

SUPPLEMENTARY MATERIAL

Supplementary Table 1 Search Term Strategy - Keyword alternatives and synonyms

Concept group 1	Concept group 2	Concept group 3	Concept group 4
Population-related terms	Disease-related terms	Medication-related terms	Adherence-related terms
child*	growth	treatment	adheren*
p?diatric	growth hormone	therapy	
infant	Growth-hormone	replacement	nonadheren*
minor	GH		non-adheren*
juvenile	Human growth hormone	medic*	non adheren*
youth	HGH	synthetic	
dependent		recombinant	complan*
Human	somatotro?in	rGH	noncomplan*
	somatotro?ic	rhGH	non-complan*
female	pituitary		non complian*
male		somatropin	
girl	growth hormone deficiency	Genotropin	persistence
boy	growth hormone disorder	Saizen	nonpersisten*
	growth hormone disease	Zomacton	non-persisten*
prepubertal	growth hormone condition	NutropinAq	non persisten*
pre-pubertal	growth hormone insufficiency	Norditropin	
preadolescen*	GHD	Omnitrope	concordan*
pre-adolescen*		Humatrope	discordan*
preteen*			
pre-teen*		regim*	continu*
preschool*		adminst*	discontinu*
pre-school*		inject*	dis-continu*
		dos*	
patient*		needle	duration
		device	cessation
parent*		syringe	
mother		pen	
father		delivery	
guardian			
carer			
caregiver			
care-giver			

Supplementary Table 2 Full search strategy

Ovid Medline (R), Embase, PsycINFO, International Pharmaceutical Abstracts

(child* OR p?diatric OR infant OR minor OR juvenile OR youth OR dependent OR human OR female OR male OR girl OR boy OR prepubertal OR pre-pubertal OR preadolescen* OR pre-adolescen* OR preteen* OR pre-teen* OR preschool* OR pre-school* OR adolescen* OR pubertal OR teen* OR patient OR parent OR mother OR father OR guardian OR carer OR caregiver OR care-giver).mp

AND

(growth OR growth hormone OR growth-hormone OR GH OR human growth hormone OR HGH OR somatotro?in OR somatotro?ic OR pituitary OR growth hormone deficiency OR growth hormone disorder OR growth hormone disease OR growth hormone condition OR growth hormone insufficiency OR GHD).mp

AND

(treatment OR therapy OR replacement OR medic* OR synthetic OR recombinant OR rGH OR rhGH OR somatropin OR Genotropin OR Saizen OR Zomacton OR NutropinAq OR Norditropin OR Omnitrope OR Humatrope OR regim* OR adminst* OR inject* OR dos* OR needle OR device OR syringe OR pen OR delivery).mp

AND

(adheren* OR nonadheren* OR non-adheren* OR non adheren* OR complian* OR noncomplian* OR non-complian* OR non complian* OR persistence OR nonpersisten* OR non-persisten* OR non persisten* OR concordan* OR discordan* OR continu* OR discontinu* OR dis-continu* OR duration OR cessation).mp.

Limits: English Language, Publication Year: 1985-current

Cochrane Library (Search Manager)

child* OR p?diatric OR infant OR minor OR juvenile OR youth OR dependent OR human OR female OR male OR girl OR boy OR prepubertal OR pre-pubertal OR preadolescen* OR pre-adolescen* OR preteen* OR pre-teen* OR preschool* OR pre-school* OR adolescen* OR pubertal OR teen* OR patient OR parent OR mother OR father OR guardian OR carer OR caregiver OR care-giver

AND

growth OR "growth hormone" OR growth-hormone OR GH OR "human growth hormone" OR HGH OR somatotro?in OR somatotro?ic OR pituitary OR "growth hormone deficiency" OR "growth hormone disorder" OR "growth hormone disease" OR "growth hormone condition" OR "growth hormone insufficiency" OR GHD

AND

treatment OR therapy OR replacement OR medic* OR synthetic OR recombinant OR rGH OR rhGH OR somatropin OR Genotropin OR Saizen OR Zomacton OR NutropinAq OR Norditropin OR Omnitrope OR Humatrope OR regim* OR adminst* OR inject* OR dos* OR needle OR device OR syringe OR pen OR delivery

