition and cope with negative social attitudes.

Short stature may have a negative influence on the affected child and the whole family (Sandberg & Voss, 2002). Some children may present with anxiety, aggressiveness, social isolation, immaturity, low self-esteem and depression. However the current data is not sufficient to evaluate the impact of short stature on psychosocial adaptation (Sandberg & Colsman, 2005; Visser-van Balen et al., 2007). Because short-stature treatment has to be started in early childhood in order to be successful, parent's views and priorities are important in the decision process. However, the question is whether impairments in wellbeing and functioning are experienced by children at the time of diagnosis and whether this can be projected into the future. It is important to understand how parents view the impact of short stature on their children, themselves and their families. The treatment indication for short stature focuses on increasing height, and thereby also increasing wellbeing and functioning and making life easier for children as they catch up to normal height. However, in order to understand the effects of height in wellbeing and functioning, it is important to capture the view both of the young patients as well as of their families, and to understand how wellbeing and functioning are regulated.

The psychological burden of SS has been addressed by the literature over many years, starting with earlier publications about the impact of short stature on psychological functioning and the role of adaptation. However, this research approach rarely considered the view of short-stature persons themselves. With the introduction of the quality of life concept into medicine, and paediatric endocrinology, the question arose how wellbeing and function can be assessed from both, the patient's and parent's point of view. Although this line of research is now growing, there still is a paucity of measures to assess quality of life in this population. The psychosocial stress that can be caused by the awareness of height disparity can have a detrimental effect upon the child that can persist into adult life (Magnusson, Gunnell, Tynelius, Davey Smith, & Rasmussen, 2005). Secondary psychological consequences can also occur when the negative social stereotype of short stature affects how the child is treated by others (Sandberg & Voss, 2002). The way others respond to the child and his or her self-perception will in turn influence the child's behaviour and self-esteem (Harter, 2001) and may contribute to the child being bullied in school (Voss & Mulligan, 2000). Therefore, the self-perception of height is an important determinant of children's self-image and shapes their interactions with the people they meet.

Attempts to measure the social and psychological consequences of short stature have proven difficult (Sandberg, Bukowski, Fung, & Noll, 2004; Voss, 2001). Short-stature can have serious psychological consequences in the form of stigmatisation, social isolation and "juve-

nilisation" (Sandberg & Voss, 2002; Voss & Mulligan, 2000). Because short stature can act as an "easy" explanation for psycho-social problems the clinician should consider incorporating a psychosocial component in their diagnostic evaluation to broaden potential treatment recommendations (Sandberg & Colsman, 2005).

Studies of impairments associated with SS are often confounded with conditions in which SS is a feature of a phenotype specific to a particular medical condition or syndrome. In a review limited to children with SS (as the major diagnosis), Wheeler, Bresnahan, Shephard, Lau, & Balk (2004) concluded that short children scored lower than their peers on intelligence tests, academic achievement and behavioural adaptation, but the scores fell within the normative range (1 SD). Deficits for youths with SS were reported in visual-motor skills as well as psychological, educational and behavioural functioning. Nonetheless, it remains unclear whether the deficits are the consequence of an underlying condition causing SS and cognitive and psychological sequelae or whether they are directly associated with SS. Taking into account other studies on SS and functional impairment, no direct link has been found.

Psychosocial effects of SS have been reported to include stigmatization and social isolation due to stature-related stereotypes. Some studies report that short children experience chronic psychosocial stress, although these experiences do not generally result in clinically significant problems of psychosocial adaptation.

Recent literature is inconclusive with regard to whether or not SS, per se, is a handicapping condition. Furthermore, emotional problems secondary to teasing or low self-esteem have not been unequivocally confirmed. According to parent reports, short children exhibit lower social competencies and more problems in social interaction than children with a stature within the normal range. Other studies, however, have failed to detect deficits in academic or psychosocial functioning among children with SS.

Risk factors potentially affecting psychosocial adaptation among those with SS include male gender, the presence of a younger but taller sibling, being perceived and treated as younger than chronological age, lower intelligence, and lower family socioeconomic status. As many of these constitute "risk factors" for children with average stature, they are not specific for those with SS. Thus it remains unclear, why some children with SS develop psychologically well and others do not.

