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Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Clinical background, current care pathway and technologies assessed

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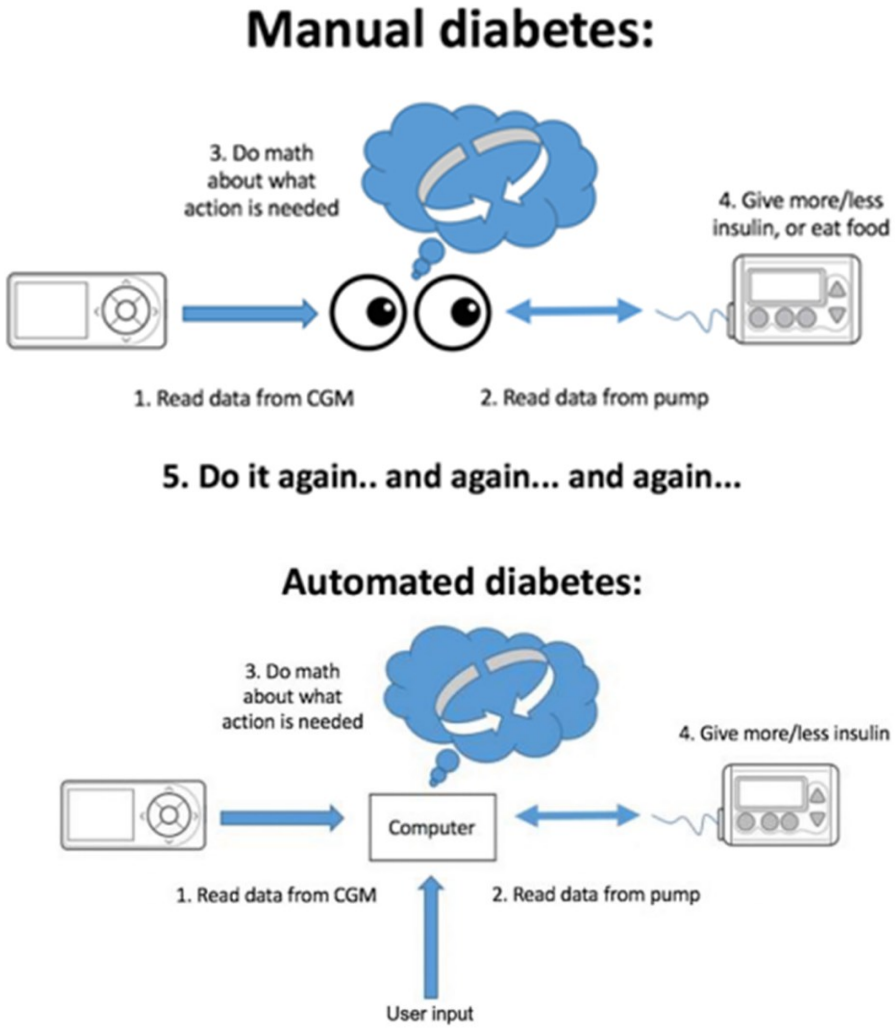
29 November 2022

NICE National Institute for Health and Care Excellence

Background

- Type 1 diabetes is a condition which requires intensive management with regular glucose checks and insulin administration.
- It can lead to significant morbidity, mortality and psychological burden.
- Recent years have seen significant advances in the development of **hybrid-closed loop systems**, which can improve glycaemic outcomes and burden of treatment for people with diabetes (PwD) with automation[1].



1. Phillip M, Nimri R, Bergenstal RM, et al. Consensus Recommendations for the Use of Automated Insulin Delivery (AID) Technologies in Clinical Practice. Endocr Rev 2022; published online Sept 6. DOI:10.1210/endrev/bnac022

Figure adapted with permission from Lewis D, Automated Insulin Delivery, ISBN 9781797763699, https://www.artificialpancreasbook. com Dana Lewis 2019

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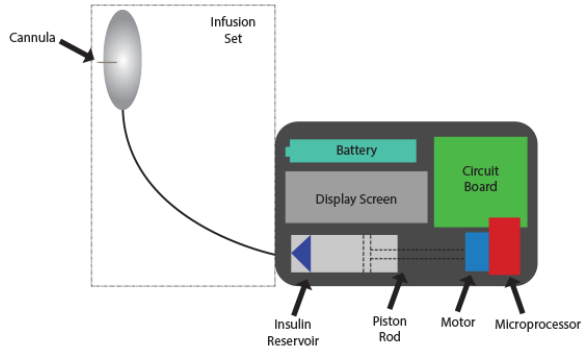
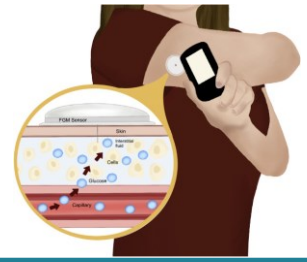
Background: Devices

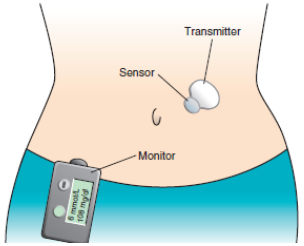
CSII or insulin pump (constant subcutaneous insulin infusion)



Continuous glucose monitor (CGM)

- is-CGM (intermittently scanned continuous glucose monitor)
- rt-CGM (real time continuous glucose monitor)



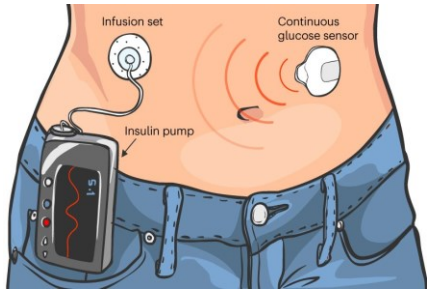


	is-CGM	rt-CGM
Types of CGM	Display of glucose values only on demand with trend arrows. Alarm functions to warn of adverse glucose levels (threshold based alarm).	Contemporaneous display of glucose and trends Alarm functions to warn of impending adverse glucose levels (predictive alarm).

Background: Devices

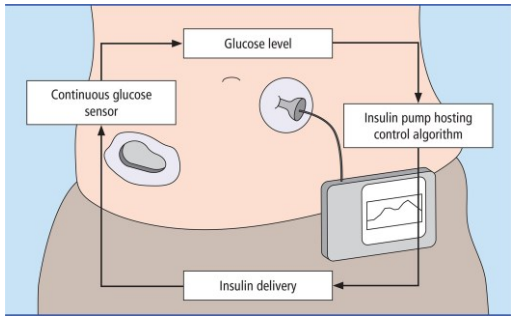
Sensor-augmented pump therapy (SAP)

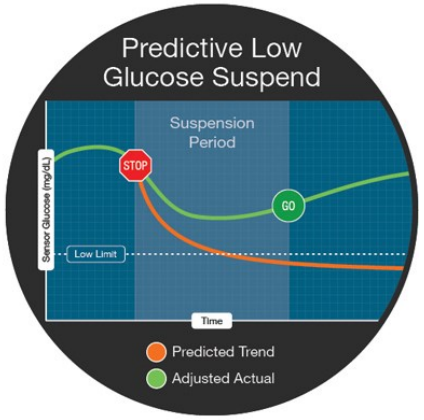
Manual dosing of insulin



Predictive low-glucose suspend (PLGS)

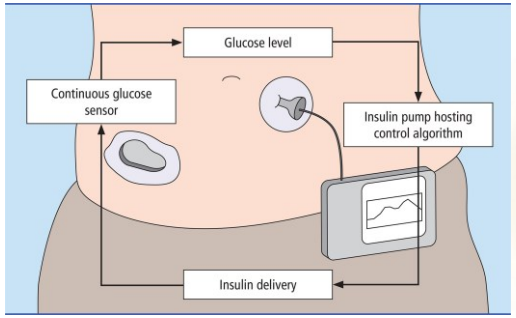
Manual dosing with suspension of insulin when low glucose levels are predicted

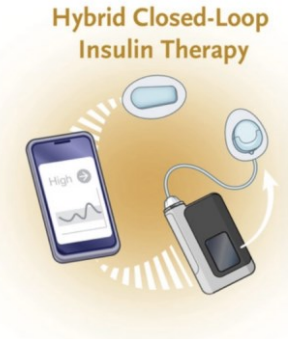


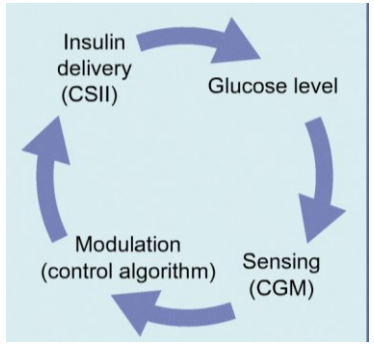


Hybrid-closed loop systems (HCL)

Manual dosing at mealtimes with continuous adjustments of insulin delivery directed by an algorithm in response to changes in glucose







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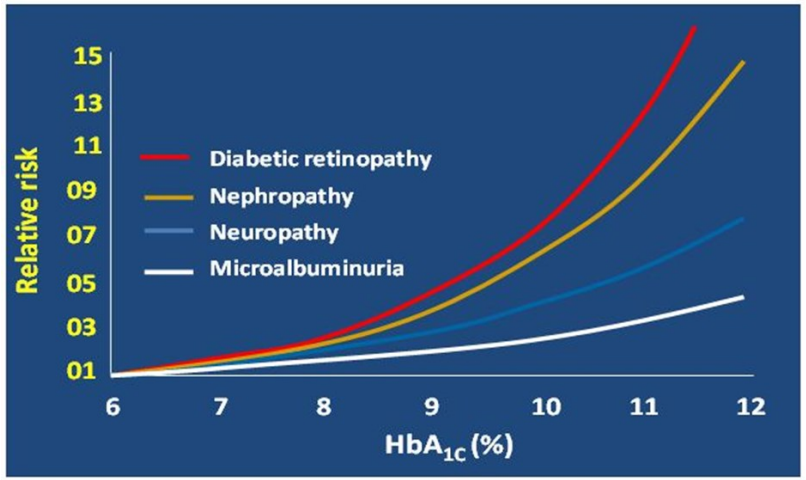
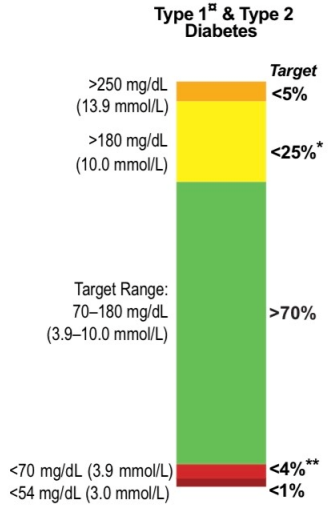
Outcomes