AND

adheren* OR nonadheren* OR non-adheren* OR "non adheren*" OR complian* OR noncomplian* OR non-complian* OR "non complian*" OR persistence OR nonpersisten* OR non-persisten* OR "non persisten*" OR concordan* OR discordan* OR continu* OR discontinu* OR dis-continu* OR duration OR cessation

Web of Science

TS=(child* OR p?diatric OR infant OR minor OR juvenile OR youth OR dependent OR human OR female OR male OR girl OR boy OR prepubertal OR pre-pubertal OR preadolescen* OR pre-adolescenc* OR preteen* OR pre-teen* OR preschool* OR pre-school* OR adolescen* OR pubertal OR teen* OR patient OR parent OR mother OR father OR guardian OR carer OR caregiver OR care-giver)

AND

TS=(growth OR "growth hormone" OR "growth-hormone" OR GH OR "human growth hormone" OR HGH OR somatotro?in OR somatotro?ic OR pituitary OR "growth hormone deficiency" OR "growth hormone disorder" OR "growth hormone disease" OR "growth hormone condition" OR "growth hormone insufficiency" OR GHD)

AND

TS=(treatment OR therapy OR replacement OR medic* OR synthetic OR recombinant OR rGH OR rhGH OR somatropin OR Genotropin OR Saizen OR Zomacton OR NutropinAq OR Norditropin OR Omnitrope OR Humatrope OR regim* OR adminst* OR inject* OR dos* OR needle OR device OR syringe OR pen OR delivery)

AND

TS=(adheren* OR nonadheren* OR non-adheren* OR non adheren* OR complian* OR noncomplian* OR non-complian* OR "non complian*" OR persistence OR nonpersisten* OR non-persisten* OR "non persisten*" OR concordan* OR discordan* OR continu* OR discontinu* OR dis-continu* OR duration OR cessation)

Limits: Language=English. Timespan=1985-2018

Applied Social Sciences Index and Abstracts (ASSIA)

(ANYWHERE) child* OR p?diatric OR infant OR minor OR juvenile OR youth OR dependent OR human OR female OR male OR girl OR boy OR prepubertal OR pre-pubertal OR preadolescen* OR pre-adolescenc* OR preteen* OR pre-teen* OR preschool* OR pre-school* OR adolescen* OR pubertal OR teen* OR patient OR parent OR mother OR father OR guardian OR carer OR caregiver OR care-giver

AND

(ANYWHERE) growth OR "growth hormone" OR "growth-hormone" OR GH OR "human growth hormone" OR somatotro?in OR somatotro?ic OR pituitary OR "growth hormone deficiency" OR "growth hormone disorder" OR "growth hormone disease" OR "growth hormone condition" OR "growth hormone insufficiency"

AND

(ANYWHERE) treatment OR therapy OR replacement OR medic* OR synthetic OR recombinant OR somatropin OR regim* OR adminst* OR inject* OR dos* OR needle OR device OR syringe OR pen OR delivery

AND

(ANYWHERE) adheren* OR nonadheren* OR non-adheren* OR "non adheren*" OR complian* OR noncomplian* OR non-complian* OR "non complian*" OR persistence OR nonpersisten* OR non-persisten* OR "non persisten*" OR concordan* OR discordan* OR continu* OR discontinu* OR dis-continu* OR duration OR cessation

Limits: Language: English. Publication Date: After this Date: 1 January 1985

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

(TX) child* OR p#diatric OR infant OR minor OR juvenile OR youth OR dependent OR human OR female OR male OR girl OR boy OR prepubertal OR pre-pubertal OR preadolescen* OR pre-adolescen* OR preteen* OR pre-teen* OR preschool* OR pre-school* OR adolescen* OR pubertal OR teen* OR patient* OR parent* OR mother OR father OR guardian OR carer OR caregiver OR care-giver

AND

(TX) growth OR "growth hormone" OR "growth-hormone" OR GH OR "human growth hormone" OR somatotro#in" OR "somatotro#ic" OR pituitary OR "growth hormone deficiency" OR "growth hormone disorder" OR "growth hormone disease" OR "growth hormone condition" OR "growth hormone insufficiency"