2.4 Treatment

2.4.1 Options

Since short-stature is considered to be a potential risk for child development and health, growth hormone (GH) treatment is initiated in order to assist the child to follow their estimated normal development. GH treatment can help the short-stature child to grow in height. An increased quality of life (QoL) is considered to be an important and relevant goal for GH treatment (Cohen et al., 2008). A standardized QoL instrument for this population has not been available and therefore it has not been possible to determine the nature of the QoL benefit. Hunt and colleagues (Hunt, Hazen, & Sandberg, 2000) suggest that it is the experienced height rather than actual height which effects QoL and psycho-social health. Equally there is little evidence available of the effect that short-stature has upon the adult in terms of quality of life.

A treatment decision is made on behalf of the child by its parents and by the family physician. This decision is based on both the medical aspects, which motivate the treatment but also on the concerns of the parents who consider the child's future experience as a short-stature person. Where the goal is the child's QoL, it is important to understand what effect short stature has on the child and the influence of GH treatment on the child during the treatment period. In these children catch-up growth can be stimulated via growth hormone (GH) treatment. The initial phase of GH treatment is a phase of rapid growth that aims to accelerate the child's growth towards their expected height if growth retardation had not occurred (Boersma & Wit, 1997). The success of the catch-up growth is dependent upon treatment starting early in childhood and on how the body responds to the hormone replacement, therefore despite treatment the child's final height may remain below the mid-point of average parental height (Westphal & Lindberg, 2008).

2.4.2 Indications for Recombinant Human GH (rhGH)

GHD remains the primary indication for rhGH treatment in childhood. There are several important issues regarding therapy of children with short stature of various aetiologies. Indication of recombinant human GH (rhGH) in children has been approved by the US Food and Drug Administration in GHD, chronic kidney disease, Turner syndrome, small-for-gestational age with failure to catch up to the normal height percentiles, Prader-Willi syndrome, ISS, SHOX gene haploinsufficiency and Noonan syndrome. The same indications are approved in Europe by the European Agency for the Evaluation of Medicinal Products, except for ISS and Noonan syndrome (Richmond & Rogol, 2010). Current consensus guidelines recommend a dose in the range of 0.025-0.05 mg/kg/day.

The main objectives of rhGH therapy in children are an increase of height velocity, an improvement of body composition and a normalisation of adult height. The incidence of side-

effects is low, but in a few cases increased intracranial pressure, scoliosis, muscle and joint problems, and slipped capital femoral epiphysis have been reported (Tanaka et al., 2002).

RhGH was approved for treatment of ISS in the United States and seven other countries (with a dosage up to 0.053 mg/kg/day) for children shorter than –2.25 SDS. Lower cut-offs are proposed in several other countries (Cohen et al., 2008). An increase in height SDS of more than 0.3-0.5 and in height velocity SDS of more than 1 during the first year of therapy are considered as a positive response (Cohen et al., 2008).

In a recent Cochrane Review (Bryant, Baxter, Cave, & Milne, 2007; Cohen et al., 2008), a meta-analysis of 10 randomised controlled trials, carried out in children with ISS with normal GH secretion, showed that only 2 studies were of moderate quality. The remaining studies were not considered methodologically sound. The authors conclude that GH therapy can increase short-term growth and improve (near) final height. Results of GH studies in ISS show an average gain in adult height of approximately 4 to 6 cm. Increases in height are such that treated individuals remain relatively short when compared with peers of normal stature. Authors suggest that future large, multicentre RCTs should focus on final height and address quality of life and cost issues (Bryant et al., 2007).

2.4.3 Psycho-social Interventions

In addition to growth hormone substitution and in correspondence to the psycho-social needs of children with short stature and their families, psycho-social interventions have been suggested (Noeker, 2009). As the literature on coping and adaptation in short stature children shows, strengthening of the self-concept and assertiveness should be in the foreground. Such psycho-social interventions are offered individually at treatment centres, however infrequently. A systematic review of the effects of such treatment is lacking as well.