- HbA1c



Diabetes Control and Complications Trial (DCCT) 1993

- Time-in-range (TIR)



Battelino et al, Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range 2019

Hypoglycaemia measures:

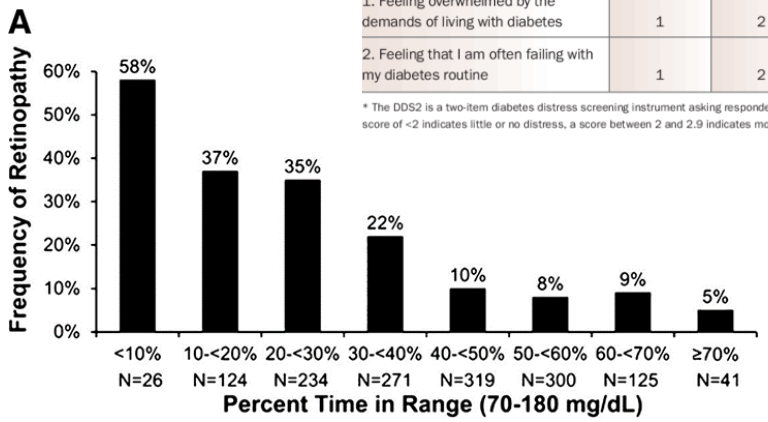
- Clarke score

Psychological scores

- Diabetes distress scale 2

Item	Not a problem	A slight problem	A moderate problem	A somewhat serious problem	A serious problem	A very serious problem
1. Feeling overwhelmed by the demands of living with diabetes	1	2	3	4	5	6
2. Feeling that I am often failing with my diabetes routine	1	2	3	4	5	6

* The DDS2 is a two-item diabetes distress screening instrument asking respondents to rate on a six-point scale the degree to which the two items above caused distress. An average score of <2 indicates little or no distress, a score between 2 and 2.9 indicates moderate diabetes distress and ≥3 indicates high level of diabetes distress.



Beck RW, Bergenstal RM, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care 2019

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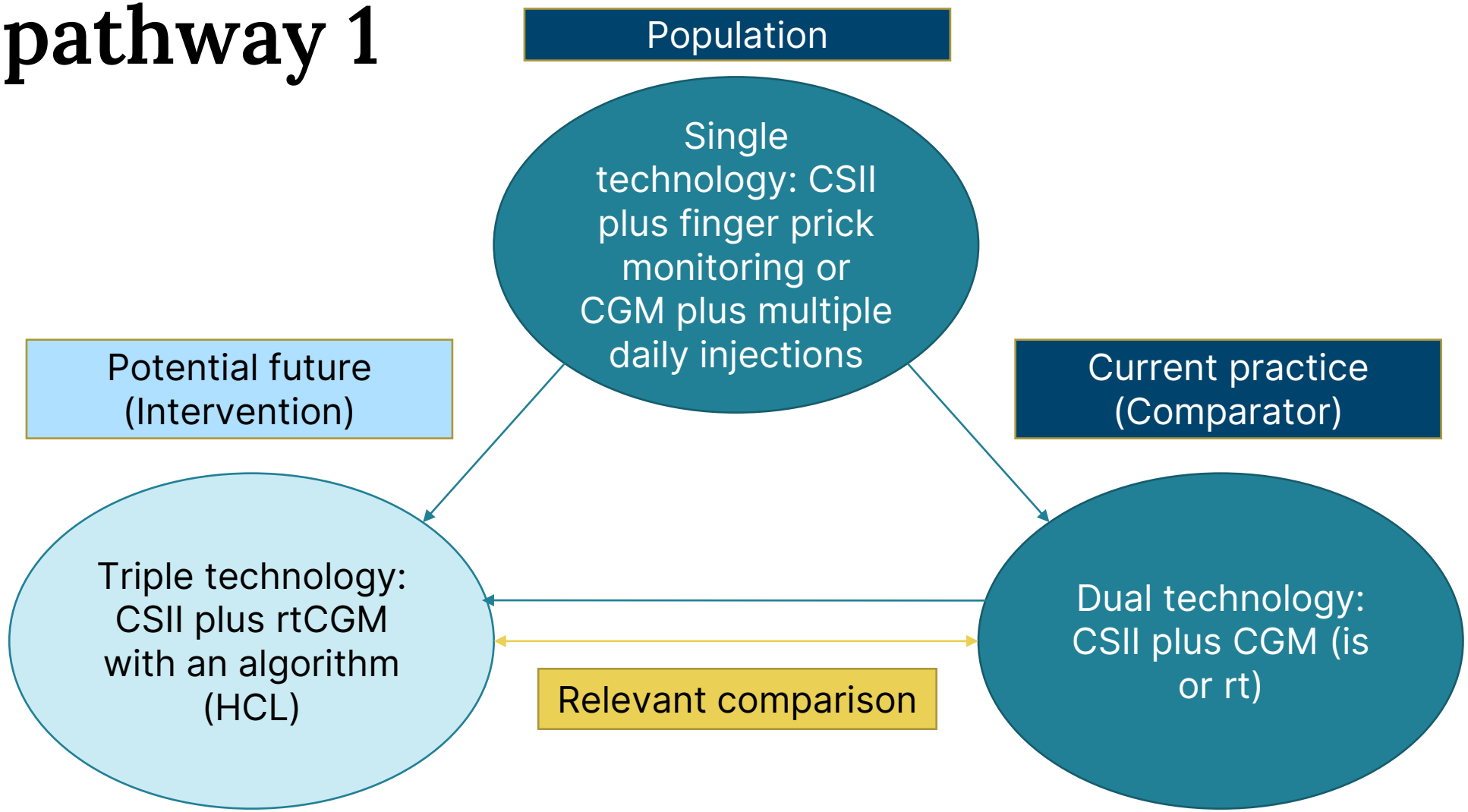
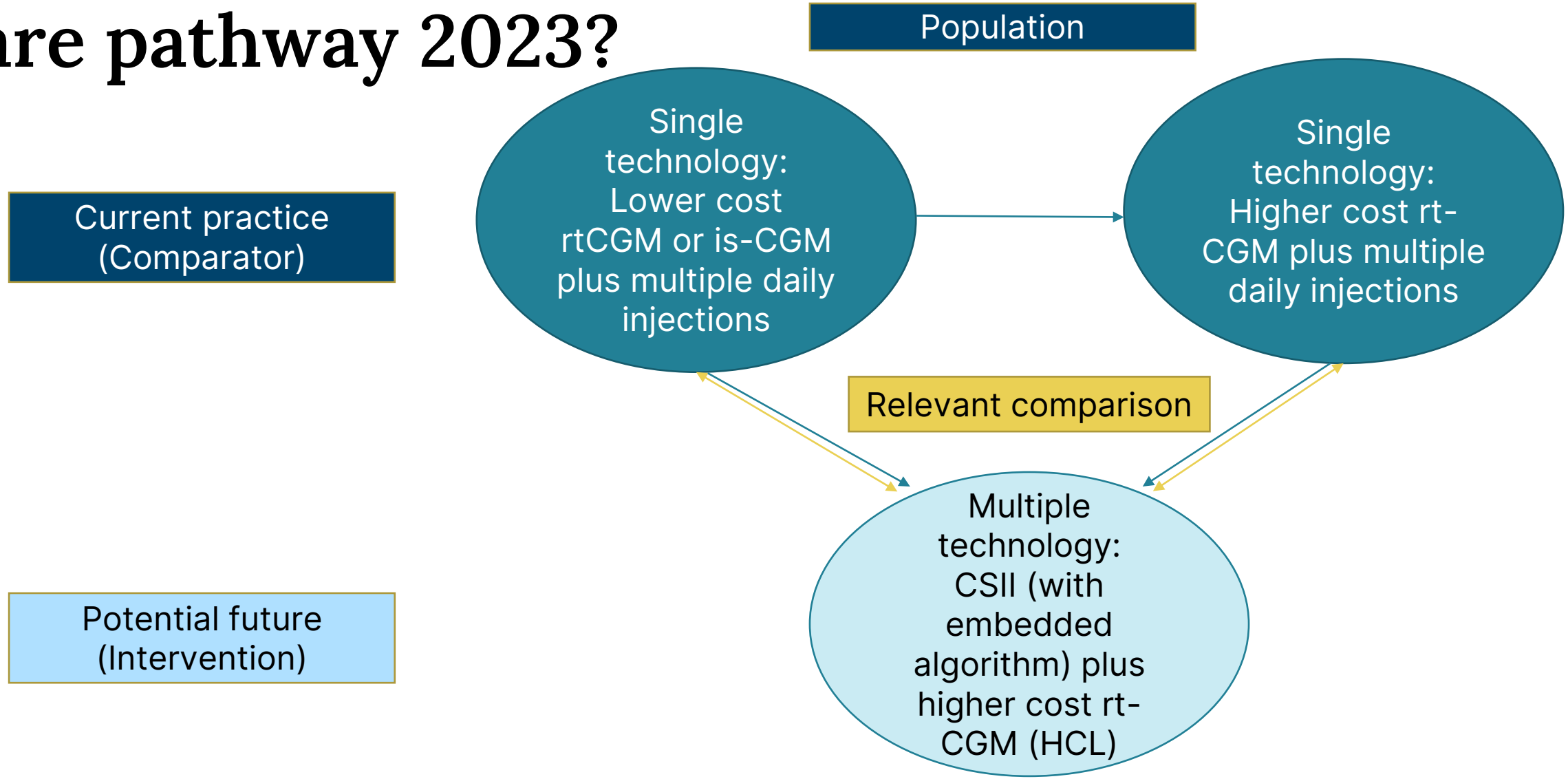
Care pathway 1



Care pathway 2023?