AND

(TX) treatment OR therapy OR replacement OR medic* OR synthetic OR recombinant OR somatropin OR regim* OR adminst* OR inject* OR dos* OR needle OR device OR syringe OR pen OR delivery

AND

(TX) adheren* OR nonadheren* OR non-adheren* OR non adheren* OR complian* OR noncomplian* OR non-complian* OR "non complian*" OR persistence OR nonpersisten* OR non-persisten* OR "non persisten*"

Limits: English Language. Published Date: January 1985– January 2018

Open Grey

child* OR pediatric OR paediatric

AND

growth OR "growth hormone"

AND

treatment OR therapy OR medic*

AND

adheren* OR complian* OR persisten*

Limits: Language: English, Year: 1985-2018

ETHOS

(Any word) child* OR pediatric OR paediatric

AND

(Any word) growth hormone

WorldCat Dissertation and Theses

(Keyword:) child* OR pediatric OR paediatric

AND

(Keyword:) growth OR "growth hormone"

Limits: Language: English, Year: 1985 to 2018

Supplementary Table 3 PICOS inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
Studies were included if they met the following criteria:	Studies were excluded if they met the following criteria:
Females and males aged between 0.0 years and an upper age limit of 18.0 years.	Female and male adults >18.0 years.
<ul style="list-style-type: none"> - Studies using single samples, (e.g. pre-pubertal, adolescents) or mixed samples (e.g. children and adolescents with GHD) 	Non-human (Animal) studies
Paediatric Patients with a clinical diagnosis of Growth Hormone Deficiency	Paediatric patients identified as having specific or significant symptoms of GHD, borderline, or undiagnosed, or patients with any other pathological conditions.
Parents/carers of Paediatric Patients with a clinical diagnosis of Growth Hormone Deficiency	Individuals diagnosed with forms of short stature or growth failure due to: chronic renal failure, Turner Syndrome, Prader-Willi Syndrome, small for gestational age, idiopathic short stature, short stature homeobox-containing gene deficiency (SHOX), Noonan Syndrome and Silver Russell Syndrome.
<ul style="list-style-type: none"> - Growth Hormone Deficiency includes sub-groups of idiopathic or secondary/acquired, isolated or multiple pituitary hormone deficiency 	
Patients prescribed with Growth Hormone Treatment.	Growth hormone not prescribed
Randomised controlled trials (RCT) and non-RCTs (prospective cohort and retrospective cohort studies) or Cross-sectional.	Non-empirical, general discussion, or, narrative reviews or theoretical papers, case studies, or qualitative studies.
Standardised measure/method of assessment of adherence (both validated/non-validated methods) explicitly identifiable.	No measure method of assessment of adherence.
Prevalence rate of adherence/non-adherence for Growth Hormone Deficiency explicitly extractable.	No prevalence rate of adherence/non-adherence.
	Prevalence rate of adherence/non-adherence for combined growth disorders.
Psychosocial, clinical or socio-demographic factors associated with adherence explicitly identifiable	Sole focus on various variables including Growth Response, Height, Height Standard Deviation Score, Growth Velocity, Growth Velocity Standard Deviation Score, Body Composition, BMI or metabolic markers or effects, adverse effects of treatment, health-related quality of life.
Studies published between 1985 – 2017	Studies published pre- 1985
English-language studies	Non-English language studies

Bozzola et al. [33]	2014	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Exclude
Drosatou et al. [34]	2014	Yes	<i>Not specified</i>	Yes	Yes	Yes	No	Yes	Yes	No	Exclude
Miller et al. [35]	2014	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Exclude
Hartman et al. [12]	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Cutfield et al. [3]	2011	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Kapoor et al. [17]	2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Rosenfeld & Bakker [2]	2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Oyarzabel et al. [36]	1998	No	<i>Not specified</i>	Yes	Yes	Yes	No	Yes	Yes	Yes	Exclude
Smith et al. [10]	1993	<i>Not specified</i>	<i>Not specified</i>	Yes	Yes	Yes	No	Yes	Yes	Yes	Exclude
Leiberman et al. [37]	1993	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Exclude
Gacs et al. [38]	1991	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Exclude

