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Recombinant Human Growth Hormone for Treatment of Turner Syndrome: Systematic Review and Economic Evaluation

Supporting Informed Decisions

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Recombinant Human Growth Hormone for Treatment of Turner Syndrome: Systematic Review and Economic Evaluation

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Huimin Li was initially the overall research lead. After Huimin Li's departure from CADTH, Srabani Banerjee was the overall research lead.

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All authors contributed to the revisions of the report.

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Conflicts of Interest

Dr. Denis Daneman was a co-investigator in the Canadian randomized controlled trial that is described in this review and which was funded by Eli Lilly Canada.

Dr. Jill Hamilton has received speaker fees from Eli Lilly and Serono, and a research grant (no personal compensation) from Roche for a study on "Liver function in Turner syndrome."

Dr. Cheri Deal has received speaker fees and Advisory Board fees from Eli Lilly and Serono. She has received research funds (no personal compensation) for Phase 3 and Phase 4 clinical trials with Lilly, Serono, and Roche.

REPORT *IN BRIEF*

December 2007

Recombinant human growth hormone for Turner syndrome: systematic review and economic evaluation

Technology and Condition

Recombinant human growth hormone (rhGH) for treatment of Turner syndrome (TS).

Issue

Given the high cost of rhGH treatment and the evolving evidence base for its clinical effect in patients with TS, policy makers need evidence to inform reimbursement decisions about rhGH.

Methods and Results

A systematic review was conducted to identify randomized controlled trials (RCTs) and comparative observational studies comparing rhGH with placebo or no treatment in patients with TS. The outcomes of interest were growth, adverse events (AEs), and quality of life (QoL). A meta-analysis was conducted where appropriate. Primary economic analyses were also undertaken, using the perspective of the public health care system and a lifetime horizon. Six RCTs and nine observational studies were included, ranging in duration from one to eight years. The included studies showed that rhGH treatment accelerates growth and results in improvement in height. No serious AEs were reported in the included studies. QoL data, derived from two RCTs, were variable, precluding any conclusion about rhGH's influence on QoL. Base case economic analysis showed that the incremental cost-effectiveness ratio (ICER) of rhGH treatment versus no treatment was C$23,630 per centimetre of final height improvement or C$243,078 per quality-adjusted life year (QALY) gained.

Implications for Decision Making

- **Treatment with rhGH has a demonstrated impact on final height but its effect on QoL is uncertain.** The available evidence suggests that, compared with patients receiving placebo or no treatment, patients who are treated with rhGH experience accelerated growth and improvement in final height. Treatment appears to be safe with no serious AEs and few, if any, AEs reported. QoL data, reported in two studies, were variable and inconclusive.
- **For the average patient, rhGH is cost effective if a payer is willing to pay more than C$200,000 for a QALY**. However, from an ethics perspective, the provision and funding of rhGH could be supported until those with TS reach the lower end of the normal adult height range.
- **Publicly funding rhGH treatment will require additional investment.** If it were assumed that all TS patients aged 10 to 15 years were eligible for rhGH therapy, the corresponding annual budget impact for covering ~400 patients across Canada would be C$11.3 million. The more likely scenario would be that 40% to 50% of eligible patients would receive treatment, with a proportionate decrease in expenditure.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Li H, Banerjee S, Dunfield L, Kirby J, Jones M, Hamilton J, Deal C, Hadjiyannakis S, Normandin S, Tsakonas E. *Recombinant Human Growth Hormone for Treatment of Turner Syndrome: Systematic Review and Economic Evaluation*

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EXECUTIVE SUMMARY

The Issue

Given the high cost of rhGH treatment and the evolving evidence base for its clinical effect in patients with TS, health policy makers are seeking evidence to adjust or substantiate the reimbursement decisions regarding rhGH therapy. Therefore, an evaluation of rhGH treatment in patients with TS is warranted.

Objectives

The aims of this report are to evaluate the clinical efficacy of rhGH and the economic implications of its use in the treatment of TS.

Clinical Review

Methods: A systematic review was conducted to identify randomized controlled trials (RCTs) and comparative observational studies comparing rhGH with placebo or no treatment in patients with TS. The outcomes analyzed were growth, adverse events (AEs), and quality of life (QoL). A meta-analysis was conducted when appropriate.

Results: Six RCTs and nine comparative observational studies were included with numbers of patients ranging from 40 to 232 and 26 to 123 respectively, and study duration ranging from one to seven years and from two to eight years respectively. Overall the RCTs were of good quality, and the observational studies were of fair quality. Not all trials or studies could be included in the meta-analysis because of the incomplete reporting of data.

Overall, the RCTs and the observational studies showed that rhGH treatment accelerates growth and results in increased height. The Canadian RCT followed most patients for 5.7 years and showed that the mean difference (MD) and 95% confidence interval (CI) were 6.50 cm (4.28, 8.72) for final height, 1.00 (0.67, 1.33) for the height standard deviation score (HSDS), and 1.3 (1.11, 1.49) for the change in HSDS, hence favouring rhGH. The growth velocity and growth velocity standard deviation scores (GVSDSs) were also higher for patients treated with rhGH compared with those not receiving rhGH.

QoL data were available from two RCTs, but there was variability in the results, and no definitive conclusions were possible. No QoL data were available from the observational studies.

Overall there were no serious AEs reported in the studies included. One RCT reported that the frequency of AEs was similar in rhGH-treated and untreated groups. Another reported that the AEs in patients treated with rhGH were few. The Canadian RCT reported significantly higher rates of treatment-emergent AEs in the rhGH group. Because physicians were not blinded to treatment allocation, however, surveillance bias might have contributed to this observation.

Economic Review

Methods: Economic studies comparing rhGH treatment with no treatment were identified through electronic databases, web sites, and manufacturers.

Results: One economic study was identified. It reported a cost-effectiveness analysis from the perspective of the UK National Health Service (NHS) and Personal Social Services. For two base

cases, the incremental cost-effectiveness ratio (ICER) was £15,997 (C$35,991) or £17,429 (C$39,213) per centimeter of final height improvement. One-way, two-way, and scenario sensitivity analyses were performed to test the robustness of baseline results. The ICER varied from £1,563 (C$3,516) to £57,436 (C$129,224) per centimeter of final height improvement. The key variables in the sensitivity analysis included duration of treatment, continuance of treatment, final height effect due to rhGH, rhGH dose, rhGH cost, and discount rate.

Primary Economic Analysis

Methods: Cost-effectiveness and cost-utility analyses were undertaken from the perspective of the Canadian health care system, comparing rhGH treatment with no treatment for patients with TS. An analytic model was constructed for the ICER estimation. We considered a lifetime horizon and used data from the available literature. One-way and scenario sensitivity analyses were conducted.

Results: Given several assumptions, we estimated that the ICER of rhGH treatment versus no treatment was C$23,630 per centimetre of final height improvement or C$243,078 per quality-adjusted life year (QALY) gain. In the sensitivity analysis, the ICER varied from C$7,114 to C$43,713 per centimetre of final height improvement or C$63,046 to C$830,167 per QALY. To reach C$50,000 per QALY, a girl with TS would have to be willing to trade 20.4% of her lifetime for a final height improvement (4.2% in the base case). There are some limitations with the utility estimates used in this analysis.

Health Services Impact

Given the TS prevalence of 1:2,500 among female live births, it is estimated that there are 66 new cases of TS in Canada each year. If we assumed that only those aged 10 to 15 years are eligible for rhGH therapy, 396 patients with TS would be affected by a reimbursement policy regarding rhGH therapy each year in Canada. The corresponding budget for rhGH drugs in 2007 would be C$11.30 million for all of Canada if all girls with TS aged 10 to 15 years received coverage for rhGH therapy. The total budget for three years would be approximately C$32.3M, and approximately C$51.35M for five years. If 40% to 50% of girls with TS receive treatment the budget would be proportionately decreased. This is likely to be the case in the real-world situation, because of late diagnosis, non-referral, and refusal of therapy.

Conclusions

The available evidence suggests that rhGH treatment is effective in improving growth and final height, but there is no conclusive evidence about whether rhGH treatment improves QoL. In RCTs and comparative studies, AE data were sparsely reported, and there was variability. Long-term studies of high quality are needed to determine the benefits and drawbacks of rhGH treatment.

The only economic study identified showed that the per centimetre of final height gain with rhGH was >£10,000 (C$22,498) compared with no treatment, but it came to no definitive conclusion as to whether rhGH therapy is cost-effective.

Our economic evaluation showed that for the average patient with TS, rhGH treatment is unlikely to be considered cost-effective unless the payer is willing to pay >C$200,000 to obtain a quality-adjusted life year (QALY). Future research is needed to generate more robust QALY data.

From an ethics perspective, distributive and social justice arguments could support the provision of publicly funded rhGH to persons with TS, and in particular, support the provision and funding of such therapy until affected individuals have achieved the lower end of the normal adult height range.

Funding rhGH therapy for patients with TS will increase the budgets of government drug plans; hence, opportunity costs need to be considered.

ACRONYMS AND ABBREVIATIONS

ΔHSDS	change in height standard deviation score
AE	adverse event
CDC	Centers for Disease Control
CEA	cost-effectiveness analysis
CI	confidence interval
CUA	cost-utility analysis
DIN	drug identification number
FH	final height
GHD	growth hormone deficiency
GV	growth velocity
GVSDS	growth velocity standard deviation score
hGH	human growth hormone
HSDS	height standard deviation score
ICER	incremental cost-effectiveness ratio
MD	mean difference
NHS	National Health Service
NICE	National Institute for Clinical Excellence
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomized controlled trial
rhGH	recombinant human growth hormone
SD	standard deviation
SDS	standard deviation score
SE	standard error
TS	Turner syndrome
TTO	time trade-off
WMD	weighted mean difference

GLOSSARY

GV: growth velocity is the rate of growth.

GVSDS: growth velocity standard deviation score is the rate of growth expressed in terms of standard deviation score.

ICER: incremental cost-effectiveness ratio is the incremental cost of an intervention divided by the incremental effectiveness.

karyotype: standardized arrangement of all chromosomes of a cell. Normal human karyotypes contain 22 pairs of autosomal chromosomes and one pair of sex chromosomes. For women, the sex chromosomes are 46,XX. For men, they are 46,XY.

SDS: standard deviation score is the difference between observed and predicted values divided by the residual scatter about the mean predicted value.

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1 INTRODUCTION

1.1 Background

Turner syndrome (TS) is a chromosomal disorder in females, characterized by the absence of all or part of a normal second sex chromosome. Fifty per cent of patients have one sex chromosome, while the remaining half have sex chromosome abnormalities.[1]

The prenatal prevalence of TS is higher than the postnatal prevalence because of a high rate of miscarriage of fetuses with TS.[2] Among female live births, the reported prevalence is one in 2,500 to one in 3,000.[1] Given that there were 163,918 female live births in Canada in 2004,[3] each birth cohort has an estimated 55 to 66 cases of TS. In Canada, the number of girls with TS from birth to 12 years old would be estimated at 660 to 792.

The loss or structural alteration of the X chromosome in TS is a random occurrence during the formation of sex cells. There does not seem to be an increased risk of TS among different racial or ethnic groups or among mothers of older age.[4] According to the results of karyotyping, TS can be classified into subgroups:[1] monosomy X (45,X), where all cells are missing an X-chromosome; isochromosome [46,X,i(Xq)], where the long arm of one X is duplicated, and the short arm is absent; and mosaicism, [e.g., 45,X/46,Xi(Xq)], where the chromosome number or structure differs in different cells of an organism.[1,4]

Because sex chromosomes play a role in the development of reproductive tissues and organs, mutations of these chromosomes result in a range of clinical features (Table 1),[5] among which short stature is the most common (88% to 100%). It has been found that the haploinsufficiency of a gene [the short stature homeobox (SHOX) gene, located in the pseudoautosomal region of Y and Xp] may partially explain the short stature,[1] but it is uncertain which chromosomal regions and genes are responsible for the other features of TS.

The Lyon growth chart of TS,[6] which was developed in 1985, allows a prediction of growth for patients with TS who do not receive treatment (Table 2). From birth, most patients tend to be shorter (Figure 1) than normal girls. More than half of girls with TS will fall below the fifth percentile for height by two years of age.[7] The slow growth trend continues through childhood until they reach adult height (the height at which height velocity is <1 cm per year). The mean final heights of patients with TS who do not receive treatment can range from a low of 136.7 cm in Japan to a high of 146.9 cm in Germany.[8] Girls with TS are approximately 20 cm shorter than the height considered to be normal for their ethnic-specific population.[5] The variation among individual cases may be due to the height of both parents, age of onset of puberty, nutritional status, and social background.

The common triggers for TS diagnosis are lymphedema or coarctation of the aorta during infancy or short stature and delayed puberty during childhood and adolescence,[9] but the ultimate diagnosis of TS should be based on a combination of physical features and chromosomal analysis (karyotype).