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Technology under assessment 1

Commercial closed-loop systems in the UK

	Medtronic 780G	Tandem Control IQ	Cam APS	Medtrum Nano
Pump				
CGM				
Target	5.5 (default), 6.1 or 6.7 mmol/L	Range 6.1-8.9 mmol/L daytime; 6.1-6.7 mmol/L overnight; 7.8-8.9 mmol/L activity	Personalised target: 4.4-11.0 mmol/L – default 5.8 mmol/L	Personalised target: 5.6mmol/l 6.1mmol/l 6.7mmol/l
Variables	Active insulin time I:C ratio	I:C ratio Insulin sensitivity factor Basal rates	I:C ratio	I:C ratio Insulin sensitivity Factor
Insulin delivery	Basal insulin adjusted every 5 minutes	Basal insulin adjusted only if SG predicted to exit range	Basal insulin set to zero: extended bolus given every 10-12 minutes	Basal insulin adjusted every 2 minutes
Connectivity	Minimed Mobile and Carelink Connect App Carelink	Glooko-Diasend	CAMAPS FX App – Android only Glooko-Diasend	EasyPatch App (iOS/Android) EasyFollow App EasyView
CE license (age)	>7 years	>6 years	>1 years Pregnancy	>2 years

Omnipod 5 (anticipated summer 2023)

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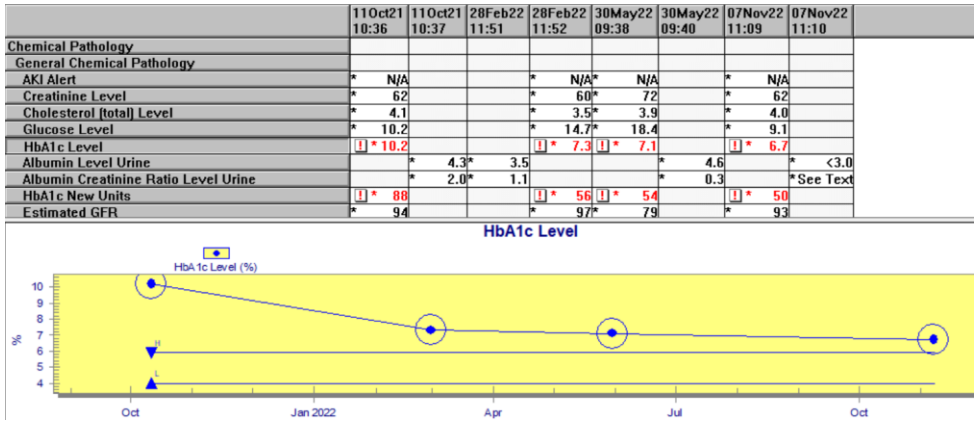
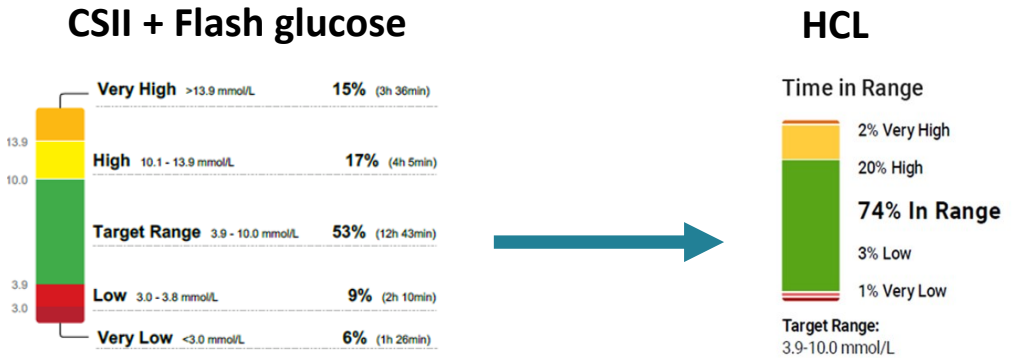
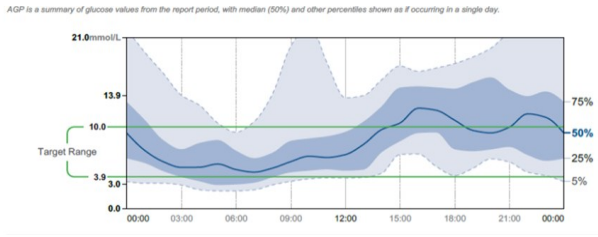
Technology under assessment 2

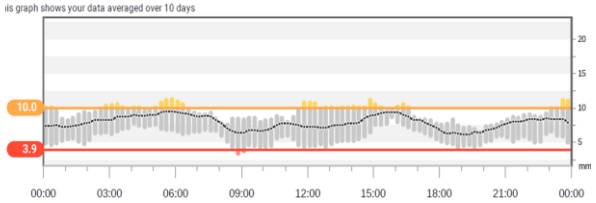
Clinical experience of HCL

- In those who are able to use CSII, rt-CGM and HCL on a long-term basis:
- Improved glycaemia with less hypoglycaemia
- Reduced mental burden and improved quality of life
- Changes in HbA1c and TIR are dependant on baseline values
    - Higher the HbA1c at the start, likely bigger drop in HbA1c with HCL
    - Lower the TIR at the start, likely bigger the increase in TIR with HCL









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Patient and carer considerations

Diane Davies

DAC standing committee lay member

29 November 2022

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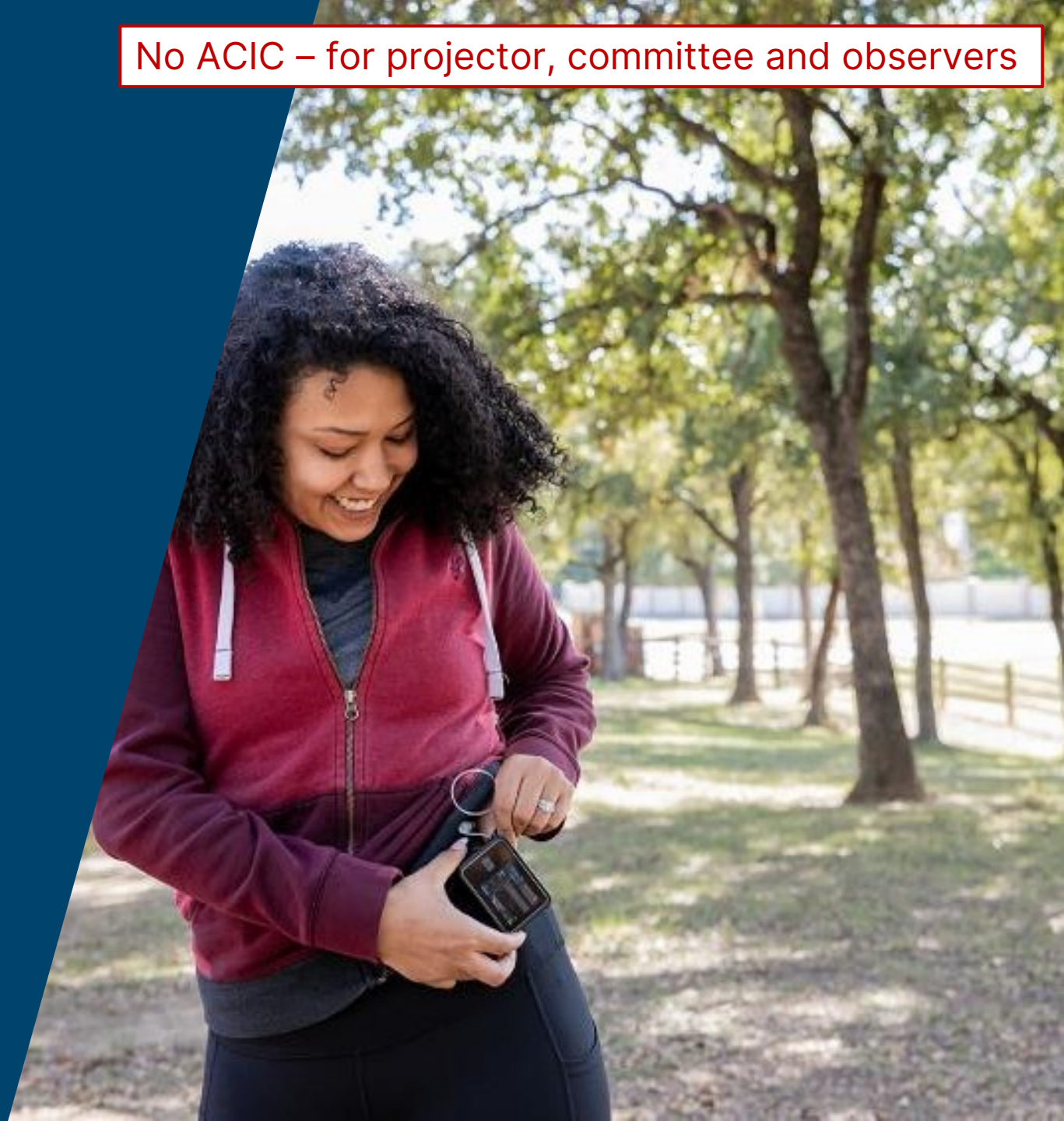

Patient and carer considerations

- **The mental load of living with diabetes is significant:** "… huge burden on the patient (or their carer) and their family in having to take a lot of decisions every day. This … is extremely wearing and can frequently lead to burn out".
- **Disrupted sleep: "**Parents are waking multiple times a night to monitor their child's blood sugar and
- administer glucose/insulin as appropriate". Patients and partners woken by CGM alarms.
- **Menstruation and menopause: "**cause significant blood glucose management challenges for women, requiring large adjustments to insulin requirements in the short and long term."
- Hormonal changes in growing children need adjustments to insulin requirements
- **Treatment and care vary hugely from area to area:** "Getting a pump took over a year … it was a frustrating and demoralising process…"
- "There is a built in need to fail in the NHS system – you qualify for more sophisticated treatment methods generally only when you've failed to achieve results with simpler ones."
- **Awareness of treatment options varies greatly**

Patient and carer: Potential benefits of HCL

- Could reduce the mental load by reducing patient and carer interventions and decision making
- Improved sleep for patients, partners, parents and carers
- Improved glycaemic control, fewer hypos with more time in range and better quality of life with possibly reduced risk of complications
- Could give people more freedom
- Parental peace of mind when apart from children
- Reduced parental intervention, so less conflict around diabetes in their relationship with children
- “… since 2019 I have been using a DIY hybrid closed loop system… My diabetes management has never been as good as it has over the last 3 years and I have good quality of life”
- Parent of a child with T1DM: “use of a hybrid closed loop system has been a complete game changer for us all.”

Concerns

- Inability to access technology, advice and help. Inability to access care. Postcode lottery still exists.
- Access to technology may be affected by ethnicity/family background and socio-economic status.
- Can also require confidence with technology, apps and systems as well as an ability to understand complex interactions that some people may have difficulty with.
- “Reliability of sensors is a concern. I’ve found them to be very accurate and reliable, but on the occasion that they fail, full control is thrust back to you. A back up plan is essential.”
- Some people may not feel comfortable wearing insulin pumps or CGMs and therefore HCL systems will not be suitable for them. For some children, the thought of wearing technology continually does not appeal as it can make their condition obvious.
- People with sight impairments or who find it difficult to use touchscreens because of loss of feeling in fingertips or manual dexterity are also likely to find it hard to benefit from this kind of technology.