Supplementary Table 5 Full reasons for exclusion table

Author	Study Title	Publication Year	Reason for Exclusion
Mohseni et al. [15]	<i>Adherence to growth hormone therapy in children and its potential barriers</i>	2018	<ul style="list-style-type: none">• Patient clinical indications not specified.
Bagnasco et al. [24]	<i>Prevalence and Correlates of Adherence in Children and Adolescents treated with Growth Hormone: a Multicenter Italian Study</i>	2017	<ul style="list-style-type: none">• Patient clinical indications not specified.• Adherence rate for GHD patients not reported.
Ergur et al. [25]	<i>The adherence to Growth Hormone Therapy in children with Growth Hormone Deficiency</i>	2017	<ul style="list-style-type: none">• Adherence rate for GHD patients not reported.• Abstract only – no access to full-text copy.• Psychosocial, clinical or sociodemographic factor(s) associated with adherence cannot be explicitly identified.
Farfel et al. [26]	<i>Long term adherence to growth Hormone Therapy in a large health maintenance organization cohort.</i>	2017	<ul style="list-style-type: none">• Patient clinical indications not specified.• Adherence rate for GHD patients not reported.• Abstract - no full-text copy.
Sayarifard et al. [27]	<i>Growth Hormone Utilization Review in a Pediatric Primary Care Setting.</i>	2017	<ul style="list-style-type: none">• Clearly-defined measure of adherence not identified.• Adherence rate for GHD patients not reported.
Hughes et al. [28]	<i>Early cessation and non-response are important and possibly related problems in growth hormone therapy: An OZGROW analysis</i>	2016	<ul style="list-style-type: none">• Clearly-defined measure of adherence not identified.• Psychosocial, clinical or sociodemographic factor(s) associated with adherence cannot be explicitly identified.• Adherence rate for GHD patients not reported.
De Pedro et al. [29]	<i>Variability in adherence to rhGH treatment: Socioeconomic causes and effect on children's growth</i>	2015	<ul style="list-style-type: none">• Adherence rate for GHD patients not reported.
Kremidas et al. [30]	<i>Administration Burden Associated with Recombinant Human Growth Hormone Treatment: Perspectives of Patients and Caregivers</i>	2015	<ul style="list-style-type: none">• Patient group includes >18 years.• Clearly-defined measure of adherence not identified.• Adherence rate for GHD patients not reported.
Bozzola et al. [33]	<i>Adherence to Growth Hormone Therapy: A Practical Approach</i>	2014	<ul style="list-style-type: none">• Clearly-defined measure of adherence not identified.• Psychosocial, clinical or sociodemographic factor(s) associated with adherence cannot be explicitly identified.• Adherence rate for GHD patients not reported.

Miller et al. [35]	<i>Persistence with Growth Hormone Therapy in Pediatric Patients</i>	2014	<ul style="list-style-type: none"> • Clearly-defined measure of adherence not identified.
Drosatou et al. [34]	<i>Assessment of Compliance with GH Therapy</i>	2014	<ul style="list-style-type: none"> • Patient clinical indications not specified. • Adherence rate for GHD patients not reported. • Abstract only- no access to full-text copy.
Oyarzabel et al. [36]	<i>Multicentre survey on compliance with growth hormone therapy: what can be improved?</i>	1998	<ul style="list-style-type: none"> • Patient clinical indications not specified. • Patient group includes >18 years. • Adherence rate for GHD patients not reported.
Leiberman et al. [37]	<i>Coping and Satisfaction with Growth Hormone Treatment among Short-Stature Children</i>	1993	<ul style="list-style-type: none"> • Adherence rate for GHD patients not reported. • Psychosocial, clinical or sociodemographic factor(s) associated with adherence cannot be explicitly identified.
Smith et al [10].	<i>Compliance with growth hormone treatment--are they getting it?</i>	1993	<ul style="list-style-type: none"> • Patient clinical indications not specified. • Patient age not specified. • Adherence rate for GHD patients not reported.
Gacs et al. [38]	<i>The effect of socio-economic conditions on the time of diagnosis and compliance during treatment in growth hormone deficiency.</i>	1991	<ul style="list-style-type: none"> • Clearly-defined measure of adherence not identified.