Although the prenatal detection of sex chromosome abnormalities is possible clinically, <10% of live patients with TS are diagnosed prenatally[9] because of a high spontaneous miscarriage rate of fetuses with TS during the first and second trimesters of pregnancy. For cases diagnosed postnatally, 15% are made at birth, 21% during childhood, 26% during the teenage years, and 38% during adulthood.[10]

The management of TS combines ongoing assessment and periodic review of specific problems at appropriate ages (Table 3). Several guidelines[7,9,11] are available. Girls with TS are treated with recombinant human growth hormone (rhGH) alone or with rhGH and estrogen or oxandrolone.[12] When estrogen therapy is needed to induce pubertal development, the form, dosing, and timing need to reflect the process of normal puberty.[11] Over the long term, a girl with TS needs multidisciplinary care for her multiple problems, such as growth, cardiovascular, ophthalmologic, and otologic issues. Experts also increasingly suggest[12] educational and behavioural interventions for girls with TS because of the potential for poor self-esteem and behavioural and social problems.

1.2 Overview of Technology

rhGH is a polypeptide consisting of 191 amino acid residues. Its structure is identical to that of growth hormone extracted from human pituitary glands. It is produced by recombinant DNA technology and has been available since the 1980s. Before the 1980s, human growth hormone (hGH) was derived from cadaveric pituitary glands, and its scarcity restricted its widespread use.[13] Since rhGH has become available, it has been widely prescribed for several indications,[14] including growth hormone deficiency (GHD), TS, chronic renal failure, birth weight that is small for gestational age, Prader-Willi syndrome, idiopathic short stature, and wasting syndrome associated with the human immunodeficiency virus (HIV) in adults.

Table 1: Phenotypic features of TS in childhood and adolescence[5]

Feature	Frequency (%)
Short stature	88 to 100
Ovarian failure	87 to 96
Skeletal abnormalities	
- abnormal upper-lower segment	90
- high arch palate	35 to 84
- increased carrying angles	27 to 82
- short fourth or fifth metacarpals	35 to 77
- broad chest	33 to 75
- micrognathia	60
- kyphoscoliosis	12 to 16
- Madelung's deformity	7
Lymphatic abnormalities	
- nail convexity or dysplasia	43 to 83
- low posterior hairline	40 to 80
- neck webbing	23 to 65
- lymphedema	21 to 47
Nevi	22 to 78
Recurrent middle ear infections	60
Hearing problems	50(?)
Congenital cardiac problems	
- bicuspid aortic valve	30 to 50
- coarctation of aorta	30
- aortic root dilation	5 (approximately)
Endocrine abnormalities	
- glucose intolerance	34
- thyroiditis	10 to 30
Renal abnormalities	30

TS=Turner syndrome

rhGH is usually administered subcutaneously at doses between 0.3 and 0.375 mg/kg/week[11,15] for patients with TS. The dose can be adapted according to the patient's growth response. The optimal age for the start of rhGH therapy has not been established.[11] rhGH is generally prescribed for several years – from the diagnosis of the growth deficit until growth is complete.[15] Compared with patients who have GHD, girls with TS have growth deficiency caused by genetic factors instead of growth hormone deficiency. Therefore, girls with TS need a higher dose of rhGH hormone to accelerate their growth rate. rhGH is injected subcutaneously at night using a syringe or a pen injector device. Monitoring every four to six months is recommended for height velocity assessment, compliance assessment, and rhGH dose adjustment. rhGH is discontinued when a final adult height is achieved (as assessed by epiphyseal closure, bone age, and slowdown in linear growth) or if the patient elects to discontinue the medication sooner.

Health Canada has approved four forms of rhGH: Humatrope (Lilly) in 1996, Saizen (Serono) in 1996, Nutropin (Roche) in 1996, and Serostim (Serono) in 1998.[16] Their generic name is somatropin. The first three are indicated for use in TS and are available on the market in various dosage forms, compositions, packages, and prices (Table 4).

The formulary status of the products varies between provinces and programs (Appendix 1). For example, Humatrope (DIN 2243079) is not listed in the Saskatchewan, Alberta, Newfoundland and Labrador, or Ontario drug plans, but has received restricted benefit status in Nova Scotia and British Columbia. Humatrope (DIN 2243079) is given limited benefit status in the Manitoba Employment & Income Assistance Program and Pharmacare, while it has full benefit status in the Manitoba Personal Home Care/Nursing Homes and Manitoba Palliative Care programs. This information is what was available to us and may not be exhaustive. Though rhGH may not be listed in the provincial formulary, it may be covered through special programs.

Table 2: Height (mean and SD) at different ages of patients with TS[6]

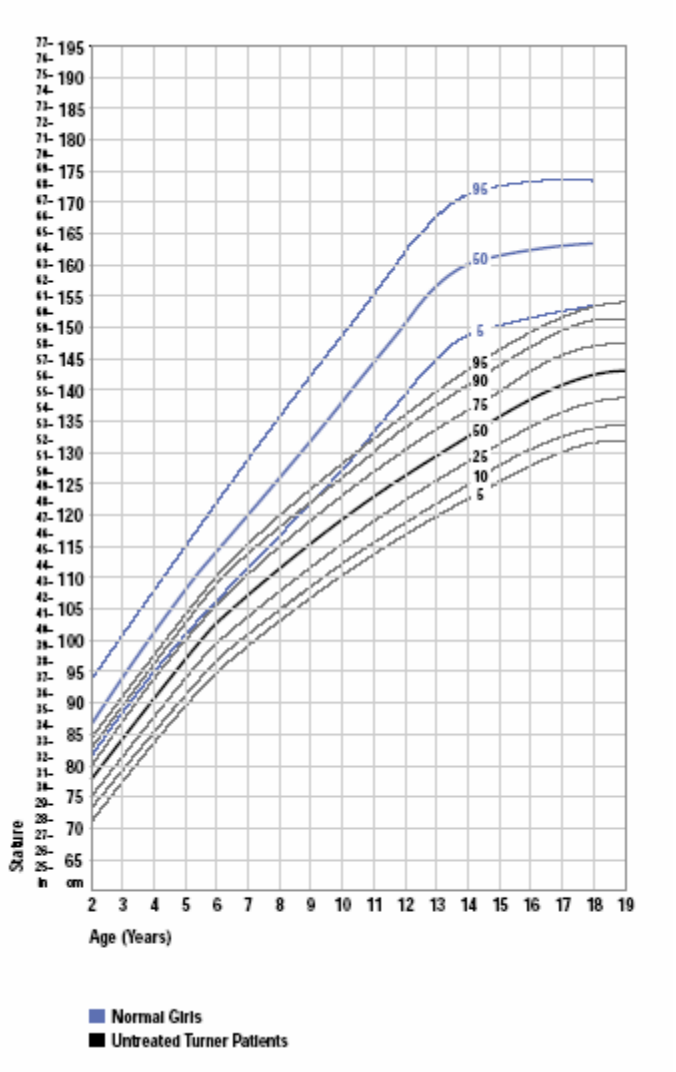
Age (years)	Number of Patients with TS	Height (cm)	
		Mean	SD
1	81	63.8	6.8
2	52	77.5	3.5
3	64	84.2	4.7
4	58	91.1	5.5
5	66	96.5	5.0
6	79	103.1	6.4
7	77	106.0	5.0
8	83	111.4	6.6
9	97	115.0	5.7
10	93	119.5	6.4
11	84	122.8	6.2
12	105	126.5	5.9
13	85	130.7	5.8
14	85	132.6	5.9
15	84	135.8	5.7
16	84	138.6	5.4
17	52	140.6	6.0
18	26	143.4	6.3
19	24	143.2	6.1
20+	138	142.9	7.3

SD=standard deviation; TS=Turner syndrome

Also, reimbursement criteria (Appendix 2) for girls with TS receiving rhGH therapy differ between provinces. Nova Scotia, New Brunswick, Manitoba, and Newfoundland and Labrador state that the provincial drug plan covers rhGH for patients with TS whose epiphyses are not closed, but some provinces do not cover rhGH therapy for patients with TS (e.g., Alberta, British Columbia, Saskatchewan). Canadian patients with TS on rhGH therapy pay for the therapy through a combination of a provincial health plan, private insurance, and compassionate coverage provided by manufacturers.

Other countries also use rhGH for the treatment of TS. A prescription survey in 1998 showed that approximately 390 girls with TS were being treated with rhGH in England and Wales.[17]

Figure 1: Growth of patients with TS[7]



TS=Turner syndrome
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rhGH treatment is expensive. The quoted price of Humatrope (6 mg/vial), one of the available somatropins in the Alberta Health and Wellness Drug Benefit Listing, is C$301.02 (i.e., C$50.17/mg). Given that its dose is weight-based (e.g., 0.3 mg/kg/week), rhGH treatment would cost C$14,088 per year for a five-year-old girl to C$32,871 per year for a 12-year-old girl. The underlying assumed weights for the five-year-old and 12-year-old girls are 18 kg and 42 kg respectively, according to the Centers for Disease Control and Prevention (CDC) growth charts.[18]

Table 3: Evaluation recommended for patients with TS[7]

	Early Childhood (1 to 5 years)	Late Childhood (5 to 13 years)	Adolescence (13 to 21 years)
Medical Evaluation			
growth failure	TBP	TBP	TBP
lymphedema	TBP		TBP
hypertension or coarctation	TBP	TBP	TBP
hearing loss	S	S	S
strabismus	O	S	S
malocclusion	TBP	TBP	TBP
thyroid dysfunction	TBP	TBP	TBP
scoliosis or kyphosis	O	O	O
pubertal delay	TBP	TBP	TBP
nevi		TBP	TBP
Psychosocial Evaluation			
development and behaviour	TBP	TBP	TBP
school performance	TBP	TBP	TBP
socialization	TBP	TBP	TBP
sexual issues		TBP	TBP

O=objective by a standard testing method; S=subjective by history; TBP=to be performed

Table 4: Available rhGH products in Canada* and price†

Name	DIN	Strength/Concentration	C$/mg
Humatrope	02243077	somatropin 6 mg + diluent 3.15 mL	46.67
Humatrope INJ	00745626	somatropin 1 mg/mL	46.67
Humatrope	02243079	somatropin 24 mg + diluent 3.15 mL	46.67
Humatrope	02243078	somatropin 12 mg + diluent 3.15 mL	46.67
Saizen	02272083	somatropin 5.83 mg/mL or 8.8 mg/vial	39.55
Saizen	02237971	somatropin 5 mg/kit + water 10 mL/kit	43.50
Saizen	02215136	somatropin 3.3 mg/kit + sodium chloride 5 mL/kit	43.51
Nutropin	02249002	somatropin 10 mg/2 mL	38.18
Nutropin	02229722	somatropin 5 mg/mL	38.18
Nutropin	02216191	somatropin 10 mg/vial + water 10 mL/vial	38.18
Nutropin	02216183	somatropin 5 mg/vial + water 10 mL/vial	38.18
Serostim	02239046	somatropin 5 mg/kit + water 1 mL/kit	46.66
Serostim	02239047	somatropin 6 mg/kit + water 1 mL/kit	—

DIN=drug identification number; rhGH=recombinant human growth hormone
*Data source: Drug Product Database[19]
†Calculated based on net price to wholesalers according to *PPS Pharma Buyers Guide*[20]

2 THE ISSUE

Given the high cost of rhGH treatment and the evolving evidence base for its clinical effect in patients with TS, health policy makers are seeking evidence to adjust or substantiate the reimbursement decisions regarding rhGH therapy. Therefore, an evaluation of rhGH treatment in patients with TS is warranted.

3 OBJECTIVES

This report aims to assess the clinical effectiveness and cost-effectiveness of rhGH therapy for TS.

- Compared to no therapy, what is the clinical effect of rhGH for treatment of the short stature associated with TS?
  - What is the effect of rhGH therapy on growth outcomes?
  - What are the adverse events (AEs) (short- and long-term) associated with rhGH therapy?
  - What is the effect of rhGH therapy on quality of life (QoL)?
- What is the cost-effectiveness of rhGH in the Canadian context for treatment of the short stature associated with TS?
- What is the budget impact of publicly reimbursing rhGH treatment for children with TS?

4 CLINICAL REVIEW

4.1 Methods

A protocol for the systematic review was written a priori.

4.1.1 Literature search strategy

Systematic literature searches were conducted for the clinical review. All search strategies were developed by the Information Specialist with input from the project team. They underwent an internal peer review by a second CADTH Information Specialist.

The following bibliographic databases were searched through the Ovid interface: Medline (1950 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), BIOSIS Previews (1985 to 1989 and 1989 to present), CINAHL (1982 to present), and PsycINFO (1967 to present). Parallel searches were run in the Cochrane Library. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords focusing on the concepts of Turner syndrome, and recombinant human growth hormone and its brand names. Methodological filters were applied to limit retrieval to clinical controlled trials, comparative studies, observational studies, meta-analyses, and systematic reviews (Appendix 3). Results were limited to publications from 1980 onwards, because rhGH (as opposed to pituitary growth hormone) has been available since 1985. There were no language restrictions. Ovid AutoAlerts were set up to send monthly updates with any new literature. Monthly updates were performed on Cochrane Library databases.

Grey literature (literature that is not commercially published) was identified by searching the web sites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional materials and information. These searches were supplemented by manually searching the bibliographies and abstracts of key papers and conference proceedings, and through contacts with appropriate experts and agencies. Manufacturers were also contacted.

In addition to the literature searches for the clinical review and economic review, a supplemental search was done to find information (e.g., QALY data) for the primary economic analysis (Appendix 3).