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Clinical effectiveness considerations

Dr Brian Shine

Consultant chemical pathologist
& DAC Chair

29 November 2022

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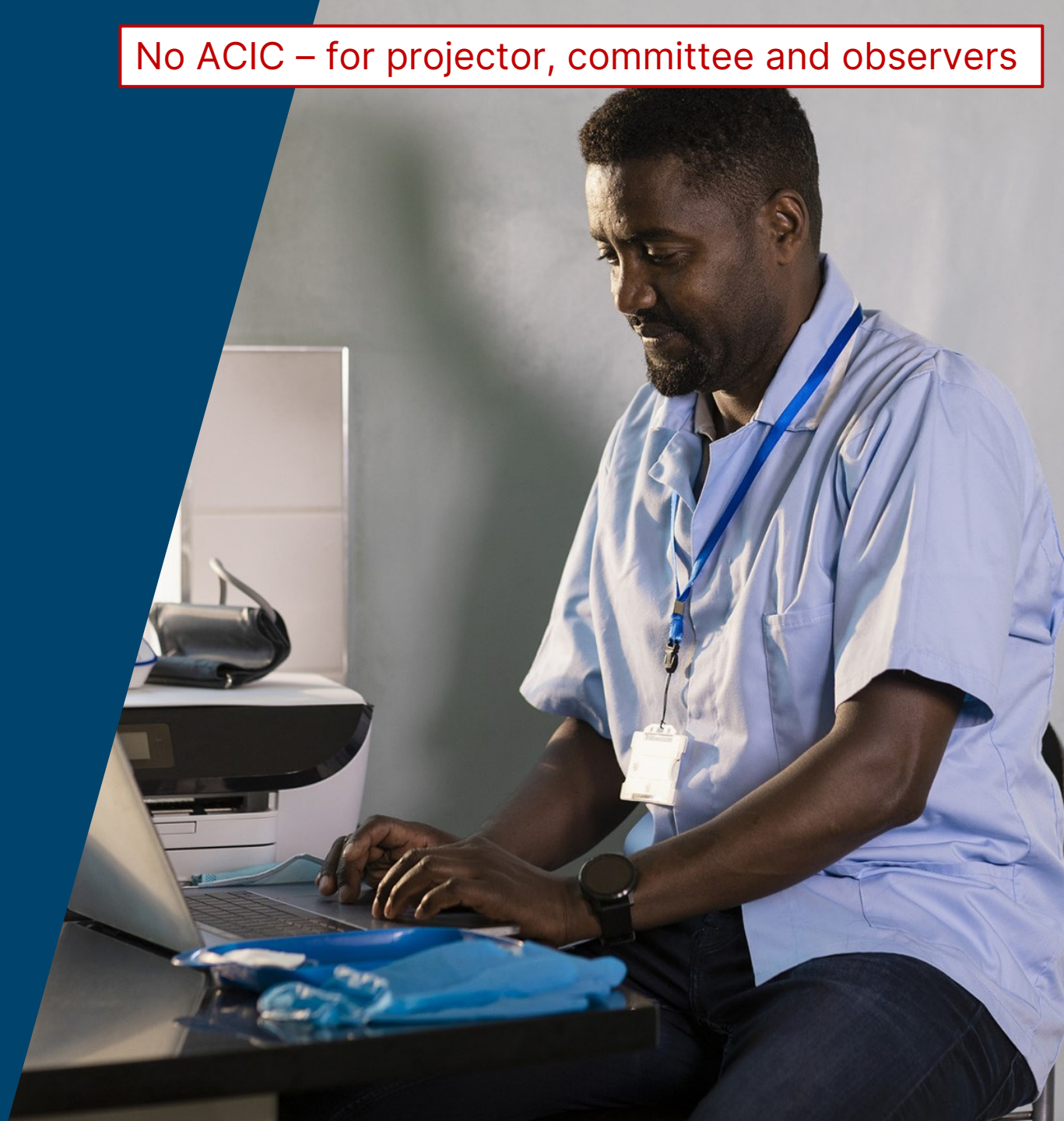


Clinical effectiveness review: inclusion criteria

Population	People with T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring. Difficulties may include: • not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below, or • not maintaining plasma glucose in range of 3.9 -10 mmol/L 70% of the time, or • ongoing disabling hypoglycaemia If evidence permits include the following T1DM subpopulations: • Pregnant women (excluding gestational diabetes)and those planning pregnancies • Children (5 years and under, 6 – 11 years, 12 - 19 years) • People with extreme fear of hypoglycaemia • People with diabetes-related complications at risk of deteriorating
Interventions	Hybrid closed loop (HCL) systems
Comparator	• Real time continuous glucose monitoring (rtCGM) not integrated with continuous subcutaneous insulin infusion (CSII) • Intermittently scanned glucose monitoring (isCGM) not integrated with CSII

Overview of 12 randomised controlled trials (RCTs)

- 12 randomised controlled trials (RCTs)

RCTs heterogeneous trial design, number and age of participants, run-in times, duration of observation periods, and number and types of previous treatments.

  - Most multinational (Australia, Austria, France, Germany, Israel, Luxembourg, New Zealand, Slovenia, UK and USA)
  - 5 adults only, 2 adults over 60 years only, 1 pregnant women only
  - 6 recruited children and/or adolescents
    - 1 RCT recruited children, adolescents and adults and reported all 3 separately
  - Interventions: HCL systems differed
  - Comparators:
    - CGM plus CSII
    - Low glucose suspend/predictive low glucose suspend (LGS/PLGS)
  - All CGMs rtCGMs; no isCGM

Study quality (RCTs)

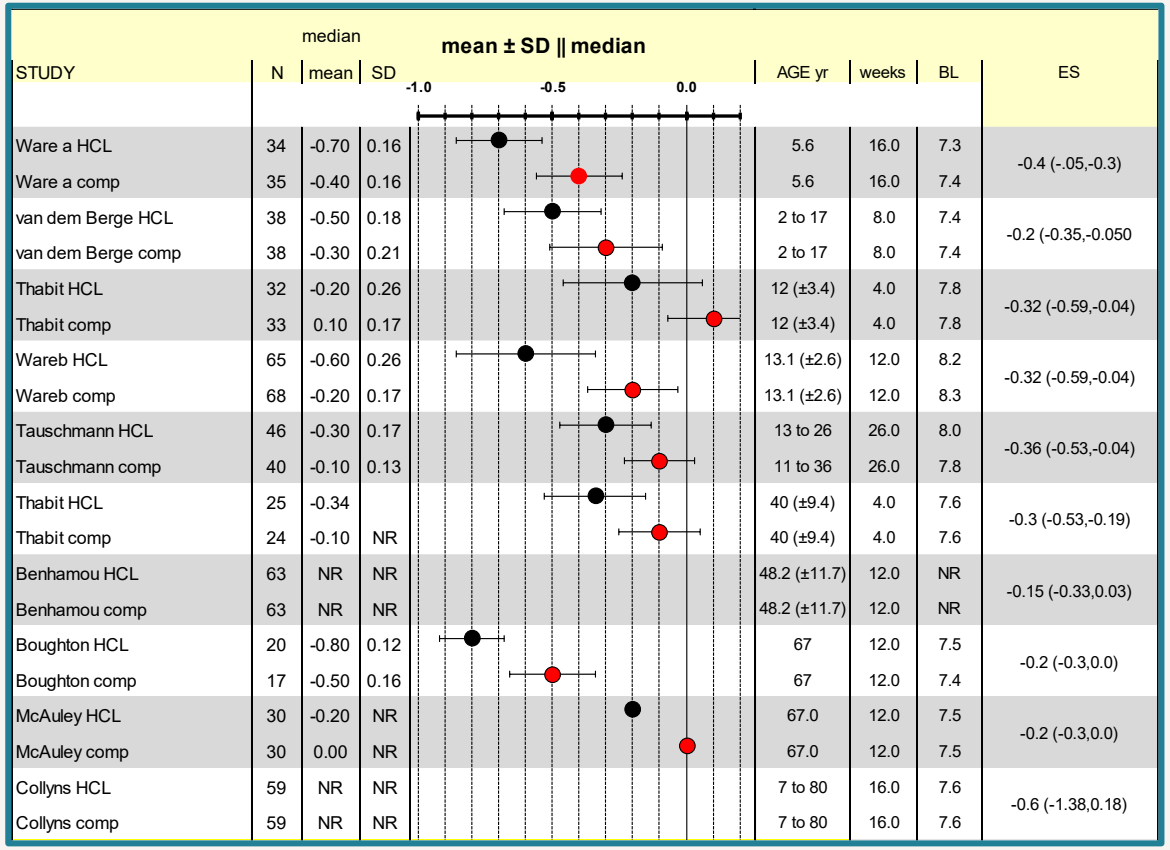
- EAG said that **5** of the RCTs had **some concerns** about their risk of bias and **3** had a **high risk** of bias (Benhamou et al. 2021, Collyns et al. 2021, and von dem Berge et al. 2022)
- **Randomisation process**: 1 RCT (Collyns et al. 2021) had a high risk of bias and 4 had some concerns
- **Deviations from intended interventions**: 1 RCT had a high risk of bias (Benhamou et al. 2022) and 6 had some concerns
- **Selection of the reported results:** 3 RCTs had some concerns of the risk of bias

Overview of observational and NHSE pilot studies

- 9 observational studies including 2 NHSE pilot studies
- Most observational studies used similar inclusion criteria to RCTs
- No quality assessment by EAG
- **NHSE adult pilot study:** 570 adults with T1DM and complete follow-up data from 31 centres in England
- **NHSE children and young people (CYP) pilot study:** 251 children and young people (under 19 years), with T1DM for at least a year and at least 2 HbA1c measures prior to the start of HCL.
- EAG: NHSE pilots were broader in recruitment and included adult participants with worse glycaemic control in terms of HbA1c and hyperglycaemia at baseline than the other observational studies.
- NHSE pilots were non-randomised studies with no control group and with a before-after study design

RCT outcomes: change in HbA1c

- Narrow range of mean baseline HbA1c (7.4 to 8.3%)
- HbA1c fell more with HCL than with comparator
- Net effect sizes range: -0.15 to -0.60%



