Growth hormone for treating Turner syndrome in Canada: structuring evidence into the EVIDEM multicriteria decision analysis framework to support decisionmaking

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Background and objectives

- Healthcare decisionmaking is a complex process involving scientific assessment of available evidence and the application of value judgment.[1,2]
- Accessibility to the evidence on which decisions are based in a transparent and explicit process is necessary to improve and legitimize decisions [3-5]
- This led to development of multicriteria models.[6-14]
- The EVIDEM framework was developed to support healthcare decisionmaking; it integrates a health technology assessment (HTA) report with a multi-criteria decision analysis (MCDA) matrix facilitating explicit consideration of all essential decision components.[15]
- Objective: To test and further develop the EVIDEM framework using treatment of Turner syndrome (TS) with growth hormone (GH) as a complex case study, for which all factors need to be considered to optimize decisions and health for children with this disease.

Methods

- Data for each quantifiable decision component of the MCDA Value Matrix was collected and synthesized using EVIDEM methodology (predefined search algorithms, standard reporting format).
- Disease impact and clinical data were obtained from peer-reviewed publications. Data on budget impact, cost-effectiveness and impact on other spending were based on a CADTH technology report on GH treatment of girls with TS.[16]
- The quality of five types of evidence (epidemiological data, clinical data, patient reported outcomes [PRO] data, economic evaluation and budget impact model) was assessed using the EVIDEM Quality Matrix instruments according to two criteria ("completeness and consistency of reporting" and "relevance and validity").
- Other components of decision such as ethical and system-related issues were identified from a review of the literature using the WHO 2004 ethical framework[17].
- The HTA report produced was validated by clinical and economic experts and an interactive web-based prototype of the framework was developed.

Results

Synthesized evidence
For selected Value Matrix components

Cluster: Disease impact – example D1

		Synthesized evidence available	Score
D1	Disease severity (*risk of death & disability, acuteness, impact on QoL*)	Turner syndrome is a female-specific genetic disorder (loss or partial loss of one of the X chromosomes) characterized by short stature and presenting a wide spectrum of abnormalities, including cardiovascular defects (17-45%), lymphedema, gonadal dysgenesis (90% requiring hormone replacement therapy to induce puberty), infertility, miscarriage, hypothyroidism (15-30%), risk of obesity, ophthalmic defects, hearing problems and ear malformations, gastrointestinal and renal manifestations, in addition to learning disabilities (70% patients), defects in visuospatial organization and nonverbal problem-solving, and impaired psychomotor and social functioning (Bondy 2007, Sybert et al. 2004).[6,8] In young patients, psychosocial issues arise: impaired peer relationship, teasing, social isolation, anxiety, shyness, and poor self-esteem (Bondy 2007, Sybert et al. 2004, Schmidt et al, Busschbach et al. 1998).[6,8-10] In audiotaped interviews, Turner Syndrome patients reported infertility as their biggest concern (range: 36% of girls aged 7–13 yrs to 74% of adults aged 20–39 yrs; Sutton et al. 2007).[11] However, many Turner Syndrome patients of all ages reported to be bothered by short stature (36% girls, 44% adolescents and adults, 55% mature adults 40–59 yrs; Sutton et al. 2007);[11] 44% of 25 adult Turner Syndrome patients (18–40 yrs) were willing to give up years of life in time trade-off to obtain an average stature (Busschbach et al. 1998).[10] Short stature is the target of GH treatment. Life expectancy is decreased in women with Turner Syndrome, mainly due to complications of cardiovascular defects, diabetes and congenital anomalies (Stochholm et al.2006; Sybert et al. 2004),[8,12] with a standard mortality ratio of 2.86 (Stochholm et al.2006).[12]	0 ☐ Not severe (minor inconvenience) 1 ☐ 2 ☐ 3 ☐ Very severe