Supplementary Table 6 Full Data Extraction Table

a) Study Details and Study Population

Author	Study Title	Publication Year	Country	Sample Size	Gender N (%)	Mean Age: y.m	Clinical Indication of GH Therapy. N (%)	Duration of GH Therapy
Lass et al.[31]	<i>Low Treatment Adherence in Pubertal Children Treated with Thyroxin or Growth Hormone</i>	2015	Germany	103 patients	67 (65) male 36 (35) female	10.1 (range 8.1-12.2)	GHD = 74 (72) Turner Syndrome= 4 (4) SHOX deficiency= 3 (3) Small for gestational age= 21 (20) Prader-Willi-syndrome= 1 (1)	Mean: 3.1 years (1.4 - 5.4)
Aydin et al.[32]	<i>Adherence to Growth Hormone Therapy: Results of a Multicenter Study.</i>	2014	Turkey	217 GH-naïve patients in 6 pediatric endocrinology clinics	114 (53) boys 103 (47) girls	11.1±3.1 years	GHD = 185 (85.3) Turner Syndrome = 16 (7.4) Neurosecretory Dysfunction = 6 (2.8) Interuterine Growth Retardation = 5 (2.3) Bioinactive GH = 5 (2.3)	1 year
Hartman et al.[12]	<i>Growth hormone treatment adherence in prepubertal and pubertal children with different growth disorders.</i>	2013	Germany	75 children	46 (61) boys 29 (39) girls	12.5±3.5 years	GHD = 48 (64) Turner Syndrome= 6 (8) Small for gestational age= 18 (24) Chronic Renal Failure = 3 (4)	<i>Not specified</i>
Cutfield et al.[3]	<i>Non-compliance with growth hormone treatment in children is common and impairs linear growth.</i>	2011	New Zealand	175 patients	84 (48) males 91 (52) females	12.1±0.6 years	GHD = 100 (57%) Turner Syndrome = 47 (27%) Idiopathic short stature = 12 (7%) Small for gestational age = 11 (6%) Prader Willi Syndrome = 5 (3%)	<i>Not specified</i>
Kapoor et al.[17]	<i>Monitoring of concordance in growth hormone therapy</i>	2008	UK	75 patients	47 (63) male 28 (37) female	Median age: 12.3 years (range 8.9–14.8) <i>Mean age not specified</i>	GHD = 75 (100%)	1.9 years (1.2–4.0)
Rosenfeld & Bakker [2]	<i>Compliance and persistence in pediatric and adult patients receiving growth hormone therapy.</i>	2008	USA	724 [326 Adolescents (13-17yrs) and 398 parents of children (4-12yrs)]	<i>Not specified</i>	Adolescents (13-17yrs) and parents of children (4-12yrs) <i>Mean age not specified</i>	GHD = 326 and 398 of parents of children with GHD, Turner Syndrome or Idiopathic short stature	<i>Not specified</i>

b) Study Details and Key Findings

Study Details				Primary Outcome Findings			Key Factor Findings			Quality
Author	Year	Country	Study Design	Method of assessing adherence	Observation Time Period	Definition of non-adherence	Prevalence of Non-adherence/ Adherence for GHD	Factors Associated with Non Adherence	Factors not Associated with Non-Adherence	Quality Score
Lass et al.[31]	2015	Germany	Retrospective	Prescription refill rates	1 year	Calculated as percentage based on the prescription refill rates according to the literature (Osterberg 2005): Prescribed dosage was divided by required dosage and multiplied by 100. Adherence data were evaluated in accordance with the cut-offs as proposed by Cutfield et al (2011) {good adherence: <1 missed dose per week (>85% adherence); medium adherence: 1-3 missed doses per week (57.1-85.7% adherence); poor adherence: >3 missed doses per week (<57.1% adherence)}.	Adherence rate of GHD children treated with with rhGH (n=74) was good in 53%, medium in 23% and poor in 24%.	Treatment duration Puberty (age) Self-administration	Type of injection device	Good
Aydin et al.[32]	2014	Turkey	Longitudinal observational	Patient Self report Questionnaire - evaluated at initiation, 3rd, 6th and 12 month of therapy.	1 year (3, 6, 12 month time-points)	Adherence categories were established following the criteria of Smith (1993) and patients categorized into 4 adherence segments based on percentage of doses omitted at each evaluation period. Classified as excellent if 0%, good if 5%, fair if 5-10%, and poor if >10%.	3 months: adherence rate was excellent in 87.0% of cases, good in 8.1%, fair in 1.6% and poor in 3.2% of cases. 6 months: adherence was excellent in 85.4%, good in 7.0%, fair in 2.7% and poor in 4.9% of patients. 12 months: adherence was excellent in 77.3%. good in 13.5%, fair in 2.2% and poor in 7.0% of patients.	Forgetting to administer GH Failure to renew the prescription Problems with the delivery service Illness Vacation/break Patient or person who administered the injection being away from home	Cause of GH treatment Socioeconomic status of the family Person who administered the injections Type of injection device GH product used	Good