4.1.2 Selection criteria and method

Studies were selected for inclusion if they satisfied the criteria described below.

a) Selection criteria

- Study design: randomized controlled trial or comparative observational study
- Population: females diagnosed with TS
- Intervention: rhGH
- Comparator: placebo or no treatment
- Outcome: growth (final height, interim height, growth velocity), AEs, and QoL

Studies having <20 patients or rhGH treatment <1 year were not considered, because small studies or short-term studies are unlikely to provide robust results.

b) Selection method

Two reviewers (SB, LD) independently selected trials for inclusion. Citations downloaded in Reference Manager 11 (bibliographic software) were exported into Microsoft Excel (spreadsheet software) to document the trial selection process. Differences in decisions between reviewers were compared and resolved by discussion and consensus. For trials with multiple publications, only relevant reports were selected.

4.1.3 Data extraction strategy

Two reviewers (SB, LD) independently extracted data from each included study. Data extraction was based on a structured form (Appendix 4). Data were inserted into the appropriate tables and compared. Differences between reviewers were resolved by consensus.

4.1.4 Strategy for quality assessment

The quality of the included RCTs and comparative observational studies was evaluated by two reviewers using a scoring procedure based on the scales of Jadad *et al.*[21] and Hailey *et al.*[22] (Appendix 5).

4.1.5 Data analysis methods

Data were analyzed and Forest plots generated using the Cochrane software Review Manager 4.2.3. Computations were performed using the fixed effects and random effects model. Wherever possible, summary estimates were computed. Weighted mean difference (WMD) was used for pooling

outcomes expressed as continuous data, and heterogeneity among studies was determined by the Higgins I^2 test.[23] If heterogeneity was greater than moderate (I^2 >50%), the results were not pooled to derive summary estimates.

4.2 Results

4.2.1 Quantity of research available

The flow chart (Figure 2) shows the study selection process. A total of 527 citations were identified from the original literature search, based on the selection criteria. From these, 81 potentially relevant reports were retrieved for scrutiny. Fifty-three were excluded, and 28 were selected for final scrutiny. From these, 18 were selected for inclusion. One study that was identified from another source (Cochrane review[15]) was also included. Thus, 19 reports were selected for inclusion. These comprised 10 reports describing six RCTs and nine reports describing nine comparative observational studies. Of the 10 RCT reports, one was a review by Quigley *et al*.,[24] which contained relevant data for two RCTs (the Canadian RCT[25] and the RCT by Quigley *et al*.[26])

4.2.2 Study characteristics

The characteristics of the six RCTs comparing rhGH treatment with no rhGH treatment in patients with TS are provided in Appendix 6. Of the six RCTs, three[25-27] mentioned industry sponsorship, and three[28-30] did not mention sponsorship. One RCT was conducted in Canada,[25] three in the US,[26,29,30] one in the UK,[27] and one in Germany.[28] Five RCTs[25-29] were multi-centre trials, and one[30] did not mention the number of centres. The number of patients ranged between 40 and 232, and the treatment duration ranged between one to seven years.

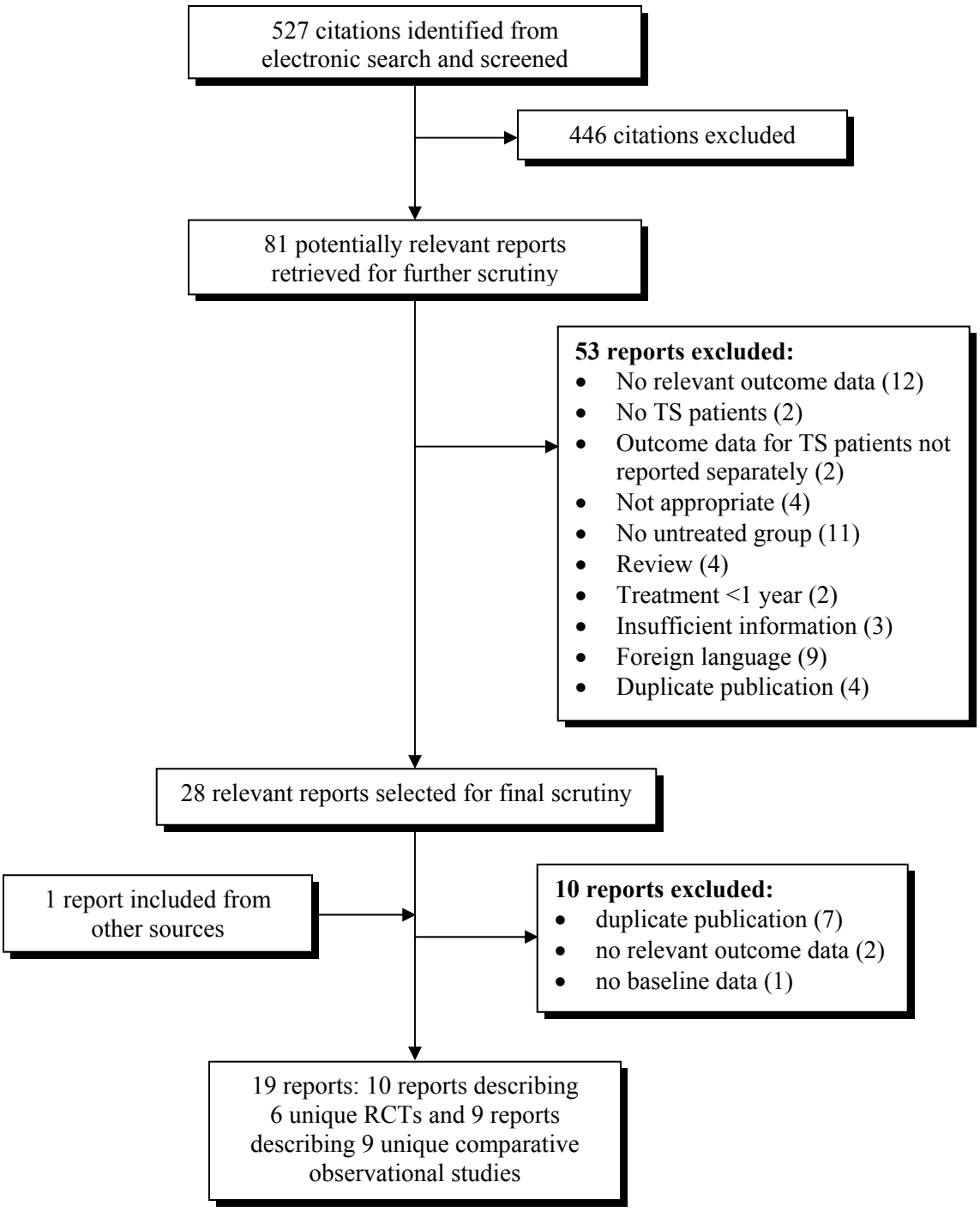
The characteristics of patients in the RCTs are provided in Appendix 7. The mean age of patients in the RCTs at baseline ranged between 8.9 and 10.9 years. The bone age and height were reported in five RCTs[25-28,31] and ranged from 7.2 to 8.9 years and 114 to 122 cm respectively. The karyotype (45,X) of the patients was reported in four RCTs.[25,28,30,31] The percentage of patients having the 45,X karyotype varied between 55% and 95%.

A modified scale (combination of Jadad and Hailey scales) was used to assess the reporting quality of RCTs. The total score for this combination scale was 15. Two RCTs[25,26] were of high quality (scores 11.5 to 12.5), three RCTs[27-29] were of good quality (scores 9.5 to 11), and one RCT[30] was of fair quality (score 7.5).

The characteristics of the nine comparative observational studies comparing rhGH treatment with no rhGH treatment in patients with TS are provided in Appendix 8. Four[32-35] were prospective studies, and five[36-40] were retrospective studies. Two studies[32,39] mentioned that the rhGH used for treatment was donated by industry; the remaining seven studies did not mention sponsorship.

One study was conducted in Canada,[40] one in the US,[36] one in Denmark and Iceland,[33] one in Germany,[37] one in Greece,[39] three in Italy,[34,35,38] and one in Israel.[32] The number of patients ranged between 26 and 123, and the treatment duration ranged between two and eight years.

Figure 2: Selection of clinical trials



RCT=randomized controlled trial; TS=Turner syndrome

The characteristics of patients in the comparative observational studies are provided in Appendix 9. The mean age of patients in the comparative observational studies ranged between 10.2 and 21.7 years.

A modifed scale (combination of Jadad and Hailey scales) was also used to assess the reporting quality of the comparative observational studies. One study[32] was of good quality (score 10), six[33-36,39,40] of fair quality (score 8 to 9), and two[37,38] of poor quality (score 6 to 7).

4.2.3 Data analyses and synthesis

RCTs and comparative observational studies were pooled separately. Not all trials or studies could be included in the meta-analysis because of the incomplete reporting of data. For continuous data, trials and studies could be pooled if they reported standard deviation (SD) values or contained enough data to enable SD to be calculated.

a) *Growth and height*

Different investigators assessed growth using different variables [e.g., final height (FH), height standard deviation score (HSDS), change in HSDS (ΔHSDS), growth velocity (GV), growth velocity SDS (GVSDS)].

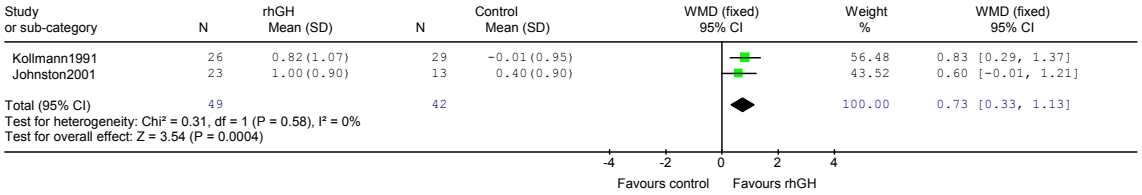
RCTs

Five[25-29,41] of the six RCTs reported growth-related data (Appendix 10). Long-term (mean ± SD = 5.7 ± 1.6 years after randomization) data were available from the Canadian RCT.[25] In this RCT, patients receiving rhGH treatment had a significantly higher growth compared to patients not treated with rhGH. The mean differences (MDs) and 95% confidence intervals (CIs) were 6.50 cm (4.28, 8.72) for final height, 1.00 (0.67, 1.33) for HSDS, and 1.30 (1.11, 1.49) for ΔHSDS. The mean final height in patients treated with rhGH was 147.5 cm. Johnston *et al*.[27] and Kollmann *et al*.[28] showed that ΔHSDS was greater for patients treated with rhGH for one year compared with patients who did not receive rhGH (Figure 3). The WMD (95% CI) on pooling these two RCTs was 0.73 (0.33, 1.13), indicating better growth with rhGH treatment.

GV and GVSDS were higher for patients treated with rhGH compared with patients not receiving rhGH (Tables 5 and 6, Figures 4 and 5), hence favouring rhGH. Rosenfeld *et al*.[29] showed that the GV and GVSDS were higher if the treatment regimen included the addition of oxandrolone. The GV in this trial (expressed as mean ± SD) was 6.60 ± 1.20 for rhGH alone, 9.80 ± 1.40 for rhGH in combination with oxandrolone, 3.8 ± 1.1 for no rhGH, and 7.6 ± 1.5 for oxandrolone alone. Quigley *et al*.[26] investigated two rhGH doses but found no difference in GV. The GV (expressed as mean ± SD) was 6.60 ± 1.10 for rhGH (0.27 mg/kg/week) and 6.80 ± 1.10 for rhGH (0.36 mg/kg/week). The Canadian study[25] showed that GV was higher in the group treated with rhGH than in the group not receiving rhGH for the first and second years of treatment, but that the difference was greater in the first year. The corresponding MD (95% CI) were 3.80 (3.29, 4.31) and 1.80 (1.27, 2.33) for the first and second years respectively. GVSDS showed a similar trend, and the corresponding MD (95% CI) were 3.20 (2.65, 3.75) and 1.60 (1.02, 2.18) for the first and second years respectively.

Overall, the RCTs show that rhGH treatment accelerates growth and results in improvement in height.