Cluster: Intervention – example I5

		Synthesized evidence available	Score
I5	Improvement of patient reported outcomes, convenience & adherence	**PATIENT REPORTED OUTCOMES** (PROs) **Limited comparative data on the effect of GH on QoL of patients during GH treatment**. One Canadian study reported a preliminary analysis of the impact of GH on the psychological status of girls enrolled in the Canadian clinical trial (Stephure et al. 2005[5] - see I3 pivotal trial) using standardized questions (Rovet & Holland 1993;[31] N=95; Age 7–12 yrs; GH 0.30 mg/kg/wk vs untreated). (see table below)	0 ☐ Worse PROs / lower convenience / lower adherence than comparators presented 1 ☐ 2 ☐ 3 ☐ Major improvement *Scoring example (for information only)* *0: Worse PROs / lower convenience / lower adherence than comparators* *1: Same PROs / convenience / adherence as comparators* *2: Some improvement in PROs / convenience / adherence vs comparators* *3: Major improvement in PROs / convenience / adherence vs comparators*

Outcomes at 18 months of GH treatment	GH N=28	No treatment N=20	*P*	*Correlation with large growth rate*
Self-concept (self-rating by patients)				
Global	76.5 ± 18.9	64.4 ± 21.7	.001	NR
Appearance	67.00 ± 24.5	55.7 ± 24.9	.08	Yes (P< .05)
Intelligence	75.00 ± 23.8	56.2 ± 25.2	.01	Yes (P< .01)
Peer relations	66.4 ± 27.4	32.4 ± 25.6	.001	NR
Other variables				
Friendships	3.15 ± 0.6	2.72 ± 0.83	.05	Yes (P< .05)
Popularity	66.4 ± 27.4	32.4 ± 25.6	.001	Yes (P< .01)
Teasing	0.69 ± 0.55	1.05 ± 0.61	.05	Yes (P< .05)
Hyperactivity (rating by the mother)	59.6 ± 7.6	65.2 ± 8.0	.05	Yes (P< .01)
Protectiveness (rating by the mother)	1.10 ± 1.31	0.63 ± 0.9	.1	No correlation
Mathematics performance (parents' rating)	NR	NR	.01	No correlation

Higher growth rate correlated with better QoL ratings, but not with family or school functioning
NR: not reported

Another questionnaire-based study from Israel failed to demonstrate significant differences between GH-treated and untreated patients (N=132 [12% of these identified as having Turner Syndrome or renal disease]; male/female; 8–16 yrs) in school achievement, participation in leisure activities, emotional and physical self-esteem, and relationship with peers (Pilpel et al. 1995).[32] GH-treated patients reported slightly lower scores for relationships with family members (3.7 vs 3.8 untreated, P=.04).

Other available PRO data are based on reports from Turner Syndrome patients who had been previously treated with GH, compared with the general population:
- **Carel et al. 2005[33]:** N=568; postal survey to evaluate HRQoL using validated French SF-36 & GHQ-12 in women (22.6 ± 2.6 yrs) previously treated with GH for 4.8 ± 2.2 yr (stopped at age: 16.7 ± 1.6 yr)
  - No significant difference between GH-treated Turner Syndrome patients and age-matched women from the general population on all SF36 dimensions (physical functioning, bodily pain, vitality, general health, social functioning, mental health, role limitations- physical, role limitations-emotional)
- **Bannink et al. 2006[34]:** N=29; postal survey to evaluate HRQoL evaluation using Dutch validated SF-36 and TAAQOL in participants of 2 earlier clinical trials, compared with the general population
  - SF36: significantly better performance of GH-treated Turner Syndrome patients vs the general population on 3 dimensions: bodily pain, social functioning, and role limitations-emotional
  - TAAQOL: GH-treated Turner Syndrome patients rated significantly better on pain, daily activities, sexuality, and aggressive emotions

Finally, GH treatment does not improve neurocognitive function in girls with Turner Syndrome (Ross et al. 1997, Ross 2005)[35,36]

CONVENIENCE:
- Subcutaneous injection given either 3 days a week or daily.(Humatrope PM. 2007; Saizen PM. 2007; Nutropin PM. 2006).[2-4] Dosage and administration schedule to be individualized for each patient (0.32–0.375 mg/kg/week). Injection site reaction and pain reported in 16% and 12.3% of patients, respectively (Saizen PM. 2007)[2]
- Physical harm of thousands of injections and psychosocial harm of reinforcing that there is something wrong about size (Gill 2006, Rose 95) [37,38]