STUDY	N	median mean	SD	mean ± SD || median -1.0 -0.5 0.0	AGE yr	weeks	BL	ES
Ware a HCL	34	-0.70	0.16		5.6	16.0	7.3	-0.4 (-.05,-0.3)
Ware a comp	35	-0.40	0.16		5.6	16.0	7.4	
van dem Berge HCL	38	-0.50	0.18		2 to 17	8.0	7.4	-0.2 (-0.35,-0.050
van dem Berge comp	38	-0.30	0.21		2 to 17	8.0	7.4	
Thabit HCL	32	-0.20	0.26		12 (±3.4)	4.0	7.8	-0.32 (-0.59,-0.04)
Thabit comp	33	0.10	0.17		12 (±3.4)	4.0	7.8	
Wareb HCL	65	-0.60	0.26		13.1 (±2.6)	12.0	8.2	-0.32 (-0.59,-0.04)
Wareb comp	68	-0.20	0.17		13.1 (±2.6)	12.0	8.3	
Tauschmann HCL	46	-0.30	0.17		13 to 26	26.0	8.0	-0.36 (-0.53,-0.04)
Tauschmann comp	40	-0.10	0.13		11 to 36	26.0	7.8	
Thabit HCL	25	-0.34			40 (±9.4)	4.0	7.6	-0.3 (-0.53,-0.19)
Thabit comp	24	-0.10	NR		40 (±9.4)	4.0	7.6	
Benhamou HCL	63	NR	NR		48.2 (±11.7)	12.0	NR	-0.15 (-0.33,0.03)
Benhamou comp	63	NR	NR		48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-0.80	0.12		67	12.0	7.5	-0.2 (-0.3,0.0)
Boughton comp	17	-0.50	0.16		67	12.0	7.4	
McAuley HCL	30	-0.20	NR		67.0	12.0	7.5	-0.2 (-0.3,0.0)
McAuley comp	30	0.00	NR		67.0	12.0	7.5	
Collyns HCL	59	NR	NR		7 to 80	16.0	7.6	-0.6 (-1.38,0.18)
Collyns comp	59	NR	NR		7 to 80	16.0	7.6	

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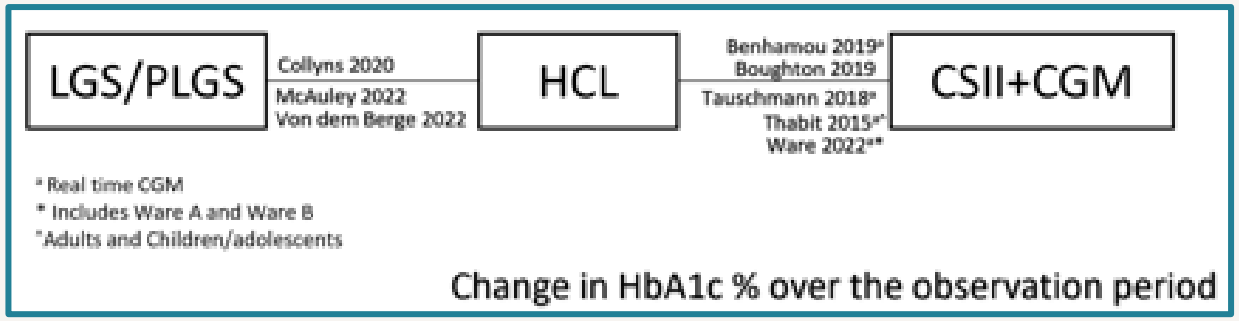
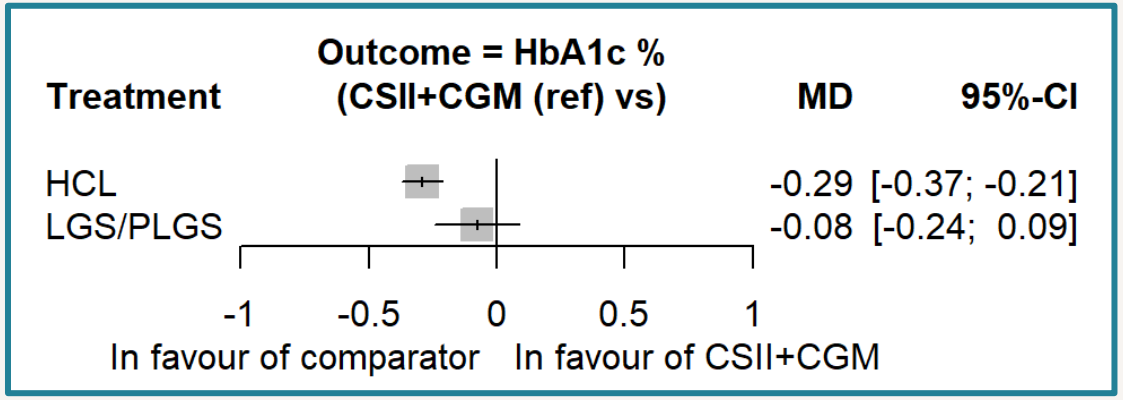
Change in HbA1c: network meta-analysis

- EAG network meta-analysis (NMA) of change in HbA1c percentage estimates
- NMA included 10 estimates
- Reference treatment class was continuous subcutaneous insulin infusion plus continuous glucose monitoring (**CSII plus CGM**)

Network map



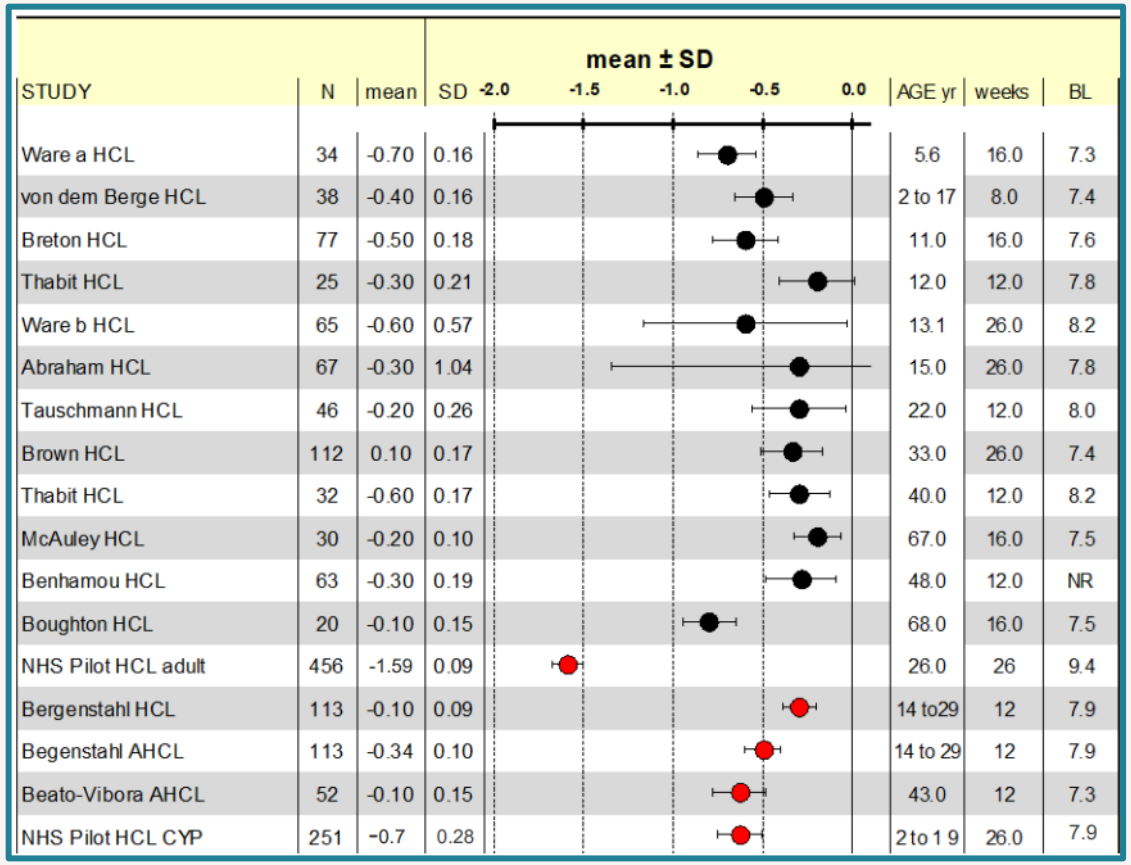
NMA results



Compared with CSII + CGM, HCL reduced HbA1c by **-0.29%** (95% CI: -0.37 to -0.21)

Observational studies: change in % HbA1c

- EAG: outcome estimates broadly in line with RCTs
- Much greater improvement in HbA1c in NHSE adult pilot study, **but** baseline ~9.4%, so greater scope for improvement **(-1.5%)**
- NHS CYP Pilot baseline HbA1c lower (~7.8%) and benefit more modest **(-0.70%)**



STUDY	N	mean	SD	AGE yr	weeks	BL
Ware a HCL	34	-0.70	0.16	5.6	16.0	7.3
von dem Berge HCL	38	-0.40	0.16	2 to 17	8.0	7.4
Breton HCL	77	-0.50	0.18	11.0	16.0	7.6
Thabit HCL	25	-0.30	0.21	12.0	12.0	7.8
Ware b HCL	65	-0.60	0.57	13.1	26.0	8.2
Abraham HCL	67	-0.30	1.04	15.0	26.0	7.8
Tauschmann HCL	46	-0.20	0.26	22.0	12.0	8.0
Brown HCL	112	0.10	0.17	33.0	26.0	7.4
Thabit HCL	32	-0.60	0.17	40.0	12.0	8.2
McAuley HCL	30	-0.20	0.10	67.0	16.0	7.5
Benhamou HCL	63	-0.30	0.19	48.0	12.0	NR
Boughton HCL	20	-0.10	0.15	68.0	16.0	7.5
NHS Pilot HCL adult	456	-1.59	0.09	26.0	26	9.4
Bergenstahl HCL	113	-0.10	0.09	14 to29	12	7.9
Begenstahl AHCL	113	-0.34	0.10	14 to 29	12	7.9
Beato-Vibora AHCL	52	-0.10	0.15	43.0	12	7.3
NHS Pilot HCL CYP	251	-0.7	0.28	2 to 1 9	26.0	7.9