Figure 3: Comparison of rhGH treatment versus no rhGH treatment with respect to ΔHSDS



ΔHSDS=change in height standard deviation score; RCT=randomized controlled trial; rhGH=recombinant human growth hormone; SD=standard deviation; WMD=weighted mean difference

Table 5: MD in GV determined from RCTs comparing rhGH treatment versus no rhGH treatment

Trial	Number of Patients	Patient Groups	Observation Period (years)	MD (95% CI)
Canadian[41]	86	All groups	1	3.8 (3.29, 4.31)
Canadian[41]	69	All groups	2	1.80 (1.27, 2.33)
Quigley[26]	90	rhGH 0.27 mg/kg/week group and control	1	2.40 (1.93, 2.87)
Quigley[26]	86	rhGH 0.36 mg/kg/week group and control	1	2.60 (2.14, 3.06)
Rosenfeld[29]	35	Groups receiving oxandrolone	1	2.20 (1.24, 3.16)
Rosenfeld[29]	35	Groups not receiving oxandrolone	1	2.80 (2.04, 3.56)

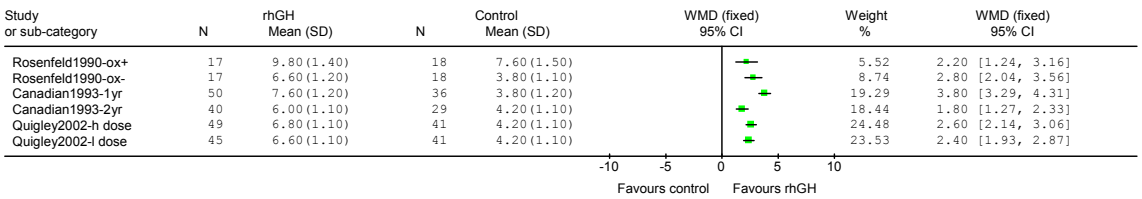
CI=confidence interval; GV=growth velocity; MD=mean difference; RCT=randomized controlled trial; rhGH=recombinant human growth hormone

Table 6: MD in GVSDS from RCTs comparing rhGH treatment versus no rhGH treatment

Trial	Number of patients	Patient groups	Observation period (years)	MD (95% CI)
Canadian[41]	86	all groups	1	3.2 (2.65, 3.75)
Canadian[41]	69	all groups	2	1.60 (1.02, 2.18)
Rosenfeld[29]	35	groups receiving oxandrolone	1	2.20 (1.19, 3.21)
Rosenfeld[29]	35	groups not receiving oxandrolone	1	3.20 (2.47, 3.93)

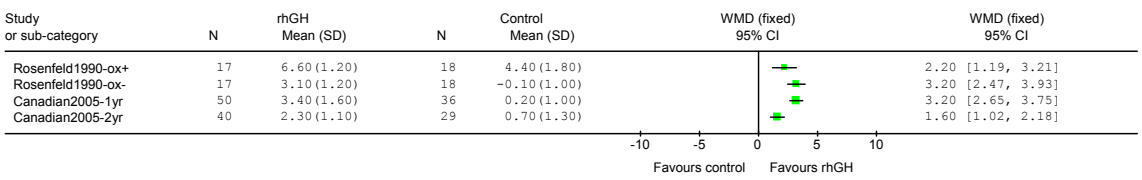
CI=confidence interval; GVSDS=growth velocity standard deviation score; MD=mean difference; RCT=randomized controlled trial; rhGH=recombinant human growth hormone

Figure 4: Comparison of rhGH treatment versus no rhGH treatment with respect to GV



CI=confidence interval; GV=growth velocity; RCT=randomized controlled trial; rhGH=recombinant human growth hormone; SD=standard deviation; WMD=weighted mean difference

Figure 5: Comparison of rhGH treatment versus no rhGH treatment with respect to GVSDS



CI=confidence interval; GVSDS=growth velocity standard deviation score; RCT=randomized controlled trial; rhGH=recombinant human growth hormone; SD=standard deviation; WMD=weighted mean difference

Comparative observational studies

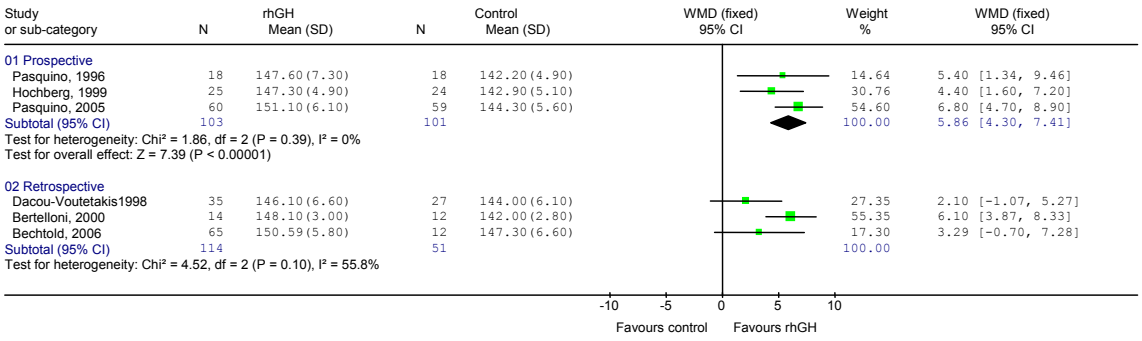
Seven[32-35,37-39] of the nine comparative observational studies reported growth-related data (Appendix 11). Of these seven studies, four were prospective and three were retrospective.

Three prospective studies[32,34,35] showed that the final height was significantly higher in rhGH-treated patients compared with patients not receiving rhGH (Figure 6). When these studies were pooled, the WMD (95% CI) was 5.86 (4.30, 7.41), favouring rhGH treatment. Three retrospective studies[37-39] also showed that the final height was higher in the rhGH-treated patients compared with patients not receiving rhGH (Figure 6). The difference was statistically significant in one study but not in the other two. There was heterogeneity (I^2 = 55.8%) among these studies, so they were not pooled.

Two prospective studies[34,35] showed that the HSDS was significantly higher in the rhGH-treated patients compared to patients not receiving rhGH (Figure 7). When these studies were pooled, the WMD (95% CI) was 1.08 (0.78, 1.38), favouring rhGH treatment.

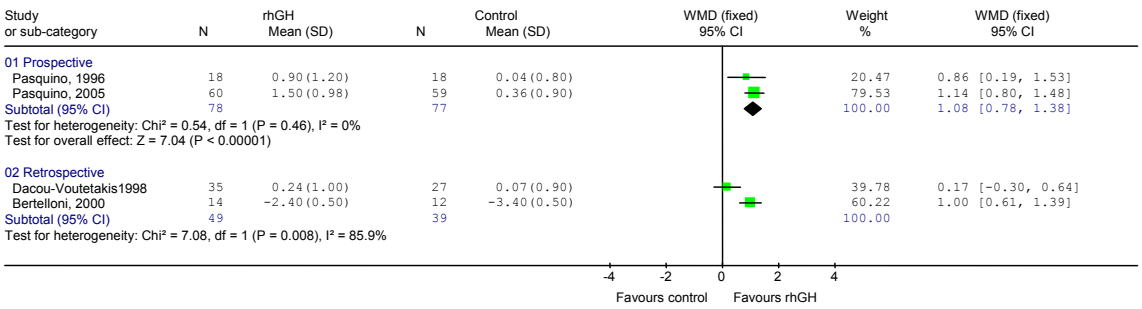
Two retrospective studies[38,39] also showed that the HSDS was higher in the rhGH treated patients compared to patients not receiving rhGH (Figure 7). The difference was statistically significant in one study but not in the other. The heterogeneity was high (I^2 = 85.9%) among these studies, so they were not pooled.

Figure 6: Comparison of rhGH treatment versus no rhGH treatment with respect to FH



CI=confidence interval; FH=final height; RCT=randomized controlled trial; rhGH=recombinant human growth hormone; SD=standard deviation; WMD=weighted mean difference

Figure 7: Comparison of rhGH treatment versus no rhGH treatment with respect to HSDS



CI=confidence interval; HSDS=height standard deviation score; RCT=randomized controlled trial; rhGH=recombinant human growth hormone; SD=standard deviation; WMD=weighted mean difference

Table 7: Mean difference in GVSDS with rhGH treatment versus no treatment in Dacou-Voutetakis *et al*.'s study[39]

Number of Patients	Patient Group	Observation Period (years)	MD (95% CI)
123	All	1	2.46 (1.87, 3.05)
123	All	2	2.51 (1.83, 3.19)
62	Patients who attained final height	1	2.23 (1.50, 2.96)
62	Patients who attained final height	2	1.93 (1.12, 2.74)

CI=confidence interval; GVSDS=growth velocity standard deviation score

Naeraa *et al*.[33] showed that there was no difference in growth velocity [MD (95% CI) = 0.00 (−1.50, 1.50). Dacou-Voutetakis *et al*.,[39] however, showed that GVSDS was higher in patients treated with rhGH compared to patients not treated with rhGH (Table 7).

The comparative observational studies show that overall rhGH treatment results in improvement in height.

b) *Quality of life*

QoL data were available from two RCTs.[30,42] No QoL data were available in the comparative observational studies.

Rovet *et al*.[42] evaluated the psychological aspects of subsets of patients from both groups of the Canadian RCT who had not started estrogen therapy. Results were available for 48 (49%) of the original 122 patients enrolled (Table 8). Values are based on the patient's perception or that of her mother. For most of the psychological aspects evaluated in this study, patients in the rhGH group seemed to do better than those not treated with rhGH.

Parental ratings of school performance indicated a decrease in mathematics performance with time in the treated group compared with the control group. This was based on significant group-by-session interaction ($p<0.01$) and not on mathematics performance tests.[42] Results reported by Rovet *et al*. come from an interim analysis and are based on a subset of patients enrolled in the trial, so the results should be viewed with caution.

Table 8: Psychological evaluation of subsets of patients from Canadian RCT[42] to compare rhGH-treated group with control group			
Category	**rhGH group (n=28)**	**Control Group (n=20)**	***P*-value**
Self-concept			
global*	76.5 ± 18.9	64.4 ± 21.7	0.001
appearance*	67.0 ± 24.5	55.7 ± 24.9	0.08
intelligence*	75.0 ± 23.8	56.2 ± 25.2	0.01
peer relations*	66.4 ± 27.4	32.4 ± 25.6	0.001
Social variables			
friendship†‡	3.15 ± 0.6	2.72 ± 0.83	0.05
popularity†‡	66.4 ± 27.4	32.4 ± 25.6	0.001
teasing**	0.69 ± 0.55	1.05 ± 0.61	0.05
Behavioural variables			
hyperactivity‡	59.6 ± 7.6	65.2 ± 8.0	0.05
Family variables			
protectiveness‡	1.10 ± 1.31	0.63 ± 0.9	0.1

RCT=randomized controlled trial; rhGH=recombinant human growth hormone
*Score by patient
†Scoring is a rating (not that of friends)
‡Score by mother
**Score in clinical range

Ross *et al*.[30] evaluated a large sample of patients from those enrolled in their placebo-controlled trial for cognitive function. They found no difference in general cognitive function [intelligence, Wechsler Intelligence Scale for Children-Revised (WISC-R) subtests and academic domains] in the rhGH-treated and control groups. Verbal ability (domains of verbal memory, language reception, and expression) were similar in both groups. Non-verbal abilities (domains of spatial memory, spatial perception, visual-motor function, attention, and aural affect recognition) were also similar in the two groups, except in one measure of memory (delayed recall of the Rey Complex), in which the rhGH-treated group performed better than the non-rhGH group.

Overall the QoL data are sparse, and it is difficult to make definitive conclusions as to whether QoL is improved in those treated with rhGH compared with those not treated

c) *AEs*

Not all studies reported AEs. Some studies reported AEs but did not report them separately for the different treatment arms, and so are excluded in this section.

RCTs

AE data reported in the Canadian RCT[25] are shown in Table 9. In the Canadian RCT,[25] for the 138 patients for whom post-baseline data were available, there were significantly higher rates of treatment-emergent AEs (surgical procedure, otitis media, ear disorder, joint disorder, respiratory disorder, and sinusitis) in patients in the rhGH group compared with patients in the control group (not treated with rhGH).

No mortality was reported in the rhGH group; one patient in the control group died because of a ruptured aortic aneurysm.

Table 9: AEs reported in Canadian RCT[25]				
Study	**Event**	**Patients Experiencing Event***		***P*-value**
		rhGH group (n=74)	**no rhGH group (n=64)**	
Canadian Growth Hormone Advisory Group, Stephure,[25] Quigley[24]	Surgical procedure	37	17	0.005
	Otitis media	35	17	0.014
	Ear disorder	15	4	0.024
	Joint disorder	10	2	0.036
	Respiratory disorder	8	1	0.037
	Sinusitis	14	4	0.041
	Goiter	0	4	0.044
	Death	NR	1 (due to ruptured aortic aneurysm)	NR
	Serious AEs†	27%	13%	NR

NR=not reported; RCT=randomized controlled trial; rhGH=recombinant human growth hormone
*Unless otherwise indicated, values represent number of patients.
†Serious AEs in the Canadian RCT were reported in Quigley's review,[24] which reported that 136 patients were in safety analysis, and 74 were treated with rhGH.

In Quigley *et al.*'s RCT[26] there were no deaths and no reports of cancer or neoplasia for any of the treatment arms during the study period (which consisted of an 18-month placebo-controlled phase). The authors reported that edema, hypothyroidism, and cardiovascular disorder occurred rarely and with equal frequency in the rhGH and placebo groups. Also, ear pain and ear disorders were similar in frequency between the two groups, but otitis media occurred or worsened to a greater extent in those receiving rhGH (29% versus 13%, $P = 0.037$).

No disorders occurred significantly more often in patients receiving the higher dose of rhGH. Quigley *et al.*[24] also reported serious AEs in 5% of the patients treated with rhGH. They did not mention serious AEs in patients not receiving rhGH.

Rosenfeld *et al.*[31] reported that AEs in patients receiving rhGH alone were few. Two such patients developed transient edema, one developed acne, and one noted increased weight.

Comparative observational studies

Five[32,33,35,36,40] comparative observational studies reported AEs. Bakalov *et al.*[36] did not find any difference in the prevalence and incidence of fracture between the two groups (Table 10).

Table 10: AEs reported in comparative observational studies				
Study	**Event**	**rhGH group (n=23)**	**no rhGH group (n=23)**	***P*-value**
Bakalov[36]	fracture prevalence (n, %)	7 (30%)	5 (22%)	0.75
	fracture incidence (per 100 TS patient years)	2.2	1.0	0.13

rhGH=recombinant human growth hormone; TS=Turner syndrome

Naeraa *et al.*,[33] Pasquino *et al.*,[35] and Taback *et al.*[40] did not provide quantitative data but reported that there were no serious side effects observed during growth hormone treatment. Hochberg *et al.*[32] reported that rhGH therapy was well tolerated, with no apparent AEs.