ADHERENCE:
In clinical trials, 80% (Stephure et al. 2005)[5] to 86% (Rosenfeld et al. 1998)[20] of patients completed GH treatment in clinical trials; 95% (range: 75–100) of GH scheduled injections were administered to toddlers (Davenport et al. 2007)[22]

Cluster: Economics – example E3

		Synthesized evidence available	Score
E3	Impact on other spending (*e.g. hospitalization, disability*)	Data based on country-specific economic evaluation prepared by Canadian Agency for Drugs and Technologies in Health (Li 2007)[40] (for information on study, see E2 above) Mean costs per patient over 6 years of treatment (discounted at 5% annually) (see table below) In the economic analysis (see E2 above), GH treatment was not assumed to impact other healthcare resource use (e.g., adverse events not included). Also, the analytic perspective (public healthcare system) did not allow the inclusion of other costs (e.g., productivity, private patient expenditures)	0 ☐ Substantial additional healthcare spending, excluding product cost 1 ☐ 2 ☐ 3 ☐ Substantial savings in healthcare spending, excluding product cost *Scoring example (for information only)* *0: Substantial additional healthcare spending (hospital, healthcare professional fees, other drugs, lab tests etc)* *1: No or very minor change in other healthcare spending* *2: Moderate reduction of other disease cost/patient* *3: Significant reduction of other disease cost/patient*

	Training of parents/patients by nurse*	GH-therapy associated outpatient visits†	Hand X-rays‡	Total	Incremental cost
GH	**$120**	**$865**	**$181**	**$1,166**	**$1,166**
No treatment	**0**	**0**	**0**	**0**	**--**

*Training in drug administration (3 1-hour sessions at $40 each); †3 visits annually during the first 5 years and 1 in the last year at $60 per visit; ‡ 4 X-rays (2nd to 4th year) at $51 per test

Decision

Extrinsic value

Intrinsic value
MCDA Value Matrix

Cluster	Value component (alphabetical by cluster)	Weight	Synthesized evidence	Score	Evaluator comments	Value contri-bution
Quality of evidence						
Q1	Adherence to requirements of decisionmaking body		Quality Matrix			
Q2	Completeness and consistency of reporting evidence					
Q3	Relevance and validity of evidence					
Disease impact						
D1	Disease severity					
D2	Size of population affected by disease					
Intervention						
I1	Clinical guidelines on interventions or similar alternatives					
I2	Comparative interventions limitations					
I3	Improvement of efficacy/effectiveness					
I4	Improvement of safety & tolerability					
I5	Improvement of PROs, convenience & adherence					
I6	Public health interest					
I7	Type of medical service *(e.g., cure, symptom relief)*					
Economics						
E1	Budget impact of reimbursing intervention on health plan					
E2	Cost-effectiveness of intervention					
E3	Impact on other spending					
Total	Value estimate (sum of all value contributions; MCDA linear model)					