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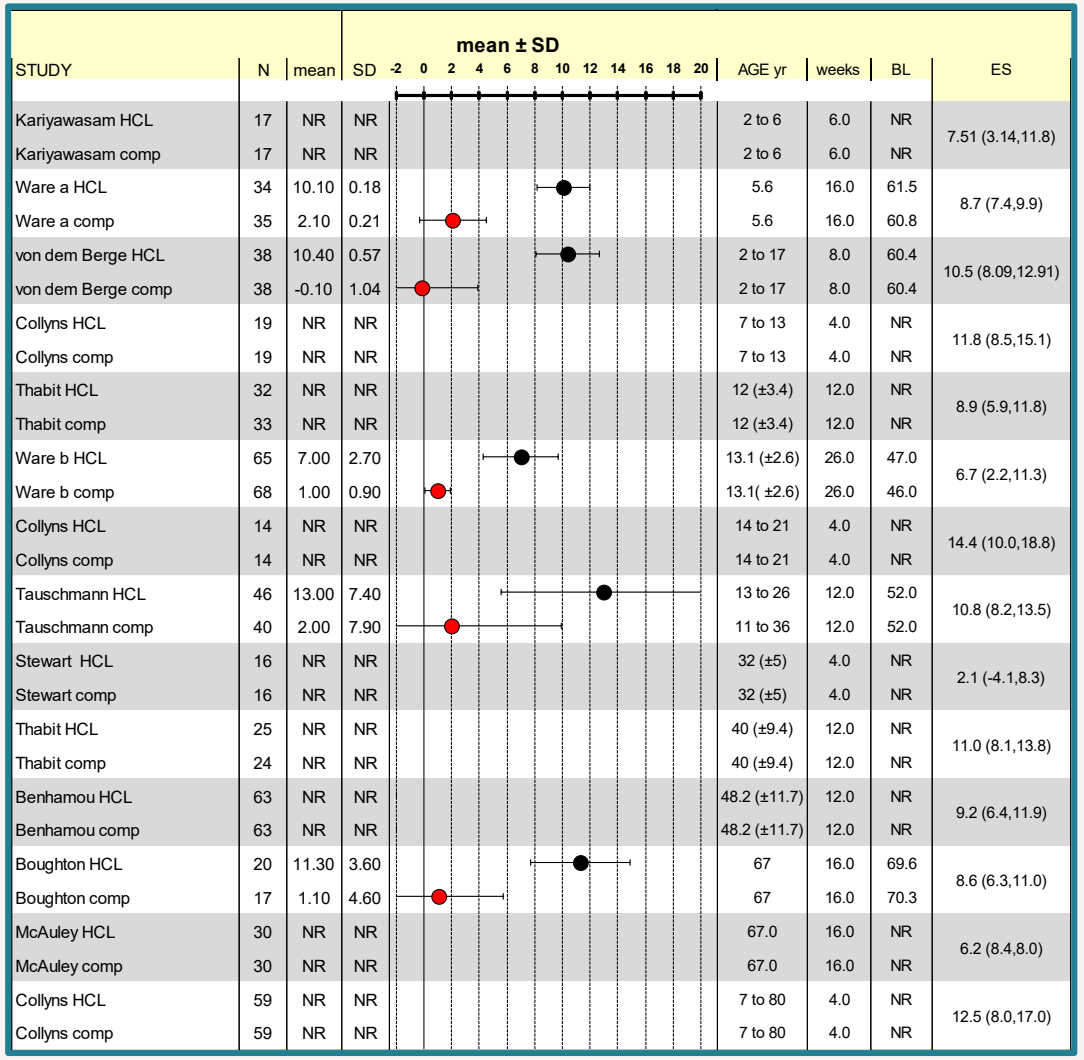
RCT intermediate outcomes: time in range (3.9 to 10 mmol/L)

- In all RCTs larger increase in percentage time in range in HCL than comparator arm
- Mean baseline percentage time in range >50% except in one study (46–47%)
- NHS Pilot study, baseline 34.2%
- Change from baseline in HCL arm of RCTs among adults of similar age range to adult NHS Pilot: 10%–15%
- NHS adult pilot, change from baseline 28.5% (unadjusted; 95% CI: 25.6–13.5)

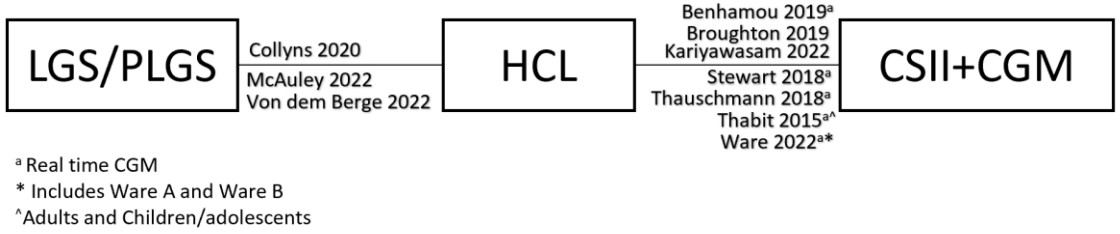


STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	7.51 (3.14,11.8)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	10.10	0.18	5.6	16.0	61.5	8.7 (7.4,9.9)
Ware a comp	35	2.10	0.21	5.6	16.0	60.8	
von dem Berge HCL	38	10.40	0.57	2 to 17	8.0	60.4	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04	2 to 17	8.0	60.4	
Collyns HCL	19	NR	NR	7 to 13	4.0	NR	11.8 (8.5,15.1)
Collyns comp	19	NR	NR	7 to 13	4.0	NR	
Thabit HCL	32	NR	NR	12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR	12 (±3.4)	12.0	NR	
Ware b HCL	65	7.00	2.70	13.1 (±2.6)	26.0	47.0	6.7 (2.2,11.3)
Ware b comp	68	1.00	0.90	13.1(±2.6)	26.0	46.0	
Collyns HCL	14	NR	NR	14 to 21	4.0	NR	14.4 (10.0,18.8)
Collyns comp	14	NR	NR	14 to 21	4.0	NR	
Tauschmann HCL	46	13.00	7.40	13 to 26	12.0	52.0	10.8 (8.2,13.5)
Tauschmann comp	40	2.00	7.90	11 to 36	12.0	52.0	
Stewart HCL	16	NR	NR	32 (±5)	4.0	NR	2.1 (-4.1,8.3)
Stewart comp	16	NR	NR	32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR	40 (±9.4)	12.0	NR	11.0 (8.1,13.8)
Thabit comp	24	NR	NR	40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	9.2 (6.4,11.9)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	11.30	3.60	67	16.0	69.6	8.6 (6.3,11.0)
Boughton comp	17	1.10	4.60	67	16.0	70.3	
McAuley HCL	30	NR	NR	67.0	16.0	NR	6.2 (8.4,8.0)
McAuley comp	30	NR	NR	67.0	16.0	NR	
Collyns HCL	59	NR	NR	7 to 80	4.0	NR	12.5 (8.0,17.0)
Collyns comp	59	NR	NR	7 to 80	4.0	NR	

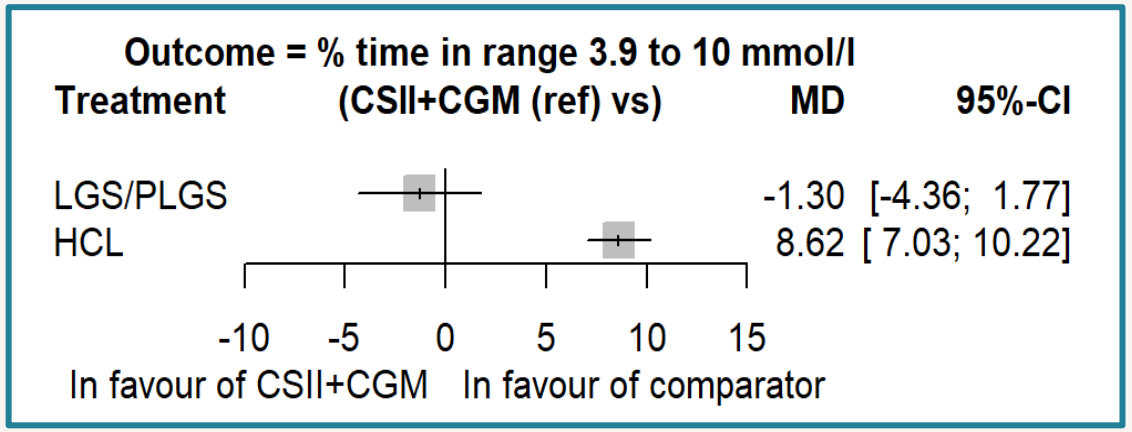
Percentage time in range (3.9 to 10 mmol/L): network meta-analysis

- NMA included 12 estimates
- Reference treatment class was continuous subcutaneous insulin infusion plus continuous glucose monitoring (**CSII plus CGM**) where estimates of less than 0 favoured CSII plus CGM

Network map



NMA results

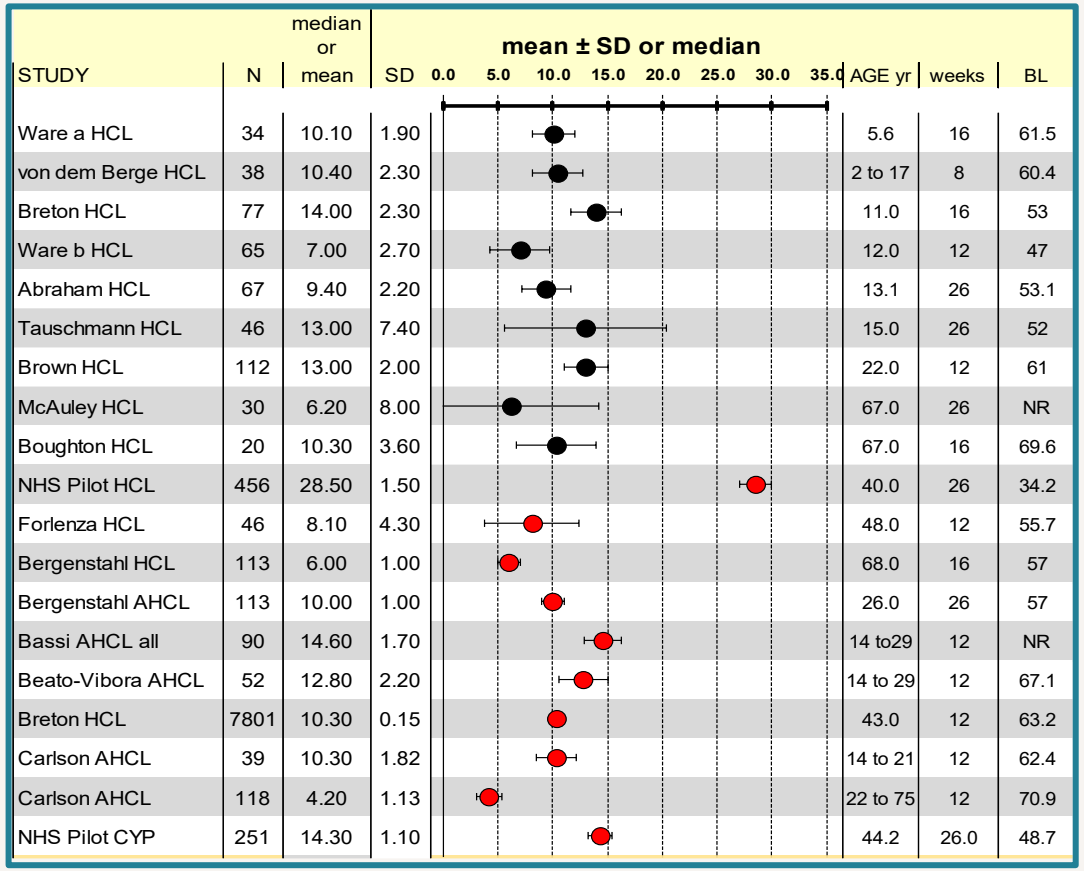


Compared with CSII + CGM, HCL significantly increased the percentage time in range:

mean difference **8.62%** (95% CI: 7.03 to 10.22).