Interestingly, structured programs to strengthen self-concept of children and to increase parenting skills in their families are available but have not yet been transferred to the area of short stature. In view of the effect of short stature on child self-concept and the social stigma potentially experienced, the question is whether psychological interventions can increase resilience in children and contribute to their health-related quality of life.

3 Health-Related Quality of Life

3.1 Health-Related Quality of Life Research in Children and Adolescents

A paradigm shift in criteria used to evaluate medical outcomes has occurred in the past 20 years (Bullinger & Hasford, 1991). Classical endpoints such as the reduction in symptom and increased survival have been supplemented by patient-reported outcomes. A broader definition of health as suggested by the WHO (1948), focusing on the psychological and social dimensions of well-being has contributed to this new view on health. The term Health-related Quality of Life (HrQoL) has been coined to integrate this changed perspective on medical outcomes. The term denotes in psychological terminology a multidimensional construct covering physical, emotional, mental, social, and behavioural components of well-being and function as perceived by patients or proxies (Kremer, Klimek, Bullinger, & Mosges, 2001). HrQoL is often distinguished from the broader concept of quality of life. In medicine, quality of life clearly relates to health and the subjective well-being of a patient with regard to a treatment. In more detail, HrQoL is a component of the more general construct of quality of life which also includes a broader range of aspects such as political freedom and economical issues. In general, HrQoL research has undergone four phases, starting with:

- early considerations of theoretical concepts of the topics in the 1970s,
- development of measurement approaches in the 1980s,
- the inclusion of measures in different studies in the year 1990, and recently
- examining the clinical significance of HrQoL tests scores from the year 2000.

While HrQoL research in adults has progressed substantially over recent years, the topic has not yet been systematically investigated in younger populations. Despite the slow development of HrQoL research in children and adolescents, the assessment of well-being and function is considered an important topic especially in paediatric research and clinical practice. With regard to the assessment of HrQoL in young populations, researchers have to face a number of challenges. Overall, progress in paediatric HrQoL research was slow due to conceptual and operational difficulties (Ravens-Sieberer, Ellert, & Erhart, 2007). These difficulties refer to age differences, parent-report, and cognitive ability of the child. Furthermore, instruments taking into account a cross-national perspective are missing.

In general, HrQoL measures can be divided into generic and condition-specific measures (Guyatt, 1995). They can be further categorised into health profiles or preference-based measures. While generic instruments measure HrQoL across health conditions, condition-specific measures do so with regard to a specific disease, treatment or symptom. The disadvantage of generic measures may be that small changes in HrQoL might not be detected. On the other hand, condition-specific instruments may provide more clinically relevant

information, but comparison across illnesses is not possible (Bullinger, 1997). Moreover, children may have more than one condition and this co-morbidity complicates the development of condition-specific measures. Since both types of measures have strengths and weaknesses, the choice of one type of measure depends on the study aims. Sometimes a combined approach is appropriate using both types of instruments.

Information can be obtained from children or adolescents themselves (self-report) or from significant others, usually the parents (parent report). Most instruments are available for different age groups; the majority of the versions were developed for adolescents from 13 to 16 years, rarely for school-aged children from 8 to 12 years, and rarely for young children. In spite of the availability of different instruments, it is unfortunate that only few instruments are usable for a cross-cultural international research. Although some instruments have been translated into other languages, this procedure reflects the sequential approach in which it is difficult to take into consideration cultural differences between countries. A unique approach for cross-cultural instrument development is the simultaneous approach in which instruments are developed conjointly in multiple countries and languages.

Health related quality of life assessment in young people includes patient self-assessment and parent reports. Two main sets of measures can be distinguished: generic measures, which are applicable independently of the context of the health condition or treatment situation, and targeted or disease-specific measures, which are tailored to fit specific patient populations. Recently also so called chronic generic measures focusing on the experience of having a chronic health condition – independent of which – as well as treatment-specific measures focusing on the type of care received have been included as well.

Within quality of life research in children, primarily generic measures have been developed; only recently disease-specific measures have been published. Thus, such measures are lacking for many young patient populations, among them short stature youth. In order to identify an appropriate instrument, it is necessary to review the literature for available measures for a given health condition and if that search does not yield appropriate instruments, to consider developing a new instrument.