Synthesized Evidence
For each component of the Value Matrix

Targeted health technology assessment report

Quality of Evidence
Quality Matrix

Evidence available

1. Baxter L, Bryant J, Cave CB, Milne R. Recombinant growth hormone for children and adolescents with Turner syndrome. Cochrane Database Syst Rev. 2007;(1):CD003887. **2.** EMD Serono Canada Inc. Saizen product monograph. 2007 Dec 18. **3.** Eli Lilly Canada Inc. Humatrope product monograph. 2007 Jun 9. **4.** Hoffmann-La Roche Limited. Nutropin product monograph. 2006 Aug 23. **5.** Stephure DK. Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. J Clin Endocrinol Metab. 2005;90(6):3360-6. **6.** Bondy CA. Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007;92(1):10-25. **7.** Khatchadourian K, Huot C, Alos N, Van Vliet G, Deal C. Impact of patient characteristics and clinical factors on the decision to initiate growth hormone treatment in Turner syndrome. Horm Res. 2008;70(5):300-8. **8.** Sybert VP, McCauley E. Turner's syndrome. N Engl J Med. 2004;351(12):1227-38. **9.** Schmidt PJ, Cardoso GM, Ross JL, Haq N, Rubinow DR, Bondy CA. Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. JAMA. 2006;295(12):1374-6. **10.** Busschbach JJ, Rikken B, Grobbee DE, De Charro FT, Wit JM. Quality of life in short adults. Horm Res. 1998;49(1):32-8. **11.** Sutton EJ, McInerney-Leo A, Bondy CA, Gollust SE, King D, Biesecker B. Turner syndrome: four challenges across the lifespan. Am J Med Genet A. 2005;139A(2):57-66. **12.** Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab. 2006;91(10):3897-902. **13.** Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. Clin Genet. 1975;8(4):223-43. **14.** Imaizumi K, Kuroki Y. Prevalence of Turner syndrome in Japan. In: HIBI I, Takano K, editors. Basic and clinical approach to Turner syndrome. Amsterdam: Excerpta Medica; 1993. p. 3-6. **15.** Bochkov NP, Kuleshov NP, Chebotarev AN, Alekhin VI, Midian SA. Population cytogenetic investigation of newborns in Moscow. Humangenetik. 1974;22(2):139-52. **16.** Nielsen J, Wohlert M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Birth Defects Orig Artic Ser. 1990;26(4):209-23. **17.** Jacobs PA, Melville M, Ratcliffe S, Keay AJ, Syme J. A cytogenetic survey of 11,680 newborn infants. Ann Hum Genet. 1974;37(4):359-76. **18.** Verweij M, Kortmann F. Moral assessment of growth hormone therapy for children with idiopathic short stature. J Med Ethics. 1997;23(5):305-9. **19.** Haverkamp F, Ranke MB. The ethical dilemma of growth hormone treatment of short stature: a scientific theoretical approach. Horm Res. 1999;51(6):301-4. **20.** Rosenfeld RG, Attie KM, Frane J, Brasel JA, Burstein S, Cara JF, et al. Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. J Pediatr. 1998;132(2):319-24. **21.** Quigley CA, Crowe BJ, Anglin DG, Chipman JJ. Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. J Clin Endocrinol Metab. 2002;87(5):2033-41. **22.** Davenport ML, Crowe BJ, Travers SH, Rubin K, Ross JL, Fechner PY, et al. Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial. J Clin Endocrinol Metab. 2007;92(9):3406-16. **23.** Hochberg Z, Zadik Z. Final height in young women with Turner syndrome after GH therapy: an open controlled study. Eur J Endocrinol. 1999;141(3):218-24. **24.** Pasquino AM, Passeri F, Municchi G, Segni M, Pucarelli I, Larizza D, et al. Final height in Turner syndrome patients treated with growth hormone. Horm Res. 1996;46(6):269-72. **25.** Pasquino AM, Pucarelli I, Segni M, Tarani L, Calcaterra V, Larizza D. Adult height in sixty girls with Turner syndrome treated with growth hormone matched with an untreated group. J Endocrinol Invest. 2005;28(4):350-6. **26.** Bertelloni S, Cinquanta L, Baroncelli GI, Simi P, Rossi S, Saggese G. Volumetric bone mineral density in young women with Turner's syndrome treated with estrogens or estrogens plus growth hormone. Horm Res. 2000;53(2):72-6. **27.** Dacou-Voutetakis C, Karavanaki-Karanassiou K, Petrou V, Georgopoulos N, Maniati-Christidi M, Mavrou A. The growth pattern and final height of girls with Turner syndrome with and without human growth hormone treatment. Pediatrics. 1998;101(4 Pt 1):663-8. **28.** Bechtold S, Dalla PR, Schmidt H, Bonfig W, Schwarz HP. Pubertal height gain in Ullrich-Turner syndrome. J Pediatr Endocrinol Metab. 2006;19(8):987-93. **29.** Darendeliler F, Karagiannis G, Wilton P. Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from the KIGS database. Horm Res. 2007;68 Suppl 5:41-7. **30.** Bolar K, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in turner syndrome. J Clin Endocrinol Metab. 2008;93(2):344-51. **31.