Observational studies: Percentage time in range (3.9 to 10 mmol/L)

- Most studies had a baseline time in range above 50%
- NHSE adult pilot baseline time in range: 34.2%
- NHSE CYP pilot baseline time in range: 48.7%
- In NHSE adult pilot, benefit from HCL greater than other studies: 28.5%



STUDY	N	median or mean	SD	AGE yr	weeks	BL
Ware a HCL	34	10.10	1.90	5.6	16	61.5
von dem Berge HCL	38	10.40	2.30	2 to 17	8	60.4
Breton HCL	77	14.00	2.30	11.0	16	53
Ware b HCL	65	7.00	2.70	12.0	12	47
Abraham HCL	67	9.40	2.20	13.1	26	53.1
Tauschmann HCL	46	13.00	7.40	15.0	26	52
Brown HCL	112	13.00	2.00	22.0	12	61
McAuley HCL	30	6.20	8.00	67.0	26	NR
Boughton HCL	20	10.30	3.60	67.0	16	69.6
NHS Pilot HCL	456	28.50	1.50	40.0	26	34.2
Forlenza HCL	46	8.10	4.30	48.0	12	55.7
Bergenstahl HCL	113	6.00	1.00	68.0	16	57
Bergenstahl AHCL	113	10.00	1.00	26.0	26	57
Bassi AHCL all	90	14.60	1.70	14 to29	12	NR
Beato-Vibora AHCL	52	12.80	2.20	14 to 29	12	67.1
Breton HCL	7801	10.30	0.15	43.0	12	63.2
Carlson AHCL	39	10.30	1.82	14 to 21	12	62.4
Carlson AHCL	118	4.20	1.13	22 to 75	12	70.9
NHS Pilot CYP	251	14.30	1.10	44.2	26.0	48.7

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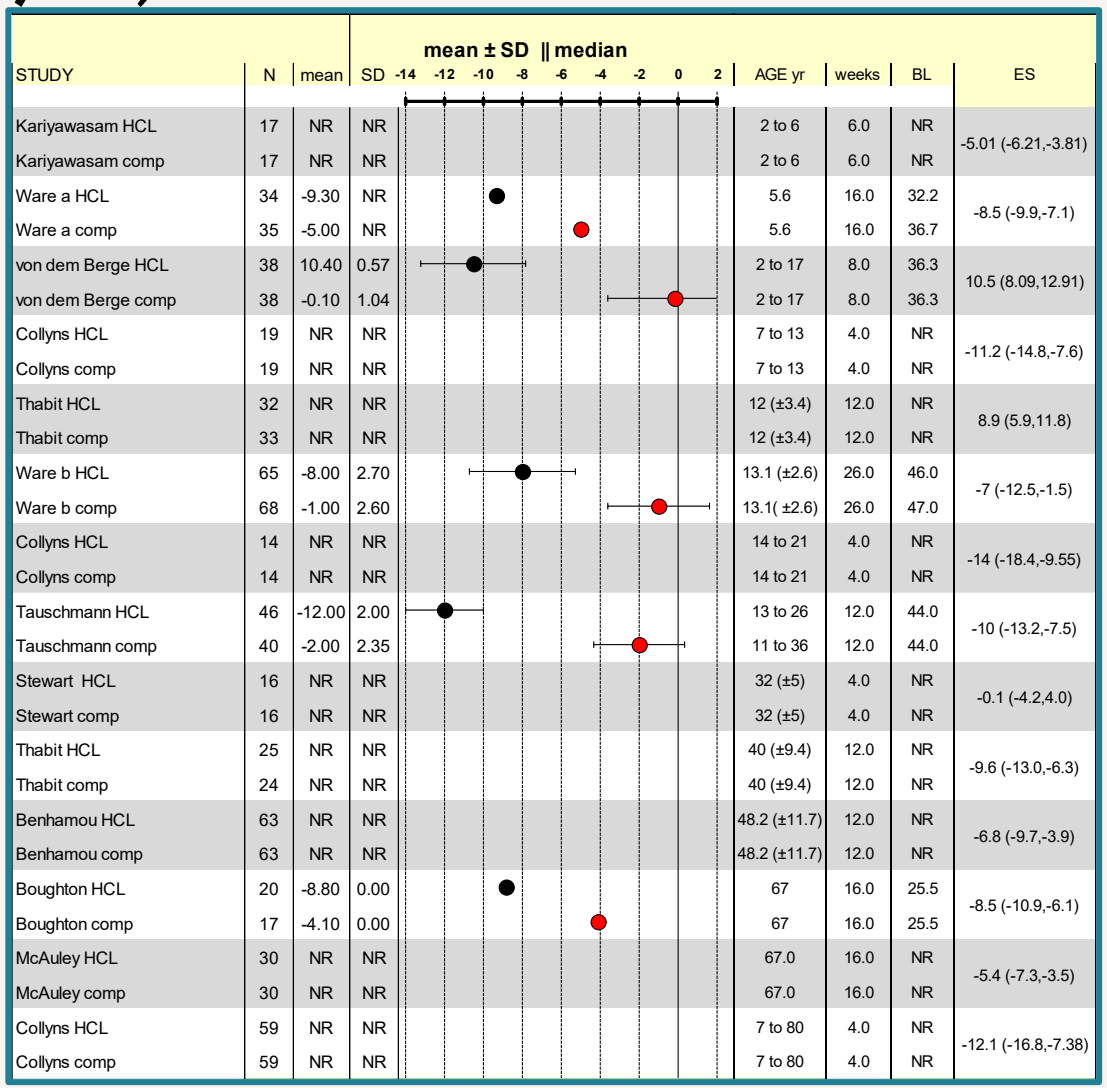
RCT intermediate outcomes: percentage time above range (above 10 mmol/L)

- Increased percentage time above range indicates a tendency to hyperglycaemia and poor glycaemic control
- In all studies HCL reduced the percentage time above range more than in the comparator arms
- EAG said that the difference between arms (net effect size) was statistically significant in all cases ($p < 0.05$).

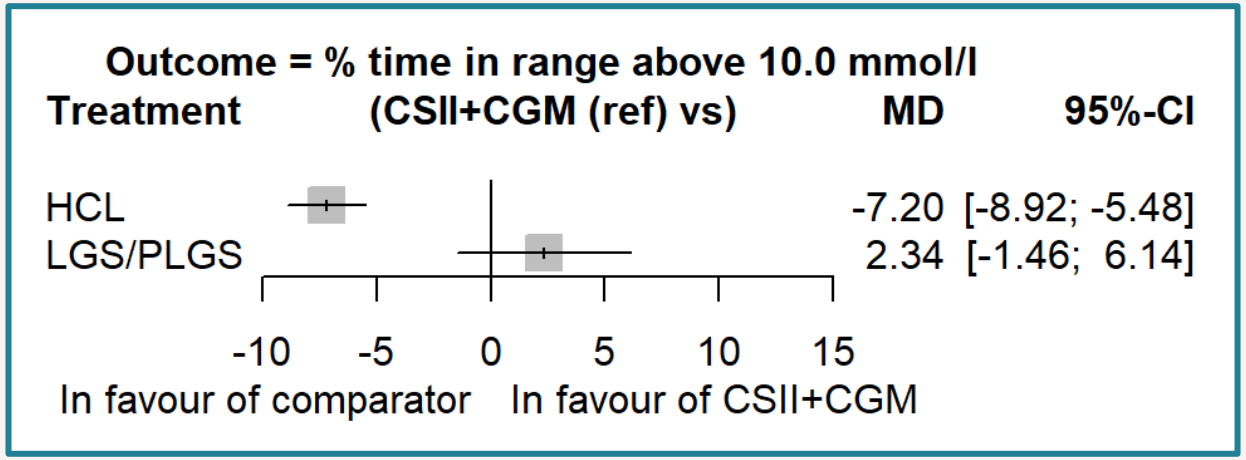


STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	-5.01 (-6.21,-3.81)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	-9.30	NR	5.6	16.0	32.2	-8.5 (-9.9,-7.1)
Ware a comp	35	-5.00	NR	5.6	16.0	36.7	
von dem Berge HCL	38	10.40	0.57	2 to 17	8.0	36.3	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04	2 to 17	8.0	36.3	
Collyns HCL	19	NR	NR	7 to 13	4.0	NR	-11.2 (-14.8,-7.6)
Collyns comp	19	NR	NR	7 to 13	4.0	NR	
Thabit HCL	32	NR	NR	12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR	12 (±3.4)	12.0	NR	
Ware b HCL	65	-8.00	2.70	13.1 (±2.6)	26.0	46.0	-7 (-12.5,-1.5)
Ware b comp	68	-1.00	2.60	13.1(±2.6)	26.0	47.0	
Collyns HCL	14	NR	NR	14 to 21	4.0	NR	-14 (-18.4,-9.55)
Collyns comp	14	NR	NR	14 to 21	4.0	NR	
Tauschmann HCL	46	-12.00	2.00	13 to 26	12.0	44.0	-10 (-13.2,-7.5)
Tauschmann comp	40	-2.00	2.35	11 to 36	12.0	44.0	
Stewart HCL	16	NR	NR	32 (±5)	4.0	NR	-0.1 (-4.2,4.0)
Stewart comp	16	NR	NR	32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR	40 (±9.4)	12.0	NR	-9.6 (-13.0,-6.3)
Thabit comp	24	NR	NR	40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-6.8 (-9.7,-3.9)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-8.80	0.00	67	16.0	25.5	-8.5 (-10.9,-6.1)
Boughton comp	17	-4.10	0.00	67	16.0	25.5	
McAuley HCL	30	NR	NR	67.0	16.0	NR	-5.4 (-7.3,-3.5)
McAuley comp	30	NR	NR	67.0	16.0	NR	
Collyns HCL	59	NR	NR	7 to 80	4.0	NR	-12.1 (-16.8,-7.38)
Collyns comp	59	NR	NR	7 to 80	4.0	NR	

Percentage time above range (above 10mmol/L): network meta-analysis

- NMA included same 12 estimates as those used in the time in range NMA
- Reference treatment class was continuous subcutaneous insulin infusion plus continuous glucose monitoring (**CSII plus CGM**) where estimates more than 0 favoured CSII plus CGM