4.3 Discussion

This systematic review includes six RCTs and nine comparative observational studies, which compared rhGH therapy with no rhGH therapy in patients with TS. The available results from RCTs and comparative observational studies suggest that rhGH is effective in improving growth velocity and final height. The Canadian study was long-term (mean follow-up of 5.7 years) and showed that final height was 6.5 cm greater in patients treated with rhGH compared with those who did not receive rhGH. The treated patients had a mean final height of 147.5 cm. When pooled, three prospective observational studies also showed that the final height was approximately 5.9 cm greater in the patients treated with rhGH compared with those who did not receive rhGH. There has been no research identifying individual patient's characteristics that could serve as predictors of treatment response, so no subgroups have been identified that would allow for treatment to be targeted to those most likely to achieve a response.

QoL data were sparsely reported, variable, and inconclusive. In a small subset of patients from the Canadian RCT,[42] it was found that with respect to psychological issues, those treated with rhGH seemed to fare better than those not receiving rhGH. This was based on an interim analysis in a subset of patients, so this finding should be viewed with caution. Ross *et al*.[30] found no difference in cognitive function or verbal or non-verbal abilities between the rhGH-treated and untreated groups. One may think that an increase in height is likely to improve a patient's QoL, for example in the case of a patient with TS who, because of short stature, would need to have a car modified to reach the pedals. Evidence in support of this, however, is equivocal.

AEs data were also sparsely reported. The Canadian RCT[25] showed significantly higher rates of treatment-emergent AEs in the rhGH group compared with the group not receiving rhGH. The statistical significance of the side effects seen in this RCT could be due to a detection bias, because the physicians were unblinded and could be more alert in monitoring side effects in the treated patients. In another RCT,[26] the rates of AEs were similar in both groups. In the comparative observational studies,[32,33,35,40] it was stated that there were no serious AEs observed during rhGH treatment.

This systematic review includes more studies than those included in a previously published systematic review[15] and a health technology assessment report,[17] because of the availability of newly published study data and the inclusion of comparative observational studies. Nevertheless, this systematic review corroborates the findings of the two reviews.

This systematic review and meta-analysis has limitations. Not all reports documented data on all the outcomes of interest. This can introduce bias. It has been shown that significant results are more likely to be reported than non-significant results.[43] Because of the incomplete reporting of data, not all RCTs or comparative observational studies could be included in the meta-analyses of all outcomes, thereby reducing power.

Nine studies published in languages other than English were identified from the literature search but were excluded from the review, because translations would have been resource-intensive. On the other hand, for any individual systematic review, the importance of the non-English literature is difficult to predict, so there exists a possibility of language bias. The exclusion of these studies, however, may not be an issue. It has been reported that for conventional therapy, the exclusion of

trials published in languages other than English has generally little effect on summary treatment effect estimates.[44-46]

During the selection of relevant trials, we found that there were multiple publications for some studies. This trend of duplicate reporting can lead to biased results. For example, it has been reported that the inclusion of duplicated data in a meta-analysis of ondansetron led to a 23% overestimation of its anti-emetic efficacy.[47] As far as possible we have excluded duplicate publications of the same trial.

The number of patients who withdraw is of concern. In one RCT,[25] almost one-third of the patients were lost to follow-up. Many of the RCTs did not report on withdrawal, so it is unknown how many patients withdrew. It is likely that those with poor response did not continue; this could lead to biased results.

There were restrictions as to which patients were eligible to participate in trials (Appendix 12, 13). Hence, the results may not be generalizable to all patients with TS.

The height gain in patients with TS is variable, and its clinical significance is a matter of debate.[48] There is no conclusive evidence as to whether rhGH treatment improves QoL and if an increase in height correlates with improved QoL.

5 ECONOMIC REVIEW

5.1 Methods

A protocol for the review was written a priori. There was one change: external validity was not evaluated with the checklist proposed in the protocol. Instead, associated issues in the text were discussed, because this seemed to be more appropriate. It was thought that discussions of the issues would provide more information than responses (yes, no, or partial) to the four questions on the checklist.

5.1.1 Literature search strategy

Literature searches were conducted for the economic evaluation. All search strategies were developed by the Information Specialist with input from the project team. They underwent an internal peer review by another CADTH Information Specialist.

The following bibliographic databases were searched through the Ovid interface: Medline (1950 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), BIOSIS Previews (1985 to 1989 and 1989 to present), CINAHL (1982 to present). Parallel searches were run in the Health Economic Evaluations Database (HEED) and the Cochrane Library. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords focusing on the concepts of Turner syndrome, and recombinant human growth hormone and its brand names. Methodological filters were applied to limit retrieval to cost analyses, QoL studies, or economic studies (Appendix 3). Results were limited to publications from 1980 onwards, because rhGH (as opposed to pituitary growth hormone) has been available since 1985. There were no language restrictions. OVID AutoAlerts were set up to send monthly

updates with any new literature. Monthly updates were performed on HEED and Cochrane Library databases.

Grey literature (literature that is not commercially published) was identified by searching the web sites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional materials and information. These searches were supplemented by hand searching the bibliographies and abstracts of key papers and conference proceedings, and through contacts with appropriate experts and agencies. Manufacturers were also contacted.

5.1.2 Selection criteria and method

For the economic review, studies were eligible for inclusion only if they satisfied all the selection criteria.

a) Selection criteria

- Study design: full (e.g., cost minimization, cost effectiveness, cost utility, or cost benefit analysis) or partial (e.g. cost analysis, cost comparison, or cost consequence analysis) economic study
- Population: females diagnosed with TS
- Intervention: rhGH
- Comparator: placebo or no treatment
- Outcomes: cost of rhGH treatment, growth, increased QALYs, incremental cost per centimetre of height gained, incremental cost per QALY gained

b) Selection method

Two reviewers (HL, SB) independently selected abstracts according to the criteria. Articles were then procured for all relevant studies. Both reviewers reviewed the full text of articles, and disagreement was resolved by discussion and consensus.

5.1.3 Data extraction strategy

The first reviewer (HL) used a previously designed data extraction form (Appendix 14) to abstract information. The second reviewer (SB) examined the results, based on which a quality assessment was performed.

5.1.4 Strategy for assessing reporting quality of included studies

The reporting quality of identified full economic evaluations was assessed by two reviewers using the *BMJ* checklist.[49] Disagreements were discussed and settled by consensus. Assessment results were tabulated and support the critical appraisal of the included studies.

5.1.5 Data analysis methods

Qualitative appraisal was provided for each identified economic study.

5.2 Results

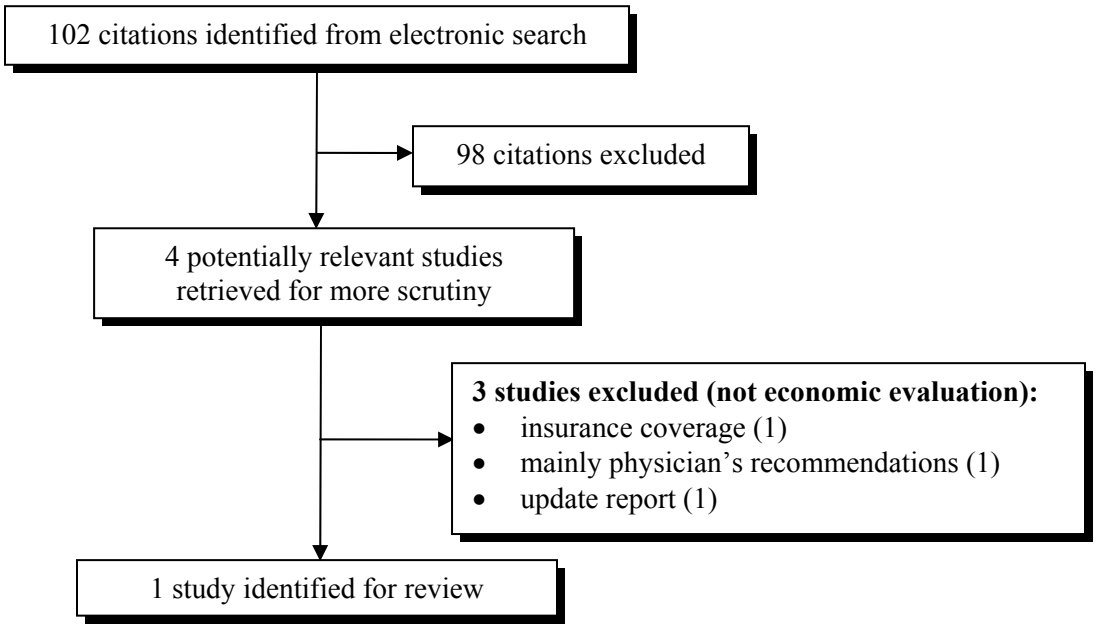
5.2.1 Quantity of research available

The flow chart (Figure 8) shows the study selection process. From 102 citations identified in the literature search, four relevant citations were identified according to the selection criteria established a priori, and full-text articles were ordered for more scrutiny. One study[17] satisfied all the criteria for the review.

5.2.2 Study characteristics

The included report[17] was published by the UK National Institute for Clinical Excellence (NICE). The study's characteristics are provided in Appendix 15. It separately examined the clinical and economic benefit of rhGH therapy for five indications, including growth hormone deficiency, TS, chronic renal failure, Prader-Willi syndrome, or idiopathic short stature. This review focused on the TS-related part, which was a model-based cost-effectiveness analysis from the perspective of the English and Welsh NHS and Personal Social Services sectors. The authors built a simple deterministic decision model with Excel 2000 software, comparing rhGH treatment with no treatment. The costs associated with health care were calculated, with previously derived treatment pathways. Epidemiological, cost, and treatment effectiveness data came from multiple secondary sources. The analytic time horizon was the duration of rhGH treatment (five years).

Figure 8: Selection of economic studies



5.2.3 Study results

The UK report assumed two base cases in terms of final height gained: base case 1 (4.8 cm) and base case 2 (4.4 cm). The corresponding incremental cost-effectiveness ratio (ICER) values were £15,997

(C$35,991 in 2000 Canadian dollars) or £17,429 (C$39,213) per centimetre for cases 1 and 2 respectively (Appendix 16).

A one-way analysis showed that the ICER value was sensitive to the input variables of the modelling. Quantitatively, it ranged from £4,690 (C$10,551) to £36,855 (C$82,919) per centimetre for base case 1 and £5,116 (C$11,510) to £40,205 (C$90,456) per centimetre for base case 2. The variables tested in the one-way sensitivity analysis included length of treatment (one year to 13 years), continuance of treatment (30% to 100%), incremental final height effect (70% to 300%), GH dose (0.175 mg/kg/week to 0.7 mg/kg/week), GH cost (£15.25 to £25.00), and annual rates of discounting for benefits (0% to 6%) and costs (0% to 12%).

A two-way sensitivity analysis was performed by varying two parameters simultaneously: rhGH dose with final height effect and duration of treatment with final height effect. Compared with the one-way analysis results, ICER variation was greater when the first pair of variables changed but less when the second pair changed. The investigators conducted additional sensitivity analyses but did not find any significant differences.

The UK report had high reporting quality according to the *BMJ* checklist (Appendix 17). It had satisfactory transparency.

5.3 Discussion

Despite a thorough search of the literature, only one economic evaluation was identified.[17] This study, which was done in a UK context, reported the value of rhGH treatment for patients with TS in terms of incremental cost per centimetre gained but did not perform a cost-utility analysis (CUA). Because QoL is an important outcome, a CUA would have provided more useful information.

The UK report indicated most of the data sources and assumptions, ensuring an adequate level of transparency. Results were presented in disaggregated and aggregated formats, and the overall reporting quality was satisfactory. The model constructed was for the purpose of computing total costs and final ICER values, so it had no complex mathematical inferences. Therefore, it was easy to determine the model's internal validity.

Nevertheless, there were several limitations to this study, and the results should be viewed with caution. First, the rhGH effectiveness was derived from two sources. One was the result of the Canadian RCT (obtained from an abstract),[50] while the other was an open, non-randomized trial.[32] Compared with our clinical review results (final height improvement of 6.5 cm), the two sources on which the UK report was based were conservative (reporting a final height improvement of 4.8 cm and 4.4 cm). As a result, the ICER estimations in the UK report were likely overestimated in this respect.

The UK technology appraisal guide[51] requires that the value of health effects be expressed in QALYs, but the UK study did not follow the guideline. The UK study noted the problems in generating QALY but did not conduct a CUA with QALY. On one hand, the authors demonstrated existing challenges, which could provide a starting point for further research. On the other hand, the results of their analysis may be difficult for policy decision makers to use because an estimation in the form of incremental cost per centimetre gained has little practical use in resource allocation decisions across different diseases.

Because neither rhGH treatment nor no treatment has an impact on mortality in patients with TS, the health-related quality of life becomes an important outcome. The issue is how well the two modalities affect the physical function, social function, and psychological well-being of girls with TS. Several studies[13,42,48,52-57] addressed this issue from various perspectives. One study conducted a multiple regression analysis to evaluate the QoL determinants in young women with TS after rhGH treatment.[53] Its authors reported that QoL (measured using the SF-36 questionnaire) was normal and unaffected by height. Although none of the available literature provided the QALY data that are needed for a CUA, overall there was no significant difference between treated and untreated short-stature children. The following questions still remain: Is short stature a disability? Does short stature impair the QoL of a patient with TS? Are differences in QoL not detected because of a lack of sensitive and suitable QoL instruments? As the UK report indicated, future studies are warranted to provide solid QALY data for more CUA.