** Rovet J, Holland J. Psychological aspects of the Canadian randomized controlled trial of human growth hormone and low-dose ethinyl oestradiol in children with Turner syndrome. The Canadian Growth Hormone Advisory Group. Horm Res. 1993;39 Suppl 2:60-4. **32.** Pilpel D, Leiberman E, Zadik Z, Carel CA. Effect of growth hormone treatment on quality of life of short-stature children. Horm Res. 1995;44(1):1-5. **33.** Carel JC, Ecosse E, Bastie-Sigeac I, Cabrol S, Tauber M, Leger J, et al. Quality of life determinants in young women with turner's syndrome after growth hormone treatment: results of the StaTur population-based cohort study. J Clin Endocrinol Metab. 2005;90(4):1992-7. **34.** Bannink EM, Raat H, Mulder PG, de Muinck Keizer-Schrama SM. Quality of life after growth hormone therapy and induced puberty in women with Turner syndrome. J Pediatr. 2006;148(1):95-101. **35.** Ross JL, Feuillan P, Kushner H, Roeltgen D, Cutler GB, Jr. Absence of growth hormone effects on cognitive function in girls with Turner syndrome. J Clin Endocrinol Metab. 1997;82(6):1814-7. **36.** Ross JL. Effects of growth hormone on cognitive function. Horm Res. 2005;64 Suppl 3:89-94. **37.** Gill DG. "Anything you can do, I can do bigger?": the ethics and equity of growth hormone for small normal children. Arch Dis Child. 2006;91(3):270-2. **38.** Rose SR. Are we overtreating children with growth hormone? The Endocrinologist. 1995;5:113-7. **39.** Sandberg DE, Voss LD. The psychosocial consequences of short stature: a review of the evidence. Best Pract Res Clin Endocrinol Metab. 2002;16(3):449-63. **40.** 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 Turner syndrome: systematic review and economic evaluation (Technology report number 96). On Canadian Agency for Drugs and Technologies in Health website [updated 2007 Dec; cited 2008 Dec 10]. Available from: http://cadth.ca/index.php/en/hta/reports-publications/search/publication/778. **41.** Canadian Institute for Health Information. Figure 3. Total drug expenditure per capita by type and source of finance, by province/territory and Canada, 2007f (Figure 13 in the report). On Canadian Institute for Health Information website [updated 2007; cited 2009 Feb 4]. Available from: http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=statistics_results_topic_drugs_e&cw_topic=Health%20Spending&cw_subtopic=Drugs. **42.** Lek Pharmaceuticals. Sandoz receives FDA approval for Omnitrope pen 10 with liquid cartridge. On Lek Pharmaceuticals website [updated 2008 Mar 9; cited 2009 Apr 8]. Available from: http://www.lek.si/eng/media-room/press-releases/3948/. **43.** Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, et al. Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation. Health Technol Assess. 2002;6(18):1-168. **44.** Daniels N. Justice, health, and healthcare. Am J Bioeth. 2001;1(2):2-16. **45.** Daniels N. Decisions about access to health care and accountability for reasonableness. J Urban Health. 1999;76(2):176-91. **46.** Kirby JC. Disability and justice: a pluralistic account. Soc Theory Pract. 2004;30(2):229-46. **47.** Voss LD, Sandberg DE. The psychological burden of short stature: evidence against. Eur J Endocrinol. 2004;151 Suppl 1:S29-S33. **48.** Judge TA, Cable DM. The effect of physical height on workplace success and income: preliminary test of a theoretical model. J Appl Psychol. 2004;89(3):428-41. **49.** Daniels N. Normal functioning and the treatment-enhancement distinction. Camb Q Healthc Ethics. 2000;9(3):309-22. **50.** Finkelstein BS, Singh J, Silvers JB, Marrero U, Neuhauser D, Cuttler L. Patient attitudes and preferences regarding treatment: GH therapy for childhood short stature. Horm Res. 1999;51 Suppl 1:67-72. **51.** World Heath Organization. Guidance on ethics and equitable access to HIV treatment and care. On World Heath Organization website [updated 2004; cited 2009 Feb 6]. Available from: http://www.who.int/ethics/Guidance%20on%20Ethics%20and%20HIV.pdf. **52.** Gruskin S, Daniels N. Justice and human rigths: priority setting and fair deliberative process. Am J Public Health. 2008;98(9):1573-7. **53.** Persad G, Werthiemer A, Emanuel EJ. Principles for allocation of scarce medical interventions. Lancet. 2009;373:423-31. **54.** Gravholt CH. Epidemiological, endocrine and metabolic features in Turner syndrome. Eur J Endocrinol. 2004;151(6):657-87. **55.** Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Mortality in women with turner syndrome in Great Britain: a national cohort study. J Clin Endocrinol Metab. 2008;93(12):4735-42. **56.** Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. On Canadian Agency for Drugs and Technologies in Health website [updated 2006 Apr; cited 2009 Feb 4]. Available from: http://www.cadth.ca.