3.2 Health-Related Quality of Life in Short Stature

A recent review identified several measures developed specifically to assess HrQOL in children with short stature (Brütt et al., 2009). However, there is little data available on the psychometric performance of some of the instruments and only one of these was a self-report instrument. In other cases, the opinions of children and parents were not explored in depth during instrument development. Furthermore, the measures have been developed on a national level, so that instruments for the comparison of the impact of short stature across countries were not available. The quality of life in short stature youth (QoLISSY) project

therefore aimed at developing cross-culturally a measure to assess health related quality of life in children and adolescents with short stature, from their own perspective (self-report) as well as from the perspective from their parents (parental report). The goal was to develop a conceptually founded and methodologically sound instrument for the use in population studies as well as in a wide range of research contexts including epidemiological studies and randomized clinical trials. Ultimately the goal is to be able to assess the effect of interventions (such as growth hormone treatment or psychological support) on patients and families.

3.2.1 Assessment Instruments for Adults

As concerns patient rated outcomes HrQoL instruments, patient preference assessments and patient satisfaction measures need to be distinguished.
A range of generic and disease-specific instruments have been developed and tested in adults with GHD, for example the Quality of Life – Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) (Barkan, 2001). This instrument consists of 25 items that can be answered by "yes" or "no" resulting in a maximum score of 25; higher scores represent lower HrQoL. The QoL-AGHDA statements address problems associated with energy level, concentration and memory, irritability and temper, strength and stamina, social isolation, coping with stress, as well as physical and mental drive. The Growth Hormone Deficiency Questionnaire (GHDQ) examines energy, mood and sleep. The Questions on Life Satisfaction-Hypopituitarism (QLS-H), is a disease-specific instrument which takes into account the importance of single aspects of functioning by a weighting scale for each of the nine items (i.e. body shape, coping, self-confidence). The values (calculated by importance and satisfaction) range from –12 to 20 with negative values indicating dissatisfaction and positive values indicating degrees of satisfaction (Attanasio, Shavrikova, Blum, & Shalet, 2005).

Generic and disease-specific quality of life instruments have been used in studies of adults with GHD. Among the generic variety, the Nottingham Health Profile (NHP) (Hunt & McEwen, 1980), the Psychological General Well-Being (PGWB) (Dupuy, 1984), and the Short Form 36 Health Survey (SF-36) (Ware & Sherbourne, 1992), have frequently been employed.

Patient preference measures: Both time-trade-off and standard gamble have been used in adults to assess patient preferences, e.g. Rekers-Mombarg, Busschbach, Massa, Dicke, & Wit (1998) assessed the impact of SS on HrQoL using time-trade-off. Preference-based measures such as the EQ-5D or the Health Utilities Index (HUI) are also frequently used in adults (Luo, Johnson, Shaw, Feeny, & Coons, 2005). It is claimed that these generic measures can be applied across all disease areas. However, as these instruments measure general health, they may be insensitive to the features of some specific conditions.

Patient satisfaction: Several studies have been conducted on impact of long-term GH replacement therapy on patient satisfaction, HrQoL, and healthcare utilization (Saller et

al., 2006). Saller et al. (2006) examined a large cohort (n = 503) of adult patients with GHD originating from three European countries. Patient satisfaction with GH treatment was rated by patients using Likert rating scale and physical activity was assessed on visual analogue scale (VAS). Significant improvements observed during the first year of treatment were maintained during the second year.

The main interest of studies in adults with GHD is the putative benefits of low-dose GH replacement on metabolism (e.g. lean to fat body mass), energy level, and general well-being. These outcomes are believed to be pharmacologically responsive to GH and not mediated by GH effects on growth/height attained earlier in the treatment cycle. In contrast, research in children and adolescents focuses, in particular, on the effects of GH-promoted growth on subjective well-being and functioning.

3.2.2 Assessment Instruments for Children

A number of generic HrQoL instruments for use in children are available. The following generic and condition-specific measures were included in studies of youths with growth disorders (Table 2: Brütt et al., 2009).