6 PRIMARY ECONOMIC ANALYSIS

6.1 Methods

A protocol for the analysis was written a priori.

6.1.1 Types of economic evaluation

Model-based cost-effectiveness and cost-utility analyses were performed because of the clinical benefit of rhGH treatment; it can improve the final height of girls with TS that is thought to be associated with an increase in QoL. In a cost-effectiveness analysis (CEA), the economic value of rhGH treatment for TS was quantified in incremental cost per centimetre of final height gained. In a CUA, outcomes with one type of health-related preferences were measured: QALYs according to the available literature and our assumptions. The computed ICER value in the CUA referred to incremental cost per QALYs gained due to rhGH treatment for patients with TS.

6.1.2 Target population

A hypothetical cohort of girls diagnosed with TS was assumed, whose epiphyses were not closed and whose rhGH treatments were started at age 10 (as in the Canadian RCT).

6.1.3 Comparators

Comparators were rhGH treatment and no treatment. Based on the Canadian RCT,[25] the duration of rhGH treatment was assumed to be six years.

6.1.4 Perspective

In the perspective of the Canadian public health care system that was chosen, the direct cost associated with rhGH therapy is absorbed by the health care system.

6.1.5 Effectiveness

Effectiveness data (in terms of final height gained because of rhGH treatments) from the clinical review were used.

6.1.6 Time horizon

A lifetime horizon was used to take into consideration the overall impact of final height improvement due to rhGH treatment. The life expectancy (81 years) was derived from reports by Statistics Canada.[58] Because AEs data between rhGH treatment and no treatment were inconsistent, it was assumed that there was no difference in rates of AEs between the two groups.

6.1.7 Modelling

A decision analytic model, constructed in Microsoft Excel, was intended to simulate the event pathways of patients with TS receiving rhGH. The values of cost and outcome parameters for the model were inserted into different cells in the spreadsheets, where a series of mathematical equations linked the parameters and facilitated the ultimate computation of ICER.

6.1.8 Valuing outcomes

For the CUA, the best available data came from a Dutch study[59] that quantitatively estimated reductions in QoL due to short stature. Using a time-trade off (TTO) approach, the study found that a patient with TS on average would choose to trade 4.2% of her lifetime to achieve normal height. The incremental QoL for each year with normal height would be 0.042. A time horizon of 80 years (the mean life span of Canadian women) and achievement of normal height would result in an overall gain of 3.36 QALYs (with no discounting) for a girl with TS. To apply these data to this analysis, additional assumptions were needed. As demonstrated in the clinical review, rhGH treatment can only improve, not normalize, the final height of girls with TS, meaning that the final height after rhGH treatment of girls with TS is still below the normal height. The corresponding impact of improved final height on QoL may not be as much as that of achieving normal height, but there is no evidence available to substantiate this. Hence, it was assumed that the incremental QALY due to rhGH effectiveness was 0.042 in this baseline analysis, but it is likely to overestimate the benefit of rhGH treatment. Sensitivity analyses were performed to test the robustness of the baseline results with respect to this assumption.

6.1.9 Resource use and costs

Only the direct costs associated with rhGH treatment were considered, including rhGH drug costs (Appendix 18) and the incremental cost of health services required (Appendix 19). Costs were determined from the available literature and clinical experts' opinions. The cost of somatropin (used for treatment) was estimated according to patients' weight (Appendix 18). Estrogen therapy is started when ovarian failure is demonstrated in girls of pubertal age, regardless of whether patients have rhGH, so this model excluded these costs. Appendix 21 presents all inputs used in this economic analysis.

6.1.10 Discount rate

A discount of 5% was used to convert future costs to present values (in 2007 Canadian dollars) and to reflect society's rate of time preference. The same discount rate was also applied to the lifetime QALY estimation.

6.1.11 Sensitivity analysis

To test the robustness of the baseline results, the ICER value was examined after varying key parameters (Appendix 21). These parameters included price of rhGH drug, dosage of rhGH, age at which rhGH treatment is started, treatment duration, final height improvement, and discount rate. Because of the lack of data, only one-way and scenario sensitivity analyses were performed, instead of a more advanced assessment, such as a probabilistic sensitivity analysis. The data sources for the one-way sensitivity analysis were literature, experts' opinions, and our assumptions. Although the CADTH guideline[60] recommends the use of the probabilistic sensitivity method, its application is not always possible because of increased data requirements. Because of time constraints, it was not possible to obtain all plausible ranges for all variables. ICER values in baseline results and the one-way sensitivity analysis, however, were beyond the conventional thresholds (e.g., C$50,000/QALY), and even in the most optimistic scenario, rhGH treatment was not cost effective according to the ICER. Therefore, it seemed unnecessary to conduct a probabilistic sensitivity analysis. In future, if robust QALY data differ from the Dutch data used for this analysis, another sensitivity analysis would be needed.

6.2 Results

6.2.1 Costs of treatment

The total costs for a hypothetical cohort of girls with TS who received rhGH treatment at age 10 and completed treatment at age 15 are shown in Table 11: C$153,593 with discounting (C$172,435 without discounting). This value represents only the incremental costs of a patient with rhGH treatment versus without treatment and excludes the costs of health services common to both scenarios.

6.2.2 Effectiveness

For the CEA, the results from the Canadian RCT were utilized, where the mean height of a girl with TS was 147.50 cm with rhGH therapy and 141.00 cm without therapy. Therefore, the final height gained over her lifetime was 6.50 cm (Table 12). For the CUA, it was assumed that QoL remained the same until rhGH therapy was completed. Thus, the QALY of each life year was the same from birth to 15 years old (the period before GH therapy is completed). Compared with a patient without rhGH, a girl with TS who completed rhGH would gain 0.042 QALY per life year from age 16 years to 81 years (the age we assumed to be the average life expectancy of patients with TS), resulting in 0.63 QALY (discounted) or 2.77 QALYs (not discounted) over her lifetime (Table 12).

6.2.3 ICER estimation

The estimated ICER was C$23,630 per centimetre with discounting (C$26,529 per centimetre without discounting) (Table 13). The estimated ICER was C$243,078 per QALY gained with discounting ($62,206 per QALY without discounting).

Table 11: Incremental cost (2007 C$) of rhGH treatment in children with TS

	Value (discounted)	Value (not discounted)
Incremental cost due to rhGH drug	152,427	171,151
Incremental cost due to health services	1,166	1,284
Total incremental cost	153,593	172,435

rhGH=recombinant human growth hormone; TS=Turner syndrome

Table 12: Incremental effectiveness of rhGH treatment versus no treatment in children with TS

	Value (discounted)	Value (not discounted)
Incremental final height	6.50	6.50
Incremental QALYs	0.63	2.77

QALY=quality-adjusted life year; rhGH=recombinant human growth hormone; TS=Turner syndrome

Table 13: ICER baseline value of rhGH treatment versus no treatment in children with TS

	Value (discounted)	Value (not discounted)
C$ per centimetre of improved final height	23,630	26,529
C$ per QALY gained	243,078	62,206

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; rhGH=recombinant human growth hormone; TS=Turner syndrome

6.2.4 Sensitivity analysis

The values of five key parameters (Table 14) were varied based on available data sources. The ICER values were sensitive to all parameters but to different extents, ranging from C$15,288 per centimetre to C$31,790 per centimetre or from C$157,270 per QALY to C$486,156 per QALY (discounted value). The ICER values for two extreme scenarios are shown in Table 15.

Table 14: Variations in ICER in one-way sensitivity analysis (discounted value)

	ICER (C$/cm gained)	ICER (C$/QALY gained)
rhGH drug price (C$38.18/mg to $46.67/mg)	20,983 to 25,609	215,854 to 263,442
Start age of therapy (7 years to 13 years)	16,819 to 28,289	173,018 to 291,005
Duration of rhGH treatment (4 years to 8 years)	15,288 to 31,790	157,270 to 327,022
Final height increased (6 cm to 8.4 cm)	18,285 to 25,599	NA
Dosage of rhGH (0.375 mg/kg/week)	29,492	303,386
Discounting (3%)	24,861	155,986
QALY gain (0.32 to 0.95)	NA	162,052 to 486,156

ICER=incremental cost-effectiveness ratio; NA=not applicable; QALY=quality-adjusted life year; rhGH=recombinant human growth hormone

Table 15: Variation in ICER in two extreme scenarios (discounted value)		
	ICER (C$/cm gained)	**ICER (C$/QALY gained)**
Case 1 • rhGH price (C$38.18/mg) • start age (7 years old) • duration of rhGH treatment (4 years) • final height gain due to rhGH (8.4 cm) • QALY gain (up by 50% over baseline value)	7,114	63,046
Case 2 • rhGH price (C$46.67/mg) • start age (13 years old) • duration of rhGH treatment (8 years) • final height gain due to GH (6 cm) • QALY gain (down by 50% over baseline value)	43,713	830,167

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; rhGH=recombinant human growth hormone

6.3 Discussion

This analysis provided the estimation of cost effectiveness and cost utility of treating TS children with somatropin in the Canadian context. The computation results of this study showed that the cost of somatropin accounts for 99.24% of the total cost associated with rhGH therapy. Hypothetically, for a girl with TS, rhGH therapy from age 10 to 15 years would cost C$20,000 for each extra centimetre of final height gained compared with no treatment. In terms of incremental cost per QALY, the therapy would cost >C$200,000 (discounted value) per QALY gained over no treatment. The ICER value was sensitive to variations of key parameters.

Compared to the UK NICE report, this analysis resulted in a different ICER value, because of difference in the values of two key parameters: gain in final height and total cost. In this study, a higher value of final height gain (6.5 cm) was used. This is 35.42% more than that in the NICE report (4.8 cm). In terms of total cost per case, this analysis computed a higher value (C$153,593) than the NICE report (C$138,975). Assumptions about final height in this analysis and in the NICE report were based on the data in the same Canadian RCT. The UK report was based on the trial's early results, which were lower than the final outcome. This analysis, however, was based on the final results. With respect to total cost estimation, the results of this analysis differ from those of the UK report because of the diverse values of three relevant parameters (the current analysis versus the UK report): duration of treatment (six years versus five years), age at start of treatment (10 years versus 11 years), and unit cost of the somatropin drug (C$42.36 per milligram versus C$46.84 per milligram).

The UK study did not perform a CUA. Instead, the authors discussed the feasibility of obtaining QALY weights that are essential for CUA. In contrast, our analysis examined the value of rhGH through CUA by assuming a QALY weight, based on the available information in the literature. The ICER of rhGH treatment versus no treatment was C$243,078 per QALY gain. Therefore, rhGH therapy would not be considered to be cost-effective if a $50,000 per QALY threshold is used.

This estimation is the first report of a CUA on rhGH therapy for TS treatment, but this analysis has several limitations. First, a sensitivity analysis was not performed for all model inputs because of

lack of data and the anticipated minor impact of these model inputs on the ICER values. For example, it was assumed that inputs in the calculation of health services associated with rhGH therapy had constant values. Moreover, it was anticipated that if the uncertainty of these parameters was incorporated, the ICER estimation would not change much, because the overall health service cost accounted for only 0.76% of the total cost associated with rhGH therapy (99.24% of the total cost was due to the cost of somatropin). The impact of those inputs that could significantly influence the total cost, such as price of somatropin and duration of the treatment, was fully analyzed in the sensitivity analysis (Table 14).

Second, the model used in this analysis used data related to the efficacy, rather than the effectiveness, of rhGH therapy. Because of delayed diagnosis, rhGH therapy may not have as much clinical benefit as demonstrated by the Canadian RCT, because with a shorter treatment duration the final height attained is likely to be less. On the other hand, a delayed diagnosis could result in a complex impact on the total cost of somatropin drugs. Patients at an older age would require a higher dose of rhGH because of increased weight. At the same time, however, the shorter duration would reduce the total rhGH treatment cost. The final height data used in the analysis were taken from the only available RCT that reported final height, hence the results of this analysis may have limited generalizability. On the other hand, the RCT was a Canadian study and is relevant to the population studied. In future, when data from real-world experience are available, the corresponding ICER estimation could be different.

Third, the CUA (ICER in C$/QALY) findings of this analysis need to be viewed with caution because of the QALY data. This review adopted the results from a Dutch study,[59] which was the only available information source. The Dutch researchers used a TTO technique (an interview technique specially designed to quantify the value of health states for economic evaluations). Patients were asked how many years they would be willing to lose from their life to attain an average stature. The maximum number of years that patients were willing to give up is proportional to the value or utility of the QoL with TS. Based on patients' answers, the analyst quantified the incremental QALY of changing short stature to average stature. Several issues need attention here. First, the QALY measured in the Dutch study was based on patients' preferences and may not reflect the societal utility gain, which seems to be more appropriate for collective resource allocation purposes. Second, it is unclear if the Dutch data adequately represent the Canadian population. Moreover, the patients' responses in the Dutch study were based on the hypothetical outcome that patients would achieve normal height, but rhGH treatment may not achieve this target for girls with TS. This clinical review showed that the final height of girls with TS on rhGH therapy was below the average normal height, even if it was improved compared with no treatment. Therefore, the QALY improvement due to rhGH therapy may be overestimated in the Dutch study. Other issues with the TTO include the potential for double discounting, although this is difficult to measure and adjust for. Current recommendations are to discount at the social rate of preference regardless of how preference rates are obtained.[61] In addition, the use of a TTO technique as a direct preference measurement method has been debated.[61] A TTO technique is simple and easy to administer, but its application needs justification.[60]

In summary, the application of this CUA's results requires caution. It is difficult to conclude that rhGH therapy for TS is cost-effective unless the payer is willing to pay >C$200,000 for a QALY. It was estimated that to reach C$50,000 per QALY, a girl with TS would have to be willing to trade 20.4% of her lifetime for a final height improvement, instead of 4.2% in our base case, or the unit cost of somatropin would have to drop to C$8.92 per milligram instead of the current price of C$42.36 per milligram.