Growth hormone for Turner syndrome in Canada

Extrinsic value

Extrinsic value components*	Synthesized information
Goals of healthcare – **utility***	Goal of healthcare is to maintain normal functioning (Daniels 2001).[44] Enhancement of otherwise normal traits is not the mission of a health plan (Daniels 1999).[45] Short stature is not a medical issue but rather a social issue (Kirby 2004).[46] Goals of GH treatment are to promote growth and to improve psychosocial adaptation of individual with short stature (Bondy 2007, Sandberg 2002);[6,39] however, psychosocial functioning of individuals with short stature is largely indistinguishable from their peers (Voss 2004).[47] Normal functioning also may be impacted by very short stature (e.g., reaching car pedals) (Li et al)[40] Shorter height has been linked to lower earnings (Judge 2004).[48]
Opportunity costs – **efficiency***	Considering maximizing impact on health for a given level of resources at: **Patient level**: "Both medical and psychological intervention should be developed so as to reinforce and support the individual's self-esteem and to ensure that individuals remain in the mainstream of social, educational, and employment activities" (Bondy 2007)[6] In considering efficiency and best distribution of resources among possible interventions for patients with Turner Syndrome, resources allocated to GH treatment may be more beneficial if allocated to other interventions such as psychological support to cope with condition overall (not just short stature). Strategies for wellbeing enhancement such as psychological support should be compared with GH treatment (Verweij 1997, Haverkamp 1999)[18,19] **Society level**: Significant cost/person but small population.
Population priority & access – **fairness***	**Fairness - prioritize worst off**: prioritizing the daily lot of those that are worst off is applicable to patients with Turner Syndrome but maybe not to the short stature part of the disease; daily lot probably not improved with daily injections for several years, but maybe as adult with less short stature than without treatment. **Fairness - treat like cases similarly**: should we treat differently short stature due to disease or due to genes (Daniels 2000)[49]? **Fairness - access to care/treatment**: Access easier in big cities where specialists are available; asking for care for short stature lower in low income/education and African Americans (US Finkelstein 1999).[50]
Appropriate use of intervention	Optimal age for initiation of GH treatment has not been established (Bondy 2007).[6] Appropriate follow up requires the intervention of skilled healthcare professionals In Canada, any physician can prescribed GH; some of the provinces that reimburse GH require it is prescribed by an endocrinologist. Potential for inappropriate use?
Stakeholder pressures	Pressure from parents, from clinicians, societal pressure on short stature?

*Ethical framework (WHO 2004)

Quality of evidence

Type of evidence	Completeness and consistency of reporting (Q2)	Relevance and validity of evidence (Q3)
Epidemiological data	75%	50%
Clinical data	75%	75%
PRO data	50%	50%
Economic evaluation	75%	50%
Budget impact model	75%	50%

Full assessment – example Q3- economic

EV431 – Relevance and validity – economic evaluation

Disease: Turner Syndrome (TS)
Intervention: recombinant human growth hormone (GH)
Setting: Canada

Study: Li H et al. Recombinant human growth hormone for Turner syndrome: systematic review and economic evaluation (Technology report number 96).[40] – Chapter 6: primary economic analysis