The Pediatric Quality of Life Inventory (PedsQL) is a generic measure developed in the US. The 23-item questionnaire, available in self- and parent-reported versions, measures HrQoL of healthy and ill children, aged 2 to 18 years. The self-report version is designed for children above 5 years. In addition to a total score, scale scores are available for physical, emotional, social and school-related domains. The instrument is psychometrically robust and translations exist in multiple languages (Sheppard et al., 2006).

Another widely used instrument developed in the US and applied to children with SS is the Child Health Questionnaire (CHQ). Self- and parent-reported forms for children 5 to 18 years old are available. Its 87 items cover 14 domains which can be aggregated into physical and psychological sum scores. Construct and convergent validity, as well as sensitivity to change, have been demonstrated (Norrby, Nordholm, Andersson-Gäre, & Fasth, 2006).

The Netherlands Organization for Applied Scientific Research – Academic Medical Centre created the child quality-of-life questionnaire (TACQOL). Available in self- and parent-reported versions for youths 5 to 15 years old, the TACQOL's 56 items cover 7 dimensions. Questionnaire reliability as well as construct and convergent validity have been established (Theunissen et al., 2002). A SS-specific version of this questionnaire also exists and is described below.

Pilpel, Leiberman, Zadik, & Carel (1995) developed a questionnaire for use in a study on GH treatment. It did not include items specifically related to SS. Instead, the 45-item measure assessed the dimensions "academic achievement level", "leisure activities", "physical

self-esteem", "emotional self-esteem," "relationships with peers and family members"; all domains hypothesized to be negatively affected by SS. The rating scale ranges from 1-4, each value defined by verbal anchors. For analysis, scores are transformed such that "4" and "1" represent the most positive and negative views of HrQoL, respectively. The dimension score is calculated as the mean of items. Data on psychometric characteristics of the questionnaire are not available.

The DucatQoL consists of 25 items, scored on a five-point scale. The questionnaire assesses home, physical, emotional and social functioning and provides a total score (Koopman et al., 1999). The French instrument Vecú de Santé Perçu Adolescent (VSP-A) has been developed for measuring self-reported HrQoL in chronically ill adolescents ages 11 to 15. The 37 items assess 10 dimensions and can be further summarized into a global index. Reliability as well as construct and convergent validity have been assessed (Cramer et al., 2005). Two instruments not explicitly measuring HrQoL, but administered to children with SS are the Self-Perception Profile (SPP) and the Child Behavior Checklist (CBCL) (Ross et al., 2004).

There are only few condition-specific questionnaires specifically designed for assessing SS relevant domains of HrQoL:

Leiberman, Pilpel, Carel, Levi & Zadik (1993) developed a 53-item questionnaire to assess coping and satisfaction with GH treatment. The questionnaire covers the following domains: emotional self-esteem, physical self-esteem, perceptions of treatment and medical outcome, relationships with peers, relationships with family members, compliance with treatment regimen, satisfaction with accessibility of treatment, with doctor-patient relationship, and with outcome of treatment. In addition, a total score can be calculated. The domains were created *a priori* according to content. The reliability of the scale domains (assessed by Cronbach's α) ranged from 0.7 to 0.9 for the sample ($n = 96$) studied. No further information regarding psychometric properties were provided.

Wiklund, Wiren, Erling, Karlberg & Albertsson-Wikland (1994) developed a measure consisting of 39 bipolar adjectives (i.e. happy-sad, strong-weak, lazy-energetic) which were selected and tested for understanding in a group of teachers and pupils. Respondents rate themselves using a visual analogue scale (100 mm in length) with the endpoints defined by words denoting the extreme opposites of the attribute to be measured. Psychometric testing was performed using a sample of 342 healthy children of three different age groups (9, 11, and 13 years) as well as a sample of 65 short children (mean $\pm$ SD = 12 $\pm$ 1.5 years) referred to a growth research centre (Gothenburg, Sweden). The six, factor-analytically derived domains include "alertness", "self-esteem", "mood", "elation", "stability" and "vitality". Internal consistencies (Cronbach's α) for the different dimensions ranged from 0.63 to 0.81. Inter-correlations among the six factors were modest ($r = .17 – .53$) indicating that relatively unique information was being captured. Construct validity was estimated with a Swedish self-perception questionnaire. The strongest relationships were found in domains related to emotion.