7 HEALTH SERVICES IMPACT

7.1 Population Impact

Although there are other indications for rhGH therapy, the population impact of publicly funding rhGH treatment was estimated as it applies to TS only. For this purpose, two variables were used: prevalence of TS and annual female live births. Multiplying the two variables resulted in an estimation of TS cases in each birth cohort (Table 16). Each year there are 66 new cases of TS in Canada, where Ontario has the most cases (26). Assuming that girls with TS at age 10 to 15 years all receive rhGH therapy, the total population impact (Table 16) of publicly funding the therapy is the aggregated number of girls with TS in that age group (10 to 15 years) — 396 girls with TS in Canada.

There are several underlying assumptions. First, it was assumed that each province had the same prevalence of TS, as province-specific prevalence data are unavailable. Second, it was assumed that all girls with TS from age 10 to 15 years would receive the rhGH treatment. This may result in overestimation, because not all girls with TS would be diagnosed before age 10 years and immediately started on rhGH.

Table 16: Population impact of rhGH therapy with respect to TS

	Live birth, female*	TS cases/birth cohort†	Girls with TS needing rhGH‡
Canada	163,918	66	396
ON	64,304	26	156
QC	36,083	14	84
AB	19,874	8	48
BC	19,685	8	48
MB	6,702	3	18
SK	5,762	2	12
NS	4,391	2	12
NB	3,404	1	6
NL	2,158	1	6
PE	675	0	0
NU	346	0	0
NT	343	0	0
YT	187	0	0
Unknown	4	0	0

AB=Alberta; BC=British Columbia; MB=Manitoba; NB=New Brunswick; NL=Newfoundland and Labrador; NS=Nova Scotia; NT=Northwest Territories; ON=Ontario; PE=Prince Edward Island; QC=Québec; rhGH=recombinant human growth hormone; SK=Saskatchewan; TS=Turner syndrome

*Statistics Canada[3]

†(TS cases/birth cohort) = (live birth, female) × (prevalence of TS), where prevalence was assumed to be 1/2,500

‡(girls with TS needing rhGH therapy) = (TS cases per birth cohort) × (duration of rhGH therapy), where rhGH therapy was available for girls with TS between ages 10 and 15 years (total=6 years) according to the assumption of the previous economic evaluation

Finally, it was assumed that the duration of rhGH treatment was six years. For individual cases in the real world, this duration is likely to vary. Some patients may start the treatment earlier, while others may start it later. In addition, if future research suggests increasing the duration of rhGH therapy, the population impact would expand accordingly with larger affected age groups. Because of a lack of

real-world data on treatment patterns with regard to age at start of therapy and duration of treatment, our estimates for these assumptions were based on observations made in the Canadian RCT.[25]

7.2 Budget Impact

A budget impact analysis was undertaken to examine the affordability issue regarding publicly funding rhGH treatment for patients with TS. Because this economic evaluation showed that the cost due to additional health services associated with rhGH therapy is negligible compared with the cost of the rhGH drug (C$1,166 per case versus C$152,427 per case respectively), only the drug cost in the budget impact analysis was considered.

7.2.1 Method

Theoretically, an impact on a drug budget equals the difference between the budgets before and after a new reimbursement policy is established. In the case of rhGH therapy, it is important not only to forecast the budget for TS treatment for the scenario of the current formulary status of somatropin but also to evaluate the budget for a scenario in which rhGH received full benefit listing in the formulary (i.e., patients with TS can be reimbursed for rhGH therapy). For this purpose, we were unsuccessful in obtaining the historical utilization data of somatropin for patients with TS and the current formulary status of somatropin. Ontario does not list any of the products of interest in its drug plan, and other provinces, even if they list somatropin, provide only its overall use in all covered patients, not just those with TS. Therefore, forecasting the budget under the scenario of the present formulary status was unfeasible. Therefore, the issue was simplified by estimating only the budget impact of the government publicly reimbursing rhGH therapy for patients with TS.

The number of girls with TS in each province and the annual cost of rhGH per case were needed for this estimation. Results from the population impact analysis and economic evaluation were used. The rhGH therapy cost by age was calculated first, and then the age-specific cost was multiplied by the number of TS cases at that age. Finally, the costs for the entire cohort (i.e., ages 10 to 15 years) were summed to give the budget estimate for one year. A budget time horizon of three and five years was assumed, with no change in the prevalence of TS during those years, and a discount of 5%. The three- and five-year budgets were then calculated accordingly. All inputs used in the budget analysis are shown in Appendix 22.

7.2.2 Results

In general, fully reimbursing rhGH therapy for patients with TS led to increased budgets for all jurisdictions except Prince Edward Island, Yukon Territory, Northwest Territories, and Nunavut, where there are no cases of TS according to the current estimation (Table 17). If a full reimbursement policy was started in 2007, the one-year budget would be from C$0.17 million to C$4.45 million, depending on the province. One key assumption was that all girls with TS aged 10 to 15 years were diagnosed and received rhGH therapy. Within a three- or five-year horizon, the total budget at the provincial level was estimated to range from C$0.49 million to C$12.72 million or C$0.78 million to C$20.23 million respectively.

Theoretically, a budget impact evaluation should result from comparing a reference scenario and a new drug plan scenario (budget impact = budget of a scenario with new formulary status of drugs – budget of a reference scenario). In the reference scenario, where the current formulary status of drugs

of interest continues, the budget forecast is computed on the basis of historical data. Although some provincial databases identified for this analysis listed somatropin, however, they failed to distinguish patients with TS from other groups of patients who also used the drug. Therefore, because of a lack of historical data, it was not possible to forecast the future budget of the reference scenario. Furthermore, the results represent only the first part of the budget impact analysis (i.e., budget of a scenario with new formulary status) and are likely higher than a more complete budget impact assessment would have shown.

Table 17: Budget impact analysis results (in C$ million, 2007, discount 5%)

	In 2007	2007 to 2009	2007 to 2011
Canada	11.30	32.30	51.35
ON	4.45	12.72	20.23
SK	0.34	0.98	1.56
BC	1.37	3.92	6.22
AB	1.37	3.92	6.22
NS	0.34	0.98	1.56
NB	0.17	0.49	0.78
MB	0.51	1.47	2.33
NL	0.17	0.49	0.78
PE	—	—	—
QC	2.40	6.85	10.89
YT	—	—	—
NT	—	—	—
NU	—	—	—

AB=Alberta; BC=British Columbia; NB=New Brunswick; NS=Nova Scotia; MB=Manitoba; NL=Newfoundland and Labrador; ON=Ontario; PE=Prince Edward Island; QC=Québec; NT=Northwest Territories; SK=Saskatchewan

This analysis assumes that rhGH for all eligible patients with TS would be reimbursed through public insurance. Some of these patients' medications, however, may be covered by private insurance. The Canadian Institute for Health Information (CIHI) estimates that approximately 52% of prescribed drug expenditure is paid for by the private sector.[62] Assumptions cannot be made regarding the proportion of patients with TS who would have such coverage. This information is difficult to obtain and estimate, and likely varies depending on factors such as a patient's age, disease, and non-clinical factors.

This estimation considered only the cost of the drug on the basis of a net price to wholesalers,[20] excluding other relevant costs such as markups, inventory allowances, or dispensing fees, which largely vary from province to province and program to program. Compared with the cost of the drug, these costs are proportionately small in rhGH treatment, and their inclusion would not affect the estimation significantly.

One assumption in this analysis is that girls with TS received rhGH therapy from age 10 to 15 years. This may be untrue. In the real world, several factors[63-65] (e.g., age at diagnosis, parents' attitude about the treatment, and growth of patients) jointly determine whether a girl with TS is treated. Hence, applying the estimations to specific decision-making situations requires caution, especially with respect to the age groups of girls with TS being considered.

In addition, this analysis looked at the maximum potential formulary costs and therefore assumed that all patients diagnosed with TS would receive treatment. According to one study[66] and a clinical expert's opinion, an estimated 40% to 50% of patients with TS receive treatment. Reasons for the lower uptake include late diagnosis, non-referral, and refusal of therapy. If this is the case, then the budget impact results in Table 17 may be as low as 40% to 50% of those presented (e.g., between C$4.5 to C$5.7 million for all of Canada in 2007 instead of C$11.3 million). In reality, this is likely to be the case.

The Patented Medicine Prices Review Board (PMPRB) has released a Canadian guideline[67] for budget impact analysis, which stresses the internal validation of a budget impact model. The PMPRB suggested comparing the model results with available data to test the model validation. It is difficult to apply the suggestion to this project, because historical utilization data were unavailable, although most of the Canadian provinces were approached. In Ontario, somatropin is not listed in the provincial drug formulary, so no historical claim data exist. Also, there is no relevant data for British Columbia, Alberta, and Saskatchewan where somatropin for the treatment of TS is ineligible for reimbursement. In Nova Scotia, coverage exists for somatropin in the treatment of TS, but data for patients with TS <18 years old were unavailable in the provincial database. Manitoba provided utilization data, but for all patients, not just for TS cases. New Brunswick reported no somatropin beneficiaries strictly for TS. No data have been received from Newfoundland and Labrador and Prince Edward Island.

Nevertheless, this analysis is the first to address the affordability issue of publicly funding somatropin for TS treatment from the provincial drug plan's perspective. Because of the low prevalence of TS and the dominant impact of the drug's cost on the total cost associated with treatment, the budget was largely accounted for by the cost of the drug and the number of cases of TS on rhGH therapy. The latter aspect contributed to the difference in budget estimations between provinces.

7.3 Ethical Issues

In addition to the pharmacoeconomic analyses that address the appropriateness of public funding of drugs to treat rare diseases, it is important to apply an "ethics lens" to the analysis, because the question being considered is value-laden and relates to matters of justice and equity. Does short stature in persons with TS constitute a legitimate health need, and if so, should Canadian taxpayers fund the meeting of this health need in the context of many competing health needs and limited health resources?

7.3.1 Identified ethics elements and issues

a) "Treatment or enhancement distinction"

An early approach taken by clinicians and theorists was to try to justify the use of rhGH by a subset of persons with short stature. This was done by drawing a distinction between persons who were being "treated" for short stature and persons whose height was being "enhanced."[68] Individuals in the "treatment group" included those with genetic disorders such as TS, while persons in the "enhancement group" included those with idiopathic short stature (i.e., whose short stature is not yet associated with an identifiable medical disorder). The purpose of making this distinction was to align decision making with respect to the provision and funding of rhGH therapy with society's presumed support for the treatment of bona fide medical conditions and presumed lack of support for the

enhancement of physical or cognitive traits that are not associated with a medical disorder.[69,70] Referencing the principle of "formal justice" attributed to Aristotle,[71] if such a distinction could be defended as a relevant difference that justifies the different management of the two groups of persons with short stature, then a formal justice argument would support the provision or funding of rhGH therapy for persons with genetic disorders and not for those with idiopathic short stature. Clinicians and theorists, however, have had difficulties successfully arguing for such a relevant difference, and many agree with Allen and Fost that the treatment or enhancement distinction "cannot do the moral work of telling us who (among those with short stature) is entitled to treatment."

b) Is short stature a disability?

An argument that has been proposed in support of the treatment of persons with TS and others with short stature with growth-promoting therapy is that short stature, regardless of etiology, is a disabling condition in societies that have been constructed to best accommodate those whose heights fall within the "normal" range.[69,70] If short stature is framed as a disabling condition, then therapies aimed to increase the height of those with short stature could be promoted on the basis of their potential elimination or lessening of a "correctable" disability. One problem with this notion of short stature as a presumed disability is that there is little evidence to support such a claim, and to establish that the achievement of a normal height through the use of rhGH (which is achievable for some persons with TS) results in improved psychosocial adaptation. Also, even if short stature is considered to be disabling, it may make more sense to put primary efforts and public funding into the social re-engineering of society rather than to develop and fund growth-promoting therapies.[72,73]

c) Disparities in access on basis of race and income

Demographic studies have indicated that, although there are no known significant differences in the prevalence of very short stature in disorders such as TS among racial groups, only 5% of parents presenting with their children to endocrinologists in the US for evaluation and treatment of their child's short stature are African American in regional populations that are characterized by an approximately 25% prevalence of African Americans.[64] Furthermore, of the parents presenting for care of their children with short stature, there is a higher proportion of parents of high income and education status than those of low income and education status.[64] Possible reasons for such differences in the accessing of care by parents include, as part of the racial analysis, the distrust of African Americans toward the health care system. It is unclear whether the demographic differential is due to organizational issues in the (US) medical care system (such as lack of universal health care coverage) or to differences in attitude about the importance of stature and the potential for treatment.[64] Regardless of the reason(s) for these demographic findings, the observed difference in parental presentation to endocrinologists suggests that if short stature in persons with TS is considered to be a legitimate health need, this health need is less likely to be met if the family of origin is African American or is of a low income and education.

d) Role and impact of gender

The claim that women and girls remain disadvantaged in developed societies is one that many would accept, given such factors as the ongoing gender disparity in equal-pay-for-equal-work. Given the female-only nature of TS, persons with TS are likely to be further disadvantaged in society over their lifetimes on the basis of their gender, beyond the disadvantages imposed on them by having a multi-system genetic disorder and for most who are affected, a "different" body habitus. Although this seems to be a straightforward gender inequity assumption, some studies have suggested that there is more discrimination on the basis of short stature in men and boys than in women and girls. As Finkelstein *et al*. have reported, several studies have indicated that parents generally believe that short stature is more disabling for males than females.[64]

e) Administration of rhGH as a "harm"

As Gill has commented, children of short stature who are managed with rhGH receive "hundreds to thousands … of subcutaneous injections" during growth-promoting treatment.[74,75] Some clinicians and authors believe that regular rhGH treatments consistently reinforce a message to children from their parents and health care providers that there is something wrong with or different about them that requires medical treatment.[75] In a distributive justice analysis based on a goal of fair distribution of benefits and burdens, this potential "harm" should be balanced against the corresponding potential "harm" of not treating children of short stature with rhGH — e.g., the possibility of experiencing discrimination on the basis of living with a shorter height than what could have been achieved with the use of such therapy.

f) Who should decide?