Type of evidence	Question	Type of evidence	Score
Economic evaluation	Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate (i.e., how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources [clinical, costs, epidemiology, and utilities])? *See dimensions below*	**Economic evaluation**	1 ☐ Low relevance/validity 2 ☐ 3 ☒ 4 ☐ High relevance/validity

	Dimension	Question	Comment
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	Yes, the target population (10-year-old girls with Turner Syndrome) is valid according to a Canadian RCT[5] and current (1998 to 2006) Canadian clinical practice.[7]
2	Intervention and setting	Are assumptions/design regarding interventions (dose & duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The rhGH dose was 0.3 mg/kg per week according to a Canadian RCT.[5] Based on a Product Monograph[3] and a 2007 international clinical guideline,[6] the recommended starting dose is up to 0.375 mg/kg per week. The weekly dose in mg was calculated based on mean weights by age of the general population (CDC growth chart). However, since girls with Turner Syndrome are shorter, they are also likely to be lighter than girls of the same age in the general population. This leads to an overestimation of drug use in the model. The age of treatment initiation (10 yrs) and treatment duration (6 yrs) were based on Canadian RCT.[5] There is a possibility that in future rhGH treatment may be initiated at a younger age (as young as 9 months) to maximize growth.[6] Since treatment is to continue until final height is reached, earlier treatment initiation is likely to lead to longer treatment duration. Mode of administration (daily or 6 times weekly subcutaneous self-injection) is valid.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	Yes, the model assumes a simple pathway that reflects current knowledge.
4	Comparator	Does the choice of comparators reflect current practice?	Yes, no treatment is currently the only intervention to treat growth restriction in Turner Syndrome.
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	Perspective of public health plan is valid; however, alternative analyses from the patient or societal perspective would have been useful to capture the impact of rhGH treatment on patients (e.g., to reflect the need to remodel car, purchase special furniture) and society as a whole. Costs of needles, injection devices and alcoholic swabs were not included, although some of these may be covered by the public healthcare system.
6	Outcome measures	Are the selected outcome measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	Since rhGH treatment may potentially affect quality of life, the outcome measure incremental cost per quality-adjusted life-year is relevant. The relevance of the second outcome measure, incremental cost per centimeter final height gained, is questionable because it implies that each additional centimeter has the same value regardless of the total height. Such an outcome measure could potentially be useful when comparing alternative interventions that increase height; however such alternatives currently do not exist. It would have been more relevant to calculate a cost per patient reaching a certain height cut-off (e.g., the 10th percentile of the general population). Utility of rhGH treatment was estimated based on a small (n=25) study of women with Turner Syndrome (mean age 28) who had never received rhGH treatment and were asked "how many years they would be willing to lose at the end of their life in order to obtain an average stature" (time trade-off technique). Given the small sample size and that only 44% of the women were willing to trade any lifetime, the validity of the utility value used in the model is questionable. Primary efficacy estimates (final heights) were used from the Canadian RCT;[5] adverse events were not included in the model. RhGH treatment of girls with Turner Syndrome is associated with specific adverse events, including headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis (Darendeliler et al. 2007,[29] Bolar et al. 2008[30]), which may have important quality of life and economic complications.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	The Canadian RCT reports the effect of rhGH treatment on final height adjusted for baseline height standard deviation score (SDS), baseline height SDS by treatment interaction, baseline age, and baseline age by treatment interaction (ANCOVA model).[5] Instead of this adjusted estimate of rhGH efficacy, the arithmetic difference in mean height between the treatment groups was used in the model, without providing a rationale. Assumption that there is no impact on patient quality of life during the 6 treatment years can be questioned. The need for daily injection could reduce quality of life, while an increase in growth velocity leading to height that is closer to that of peers may improve it. Turner Syndrome is associated with a 3-fold increase in mortality;[55] consequently, use of general population life expectancy overestimates life expectancy of women with Turner Syndrome. The model includes 3 outpatient visits during the first 5 years and annual hand X rays during the 2nd, 3rd and 4th years, but only 1 outpatient visit and no hand X ray during the last (6th) year. No explanation is provided why resource consumption was assumed to be different during the 6th year. Validity of unit costs for healthcare resources (physician visits, training session with nurse, hand X-ray) is difficult to assess since based on expert opinion (no other reference provided). Frequency of outpatient visits for treatment monitoring is valid based on clinical guideline.[6] Frequency of other healthcare resource use (3 hours of training by nurse, 1 hand X-ray per year) appears to be consistent with usual practice.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Yes, the lifetime horizon is adequate, since height affects quality of life for a lifetime.
9	Discount rate	Is the recommended discount rate applied?	Yes, 5% is recommended in Canada (CADTH 2006)[56]
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	Yes, sensitivity analyses covers rhGH price, dosage, initiation age, duration of treatment, height gain due to treatment, discount rate and quality-adjusted life-year gain.
11	Conclusion	Are conclusions supported by results?	Yes, conclusions are supported by the results obtained.