Hartman et al.[12]	2013	Germany	Prospective Observational	Easypod® administration device in conjunction with the clinical kit software - Easypod® Connect Software.	343 ±201 days	Compliance was defined by Cutfield et al.(2011) : good compliance, <1 missed dose per week (85.7–100% proportion injected); medium compliance, 1–3 missed doses per week (57.1–85.7% proportion injected), and poor compliance, >3 missed doses per week (<57.1% proportion injected).	Children with GHD showed poor compliance 22.9%, with 77.1% showing good compliance.	Age (increasing)	Diagnosis	Good
Cutfield et al.[3]	2011	New Zealand	Cross-sectional survey	Two parameters: either the number of GH vials requested (GHreq) by the family each month or the number of empty GH vials returned (GHret).	4 months	Compliance was defined as ≥85% adherence (no more than one missed dose a week on average) to prescribed treatment. High compliance (missed<1 dose a week on average), Medium (missed >1 and <3 doses/week), and Low (missed ≥3 doses/week).	The overall estimated rate of non-compliance (i.e. patients missing more than one injection per week) was 66% (73/110) according to GHret (and 34% (59/172) according to Ghreq).	Maori ethnicity	Age Gender Clinical diagnosis Area of residence	Good
Kapoor et al.[17]	2008	UK	Retrospective observational	Issued rhGH prescriptions	3 x 1 year (1999–2000; 2000–2001;2002–2003)	Concordance was objectively assessed by comparing total expected GH usage to the total amount of GH prescribed by GPs during a 12-month period. The annual deficit in GH prescribed compared to that expected was calculated. The estimated number of missed injections per week was calculated. Frequency of missed injections: injections missed: >1 per week; injections missed: 1-2 per week; injections missed: >2 per week.	[62% non-compliant] More than >1 injection/week was missed by 39% (29/75) of the children, and 23% (17/75) missed >2 injections/week.	Longer duration of treatment Lack of choice of injection device Short duration of GH prescriptions (<4 weeks) Type of health professional providing training Growth response - reduced height velocity	Age Type of injection device used Initial height standard deviation score SDS	Good

Rosenfeld & Bakker [2]	2008	USA	Retrospective	Self-report questionnaire and interview via telephone or internet	3 months	Compliance was defined by a categorical assessment of frequency of missed GH doses based on potential reasons. Compliance segments were created on the basis of the number of '4'(never) responses. Patients categorised into 3 segments: Highly compliant (8-9 'never' responses), occasionally noncompliant (6-7 'never' responses), or noncompliant and skeptical (5 or fewer 'never' responses).	[Overall = 71%] 64% of parents of children and 77% of teens yielded noncompliance levels.	Understanding about GHD Understanding of prescribed rhGH treatment Misperceptions about the consequences of missed rhGH doses/minimisation of the seriousness of missed doses of GH Inadequate contact with health-care providers Training and rhGH administration technique (poor injection technique) Acceptance and satisfaction with GH therapy Discomfort with injections / Pain Age - Adolescence Dissatisfaction with treatment results Doctor-patient relationship	Diagnosis Type of injection device used	Fair
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Supplementary Table 7 Full Quality Assessment table for included studies

Criteria	Study Lass et al.[31]	Aydin et al.[32]	Hartman et al.[12]	Cutfield et al.[3]	Kapoor et al.[17]	Rosenfeld& Bakker [2]
1. Research Question Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y
2. Study Population Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y
3. Participation Rate Was the participation rate of eligible persons at least 50%?	NR	CD	Y	Y	Y	N
4. Inclusion Criteria Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y
5. Sample Size Was a sample size justification, power description, or variance and effect estimates provided?	N	N	N	N	N	N
6. Exposure prior to outcome For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	CD	Y	N
7. Sufficient timeframe Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y	Y
8. Different levels of exposure For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	Y	Y	Y	Y

NOTE: *Y = Yes; N= No, NR = not reported; CD = cannot determine; N/A = not applicable.