Given that rhGH therapy is often started in pre- and peri-adolescent ages, the (individual) autonomy issue emerges as to who should make the decision to start and maintain rhGH therapy: the parent(s), the girl with TS, the attending health care provider(s), or all of these people. Applying and extending newly established norms for decision making about care options for other, serious medical illnesses in pediatric settings, girls with TS should be encouraged to participate as much as possible in the decision-making process regarding the start and maintenance of rhGH therapy.[76] In most clinical settings, the ultimate decision-making authority of the parent(s) remains privileged (at least theoretically) with, ideally, the attending health providers sharing and contributing in the process through relevant knowledge transfer and the provision of appropriate, empathic support to the parents and child.[77]

7.3.2 Broader ethics context

By virtue of the high cost of rhGH, the provision and funding of this therapy for persons with TS is a matter of distributive justice. In this resource allocation context, the "scarcity of relevance" is not the therapy but the limited availability of public funds for the meeting of the health care needs of all Canadian citizens. Given that there are insufficient public monies to meet all these health needs, difficult choices must be made by the appropriate macro- and meso-level decision makers. From a distributive justice perspective, such decisions should be informed by an acknowledged, explicit goal — i.e., the fair and proper distribution of health benefits and burdens.[78] Under the circumstances of a "fixed pot of limited resources," the choice to fund a therapy to meet one set of health needs necessarily creates "opportunity costs" for the funding of therapies or interventions to meet other sets of health needs. With reference to the public funding of rhGH, a potential opportunity cost mentioned in the literature relates to the contention (by some) that the public monies that might be allocated for the treatment of short stature could be better spent on the improvement of a social determinant of health — i.e., nutritional inadequacies, given that nutritional deficiency is the most important cause of short stature in the population at large.[74] Although such comparators are useful as "thought experiments," however, the analysis of obligations arising from distributive justice principles is more complicated in a real world-setting characterized by the existence of constraints on the spending of public monies in health and social domains.

Several justice and health care theorists have tried to provide some guidance to decision making in health resources allocation. In his "theory of justice" John Rawls argues that whatever the other goals and ends of a society are, the societal arrangements chosen and established by its citizens should benefit "the worst off." In this context, persons with TS could be considered to be a cohort of the worst off, given the multi-system nature of this genetic disorder. According to Rawls, special or

"extra" efforts should be made to improve the daily lot of persons who are among the worst off in a "just society."[79]

In an attempt to subsume Rawls' theory of justice into a health care context, Normal Daniels has proposed an influential theory of health justice that may be relevant.[80] For Daniels, "legitimate health care needs" are those that should be met to bring persons up to and maintain them at a state of "normal human functioning." This concept is linked to Rawls' conception of "fair equality of opportunity" because presumably, a state of "normal human functioning" helps the access of individuals to a normal array of life plans. If "normal human functioning" is considered to include the attainment of a height within the normal range, then according to Daniels, the experience of short stature of any etiology should be considered to be a legitimate health care need that should be met by society.[80] In such a conception, the achievement of the lower end of the normal range (often statistically defined as the third percentile on the basis of the 2000 CDC recommendations[81]) through the use of publicly funded growth-promoting therapies could be justified on justice grounds. Two limits to the usefulness of Daniel's conception in this context should be noted: this argument does not address the question of what the endpoint of growth-promoting therapies should be – the achievement of a normal height or improved psychosocial adaptation (should the former be considered to be a surrogate measure for the latter?) – and although this conception may assist in the identification of those whose health needs should not be met and, for those whose needs should be met, when to stop, it does not assist decision makers in answering the question of whether society can afford to publicly fund such health care needs that have been identified as legitimate?

Theorists such as Iris Marion Young and Susan Sherwin have provided social justice conceptions that may be relevant in this context. For Young, members of disadvantaged social groups, such as persons with medical illnesses and female persons, should assert their (positive) "difference" and be assisted by society in ways to meaningfully level "power" in the uneven playing field.[82] In Sherwin's view, it is important for all, particularly members of disadvantaged social groups, to have access to a reasonable array of health care choices, which, one could argue, should include access to rhGH by persons with TS.[83] (At the same time, Sherwin argues that attention should be paid to improving the known social determinants of health, including those related to income, nutrition, education, and housing).

In addition to these justice considerations, it is important on other health equity and (global health resource) sustainability grounds for macro- and meso-level decision makers to reflect on an ethics question in this context: how should society balance as fairly as possible two fundamental, beneficence-related, competing obligations — i.e., to meet the legitimate health care needs of a set of persons (e.g., those with TS), and at the same time, to meet the legitimate health care needs of all Canadian citizens.

In summary, there are distributive and social justice arguments that could be used to support the provision of publicly funded rhGH to persons with TS, and particularly to support the provision and funding of such therapy until the lower end of the normal height range is achieved in these individuals. Such ethics arguments should and must be considered with relevant pharmacoeconomic considerations in the real-life context of multiple competing claims for limited health resources.

7.4 Psychosocial Issues

The treatment of TS with rhGH or hormone replacement therapy to increase height and improve ovarian function can positively affect the psychological well-being of girls and women with TS.[42,54] To achieve an understanding of the implications of this clinical route, however, this statement should be qualified through a discussion of the psychological and social factors associated with TS.

The most common physical symptoms of TS — below-average stature, premature ovarian failure, and difficulties with social skills (associated with attention, visuospatial, and spatial-temporal processing) — are each capable of posing psychosocial challenges for the affected person. Girls and women with TS may be considered to be at risk of moderate psychological problems related to adjustment and social anxiety.[84-91] This is supported by studies showing that women with TS report significantly higher levels of shyness and social anxiety and lower levels of self-esteem than unaffected control groups.[92]

It is clear from the literature that the extent of variability in the way that TS is manifested means that it is difficult to predict how an affected individual will experience TS.[84,85] As a result, although there is consensus on the psychosocial risks associated with TS, there remains debate on the nature of its psychosocial impact, especially regarding the level of social anxiety experienced by TS-affected individuals. Some of this may be due to cross-cultural differences shaping the conclusions or indications of TS studies internationally.[84,93] There is also the conventional problem of self-report in the measurement of well-being. One study found that girls with TS measured significantly higher than non-affected controls on the Lie scale of the Revised Children's Manifest Anxiety Scale, which measures the tendency to respond in a socially acceptable manner (even if this does not accurately reflect the experience of symptoms).[87]

Because of this variability, there is an emphasis in most studies on a case-by-case approach to understanding the impact of TS, an approach that should carry over into treatment plans. This is especially the case with treatments that bear some risk to the patient (such as biologics), and where the severity of TS is sufficiently low that the individual may not experience a physical or psychological impact. The following addresses some considerations for the diagnosis and treatment of TS.

7.4.1 Potential psychosocial impacts of rhGH therapy on persons with TS

The manifestations of TS may have lifelong psychosocial implications if not diagnosed and treated early. Despite some physical traits associated with TS, such as the webbed neck, it is a condition that may not be obvious to parents or health professionals until later in puberty,[91] when treatment may be less effective on sexual development and possibly final adult height. One study suggests that these additional physical traits have little impact on adults' psychological well-being, although they may be stressors in earlier life.[85] Just as the experience of TS in girls will differ from that in women, the psychosocial implications of the treatment will differ for patients at these two stages of development. There may be psychosocial risks associated with treatment-related stigmatization in childhood and adolescence. For example, though there is little in the literature on the effects of daily injection,[42] studies on other conditions that are treatable by injection, such as diabetes,[94] do report some social effects of treatment. In addition, there may be psychosocial implications related to the variance between expectations and outcomes of hormone treatment.[95] In addition, there are questionable effects of hormone-based therapy that should be considered before starting treatment. First, at least

one study has indicated that rhGH treatment may result in voice and speech alteration, which may in turn have implications for social anxiety.[96] Second, the use of estrogen in pubertal development may reduce final adult height, so the relative psychosocial impact of taller stature versus "normal" puberty should be taken into account.[85] Third, the long-term consequences of these doses of hormones are unknown, and therefore, precautions should be taken when deciding to incorporate rhGH into the treatment plan for low-severity cases of TS.[48]

7.4.2 Additional psychosocial considerations

a) Parental involvement

A Swedish study of parents' perceptions of the diagnostic process for TS found that because of inconsistent knowledge throughout the health professional community regarding TS, parents were often confused about the consequences of the diagnosis for their child.[97] In particular, misinformation related to the "syndrome" aspect of TS occasionally resulted in concerns about mental retardation — which occurs in no higher proportion in the TS population than in the general population — because of associations with Down's syndrome. This study notes the "disability" stigmatization that TS-affected girls may face from their families and peer communities, even when the severity of TS is low. Psychological and educational resources to support parents and TS-affected children may decrease the stresses related to coping with the syndrome.[89]

When a diagnosis is achieved, there are other considerations for families coping with the syndrome. There is some disagreement in the literature on parental reporting of a TS daughter's social anxiety, with McCauley *et al*.[87] finding that parents believed their daughter's anxiety to be higher than their daughter believed it to be in self-report; and Lesniak-Karpiak *et al*.[86] finding no significant difference between parent- and child-reported levels of social anxiety. Nevertheless, the potential for parents to be affected in treatment decision making by higher levels of anxiety than experienced by children may be linked to differential levels of knowledge about informed consent to treatment.

b) What rhGH does not "cure"

Girls with TS and their families may perceive that treatment with rhGH can serve as a "cure" for the syndrome. There is, however, no conclusive evidence that this treatment will have an impact on other TS-associated problems such as learning disabilities or infertility.[57] There is research and patient support literature that describe the psychosocial impacts of learning disabilities and infertility, both of which can have an impact on emotional well-being. These effects of TS may still require the assistance of a trained professional (psychologist, psychiatrist, social worker, or other counsellor) to address adequately. Some fertility treatments available, for example oocyte donation, require the woman to undergo pregnancy, which in TS-affected women may bear a high risk of fatal aortic dissection.[98,99] Considering the emotional and psychological intensity of infertility, a higher risk is sometimes considered to be acceptable even with a small chance of a positive outcome. The discussion of complex issues such as these should be integrated into the treatment of girls with TS as soon as it is age-appropriate.

The decision to undergo rhGH treatment for TS should be made while considering the individual's experience of the syndrome's physical effects and psychosocial complexity. Thus, treatment plans should include an ongoing dialogue between health professionals and patients (and their families), to ensure that informed treatment decisions are made appropriate to each individual case.

8 CONCLUSIONS

The available evidence suggests that rhGH treatment is effective in improving growth and final height. There is no conclusive evidence about whether QoL is improved in those treated with rhGH compared with those not treated. In RCTs and comparative studies AE data were sparsely reported and there was variability. Long-term studies of high quality are needed to determine the benefit and harm of rhGH treatment. Psychological and social benefits and harms may accrue to patients as a result of this treatment, and more studies (particularly in the Canadian context) would be useful additions to an assessment of the treatment's value. rhGH may not be a viable treatment option for all TS-affected individuals, because this syndrome varies in its manifestations and psychosocial implications.

The only economic study that was identified found that the cost per centimetre of final height gained with rhGH was >£10,000 (C$22,498) compared with no treatment. There was no definitive conclusion about whether rhGH therapy is cost-effective.

Given the many assumptions made, our economic evaluation reported the ICER of rhGH versus no treatment was >C$26,000 per centimetre or C$200,000 per QALY. For average patients with TS, rhGH treatment is unlikely to be considered cost-effective unless society is willing to pay >C$200,000 to obtain a QALY. For patients whose QoL is impaired by height, rhGH treatment may be cost effective. More research is needed to obtain more reliable QALY data.

From an ethics perspective, there are distributive and social justice arguments that could support the provision of publicly funded rhGH to persons with TS, and in particular, to support the provision and funding of such therapy until affected individuals have achieved the lower end of the normal adult height range.

Funding rhGH therapy for patients with TS will increase the budget of government drug plans, hence opportunity costs need to be considered.

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APPENDICES

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