Discussion and conclusion

- The validated HTA report—integrated into the format of the MCDA Value Matrix—provided a practical tool that allowed for comprehensive assessment of the intrinsic value of GH for TS.
- Such assessment needs systematic consideration and quantification of all the essential components of decisionmaking pertaining to the relative value of the treatment (i.e., comparative efficacy, safety, patient reported outcomes, impact on drug and other spending, cost effectiveness) as well as its absolute value (i.e., severity of disease, size of population affected, types of benefit at both the population and patient level, quality of evidence) while taking into consideration clinical guidelines and the limitations of alternative interventions.
- A number of ethical and system-related considerations (extrinsic components of value) were also identified that may affect the intrinsic value estimate of the treatment.
- The framework and the web based prototype will be applied by a panel composed of a broad range of stakeholders to assess the value of GH for patients with TS as well as the practicality of the approach.

References

1. Baltussen R, Niessen L. Cost Eff Resour Alloc. 2006;4:14. **2.** Tunis SR. Health Aff (Millwood). 2007;26(4):w500-w515. **3.** Dhalla I, Laupacis A. CMAJ. 2008;178(4):428-31. **4.** Bryan S, Williams I, McIver S. Health Econ. 2007;16(2):179-93. **5.** Vuorenkoski L, Toiviainen H, Hemminki E. Health Policy. 2008;86(1):1-9. **6.** Browman GP, Manns B, Hagen N, Chambers CR, Simon A, Sinclair S. Journal of Oncology Practice. 2008;4(1):2-7. **7.** Tierney M, Manns B. CMAJ. 2008;178(4):432-5. **8.** Martin DK, Pater JL, Singer PA. Lancet. 2001;358(9294):1676-81. **9.** Mullen PM. Health Serv Manage Res. 2004;17(1):47-58. **10.** Wilson E, Sussex J, Macleod C, Fordham R. J Health Serv Res Policy. 2007;12(2):80-5. **11.** Camidge DR, Oliver JJ, Skinner C, Attwood B, Nussey F, Jodrell D, et al. Br J Clin Pharmacol. 2008;65(2):224-9. **12.** Schlander M. J Med Ethics. 2008;34(7):534-9. **13.** Wilson EC, Peacock SJ, Ruta D. Health Econ. 2008. **14.** Tappenden P, Brazier J, Ratcliffe J, Chilcott J. Pharmacoeconomics. 2007;25(8):685-93. **15.** Goetghebeur MM, Wagner M, Khoury H, Levitt RJ, Erickson LJ, Rindress D. BMC Health Serv Res. 2008;8(1):270. **16.** Li H, Banerjee S, Dunfield L, Kirby J, Jones M, Hamilton J, Deal C, Hadjiyannakis S, Normandin S, Tsakonas E. Technology report number 96, available from: http://cadth.ca/index.php/en/hta/reports-publications/search/publication/778. **17.** World Heath Organization. Guidance on ethics and equitable access to HIV treatment and care, available from: http://www.who.int/ethics/Guidance%20on%20Ethics%20and%20HIV.pdf.

Conflict of Interest

CD served as consultant or advisor for Lilly, Serono, Sandoz and Genentech; she was invited as conference speaker by these companies and by NovoNordisk and Pharmacia. The authors declare no other potential sources of conflict of interest.

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