Supplementary Table 8 Summary Data Extraction Table

Study Details		Study Population			Primary Outcome		Key Findings		Quality
Author and Publication Year	Study Design	Sample Size	Mean Age: y.m	Clinical Indication of GH Therapy. N (%)	Method of assessing adherence	Prevalence of Non-adherence/Adherence for GHD	Factors Associated with Non Adherence	Factors not Associated with Non-Adherence	Quality Rating
Lass et al. (2015) [31]	Retrospective	103 patients	10.1 (range 8.1-12.2)	GHD = 74 (72) Turner Syndrome= 4 (4) SHOX deficiency= 3 (3) Small for gestational age= 21 (20) Prader-Willi-syndrome= 1 (1)	Prescription refill rates	Adherence rate of GHD children treated with with rhGH (n=74) was good in 53%, medium in 23% and poor in 24%.	Treatment duration Puberty (age) Self-administration	Type of injection device	Good
Aydin et al. (2014) [32]	Longitudinal observational	217 GH-naïve patients	11.1±3.1 years	GHD = 185 (85.3) Turner Syndrome = 16 (7.4) Neurosecretory Dysfunction = 6 (2.8) Interuterine Growth Retardation = 5 (2.3) Bioinactive GH = 5 (2.3)	Patient Self report Questionnaire - evaluated at initiation, 3rd, 6th and 12 month of therapy.	3 months: adherence rate was excellent in 87.0% of cases, good in 8.1%, fair in 1.6% and poor in 3.2% of cases. 6 months: adherence was excellent in 85.4%, good in 7.0%, fair in 2.7% and poor in 4.9% of patients. 12 months: adherence was excellent in 77.3%. good in 13.5%, fair in 2.2% and poor in 7.0% of patients.	Forgetting to administer GH Failure to renew the prescription Problems with the delivery service Illness Vacation/break Patient or person who administered the injection being away from home	Cause of GH treatment Socioeconomic status of the family Person who administered the injections Type of injection device GH product used	Good
Hartman et al. (2013) [12]	Prospective Observational	75 children	12.5±3.5 years	GHD = 48 (64) Turner Syndrome= 6 (8) Small for gestational age= 18 (24) Chronic Renal Failure = 3 (4)	Easypod® administration device in conjunction with the clinical kit software - Easypod® Connect Software.	Children with GHD showed poor compliance 22.9%, with 77.1% showing good compliance.	Age (increasing)	Diagnosis	Good

Cutfield et al.(2011) [3]	Cross-sectional survey	175 patients	12.1±0.6 years	GHD = 100 (57%) Turner Syndrome = 47 (27%) Idiopathic short stature =12 (7%) Small for gestational age = 11 (6%) Prader Willi Syndrome = 5 (3%)	Two parameters: either the number of GH vials requested (GHreq) by the family each month or the number of empty GH vials returned (GHret).	The overall estimated rate of non-compliance (i.e. patients missing more than one injection per week) was 66% (73/110) according to GHret (<i>and 34% (59/172) according to Ghreq</i>).	Maori ethnicity	Age Gender Clinical diagnosis Area of residence	Good
Kapoor et al. (2008) [17]	Retrospective observational	75 patients	Median age: 12.3 years (range 8.9–14.8) <i>Mean age not specified</i>	GHD = 75 (100%)	Issued rhGH prescriptions	[62% non-compliant] More than >1 injection/week was missed by 39% (29/75) of the children, and 23% (17/75) missed >2 injections/week.	Longer duration of treatment Lack of choice of injection device Short duration of GH prescriptions (<4 weeks) Type of health professional providing training Growth response - reduced height velocity	Age Type of injection device used Initial height standard deviation score SDS	Good
Rosenfeld & Bakker (2008) [2]	Retrospective	724 [326 Adolescents (13-17yrs), 398 parents of children (4-12yrs)]	Adolescents (13-17yrs) and parents of children (4-12yrs) <i>Mean age not specified</i>	GHD = 326 398 of parents of children with GHD, Turner Syndrome or Idiopathic short stature	Self-report questionnaire and interview via telephone or internet	[Overall = 71%] 64% of parents of children and 77% of teens yielded noncompliance levels.	Understanding about GHD Understanding of prescribed rhGH treatment Misperceptions about the consequences of missed rhGH doses/minimisation of the seriousness of missed doses of GH Inadequate contact with health-care providers Training and rhGH administration technique (poor injection technique) Acceptance and satisfaction with GH therapy Discomfort with injections / Pain Age - Adolescence Dissatisfaction with treatment results Doctor-patient relationship	Diagnosis Type of injection device used	Fair

Supplementary Table 9 Methods of Adherence and Prevalence rates

Study Details		Primary Outcome		Key Factor Findings
Author	Year	Method of assessing adherence	Observation Time Period	Prevalence of Non-adherence/ Adherence for GHD
Lass et al.[31]	2015	Prescription refill rates	1 year	Adherence rate of GHD children treated with with rhGH was good in 53%, medium in 23% and poor in 24% .
Aydin et al.[32]	2014	Patient Self report Questionnaire - evaluated at initiation, 3rd, 6th and 12 month of therapy.	1 year (3, 6, 12 month time-points)	3 months: adherence rate was excellent in 87.0% of cases, good in 8.1%, fair in 1.6% and poor in 3.2% of cases. 6 months: adherence was excellent in 85.4%, good in 7.0%, fair in 2.7% and poor in 4.9% of patients. 12 months: adherence was excellent in 77.3%. good in 13.5%, fair in 2.2% and poor in 7.0% of patients.
Hartman et al.[12]	2013	Easypod® administration device in conjunction with the clinical kit software - Easypod® Connect Software.	343 ±201 days	Children with GHD showed poor compliance 22.9% , with 77.1% showing good compliance.
Cutfield et al.[3]	2011	Two parameters: either the number of GH vials requested (GHreq) by the family each month or the number of empty GH vials returned (GHret).	4 months	The overall estimated rate of non-compliance (i.e. patients missing more than one injection per week) was 66% (73/110) according to GHret (and 34% (59/172) according to Ghreq).
Kapoor et al.[17]	2008	Issued rhGH prescriptions	3 x 1 year (1999–2000; 2000–2001; 2002–2003)	[62% non-compliant] More than >1 injection/week was missed by 39% (29/75) of the children, and 23% (17/75) missed >2 injections/week.
Rosenfeld & Bakker [2]	2008	Self-report questionnaire and interview via telephone or internet	3 months	[Overall = 71%] 64% of parents of children and 77% of teens yielded noncompliance levels.

Supplementary Table 10 Potentially modifiable factors associated with lower adherence to rhGH treatment in paediatric GHD patients – categorised within the COM-B framework

CAPABILITY	OPPORTUNITY	MOTIVATION
Physical Capability	Physical Opportunity	Reflective Motivation
Poor GH administration technique [2]	Discomfort and pain associated with daily injections [2]	Dissatisfaction and non-acceptance of rhGH therapy [2]
Self-administration (<i>skill</i>) [31]*	Long duration of Treatment [17, 31]	Lack of choice of injection device [17]*
	Short duration of GH prescriptions (<4 weeks) [17]	Dissatisfaction with treatment results [2, 17]
	Problems with the delivery service [32]	Self-administration (<i>confidence/self-efficacy</i>) [31]*
	Lack of choice of injection device (HCP) [17]*	
Psychological Capability	Social Opportunity	Automatic Motivation
Lack of understanding about GHD [2]	rhGH administration training provided by non-hospital staff [17]	Lifestyle disruptions to routine and scheduling issues (Being away from home [32], Vacation/Break [32], Illness [32])
Lack of understanding of prescribed rhGH treatment [2]	Inadequate contact with health-care providers [2]	
Patient or family's lack of understanding of the consequences of missed rhGH doses [2]	Poor doctor-patient relationship [2]	
Forgetting to administer GH [32]		
Failure/neglect to renew the prescription [32]		

*NOTE: Two factors (self-administration [31] and lack of choice of injection device [17]) have been mapped onto two relevant COM-B sub-components (see Discussion).