NMA results

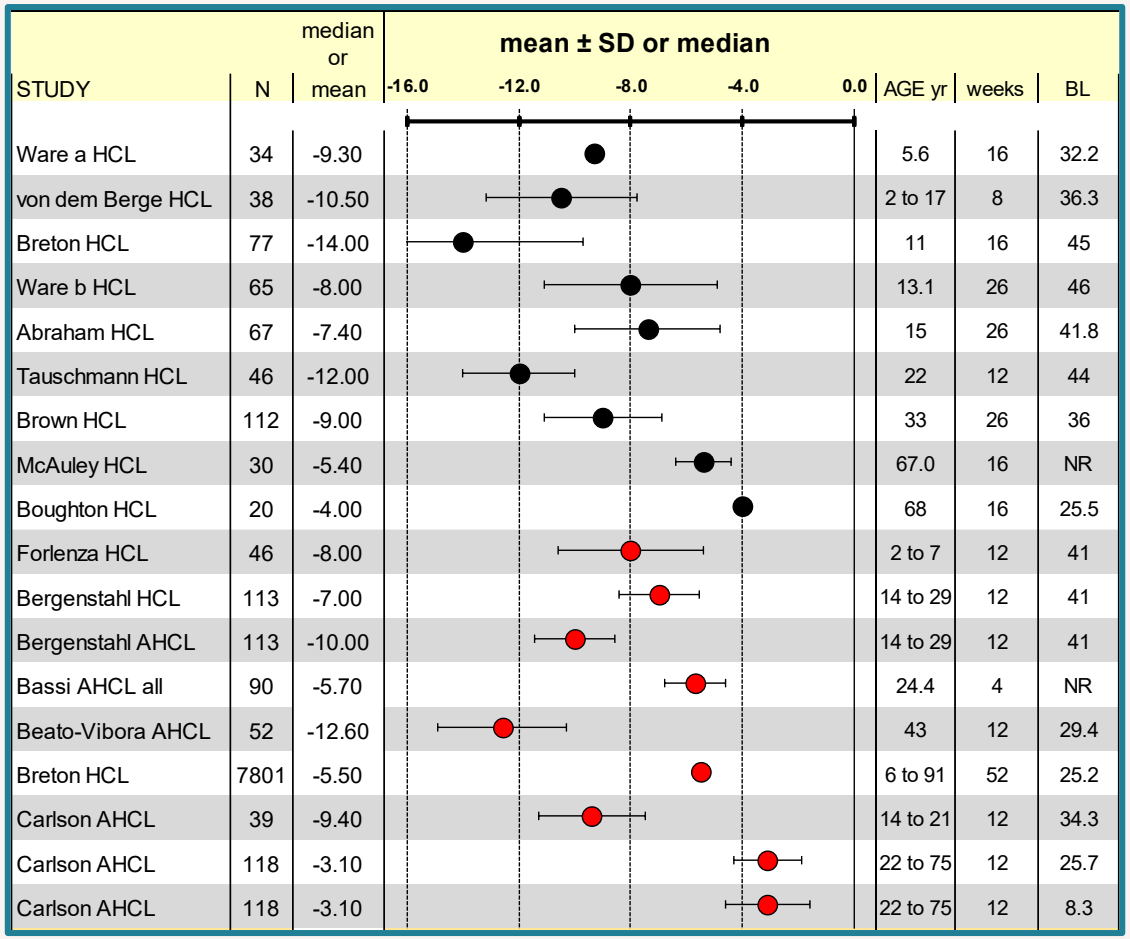


Compared with CSII plus CGM, HCL significantly decreased time above range:

mean difference **-7.2%** (95% CI -8.92 to -5.48).

Observational studies: Percentage time above range (above 10 mmol/L)

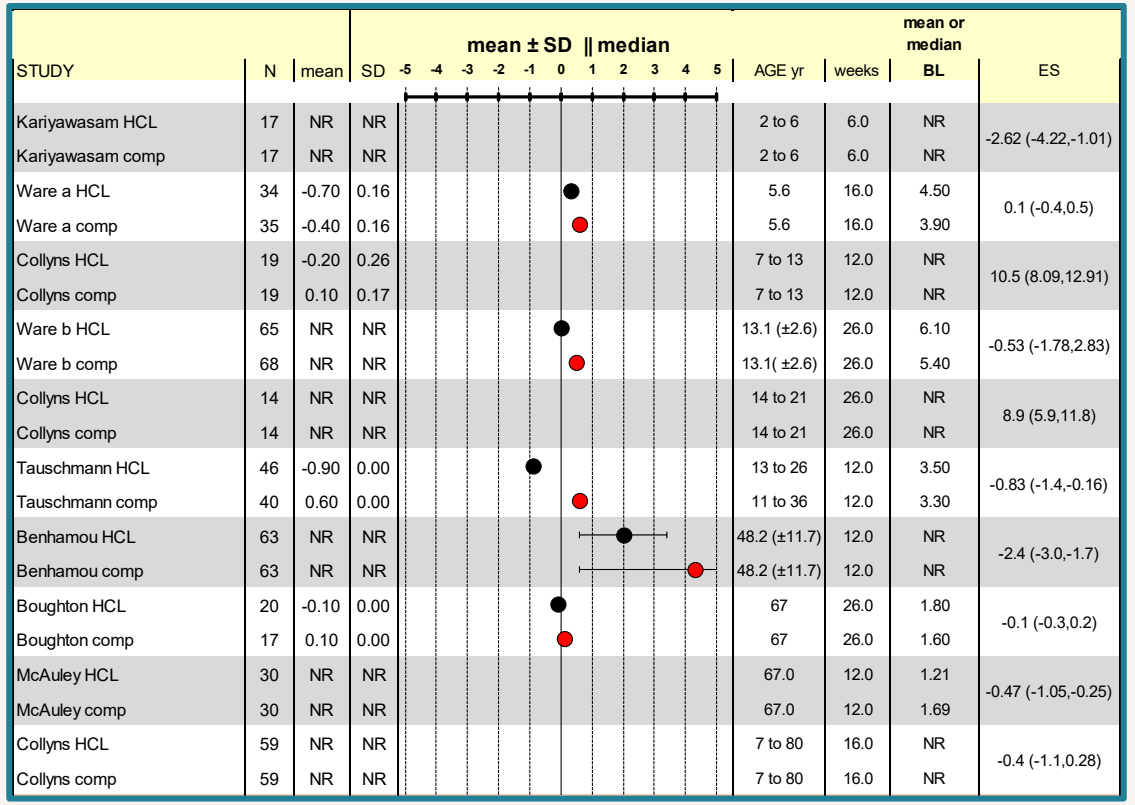
- Reduction in percentage time above range from baseline in all studies: 3.0% to 14%
- NHSE adult pilot reported percentage time above 14 mmol/litre: 37.4% at baseline, with further 26.6% of time in range of 10 to 14 mmol/L
    - HCL associated with reduction in time above 14 mmol/L of 22.6%
    - Time in range 10 to 14 mmol/L reduction 4%



STUDY	N	median or mean	AGE yr	weeks	BL
Ware a HCL	34	-9.30	5.6	16	32.2
von dem Berge HCL	38	-10.50	2 to 17	8	36.3
Breton HCL	77	-14.00	11	16	45
Ware b HCL	65	-8.00	13.1	26	46
Abraham HCL	67	-7.40	15	26	41.8
Tauschmann HCL	46	-12.00	22	12	44
Brown HCL	112	-9.00	33	26	36
McAuley HCL	30	-5.40	67.0	16	NR
Boughton HCL	20	-4.00	68	16	25.5
Forlenza HCL	46	-8.00	2 to 7	12	41
Bergenstahl HCL	113	-7.00	14 to 29	12	41
Bergenstahl AHCL	113	-10.00	14 to 29	12	41
Bassi AHCL all	90	-5.70	24.4	4	NR
Beato-Vibora AHCL	52	-12.60	43	12	29.4
Breton HCL	7801	-5.50	6 to 91	52	25.2
Carlson AHCL	39	-9.40	14 to 21	12	34.3
Carlson AHCL	118	-3.10	22 to 75	12	25.7
Carlson AHCL	118	-3.10	22 to 75	12	8.3

RCT intermediate outcomes: percentage time below range (less than 3.9 mmol/litre)

- Increased percentage time below range indicates a tendency to hypoglycaemia
- The mean or median percentage time below range at baseline was small (6% or less)
- Small effect size occasionally reaching statistical significance
- **The NHS Pilot study: change -0.5% (p<0.001)**

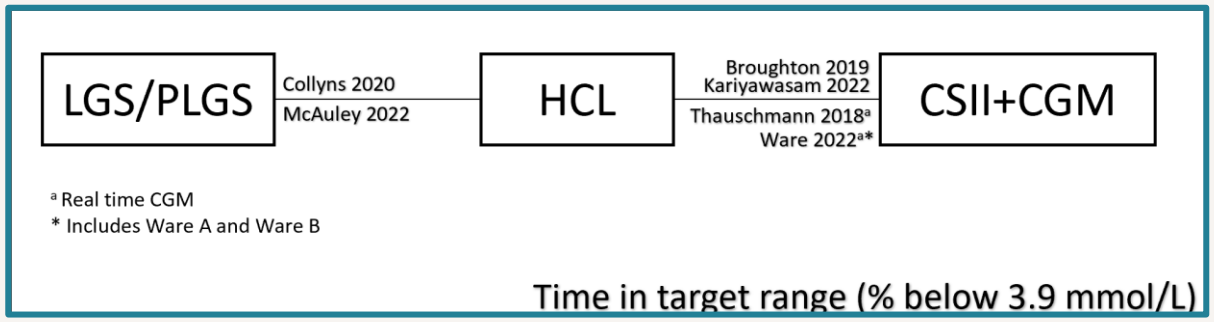


STUDY	N	mean	SD	mean ± SD ‖ median -5 -4 -3 -2 -1 0 1 2 3 4 5	AGE yr	weeks	mean or median BL	ES
Kariyawasam HCL	17	NR	NR		2 to 6	6.0	NR	-2.62 (-4.22,-1.01)
Kariyawasam comp	17	NR	NR		2 to 6	6.0	NR	
Ware a HCL	34	-0.70	0.16		5.6	16.0	4.50	0.1 (-0.4,0.5)
Ware a comp	35	-0.40	0.16		5.6	16.0	3.90	
Collyns HCL	19	-0.20	0.26		7 to 13	12.0	NR	10.5 (8.09,12.91)
Collyns comp	19	0.10	0.17		7 to 13	12.0	NR	
Ware b HCL	65	NR	NR		13.1 (±2.6)	26.0	6.10	-0.53 (-1.78,2.83)
Ware b comp	68	NR	NR		13.1(±2.6)	26.0	5.40	
Collyns HCL	14	NR	NR		14 to 21	26.0	NR	8.9 (5.9,11.8)
Collyns comp	14	NR	NR		14 to 21	26.0	NR	
Tauschmann HCL	46	-0.90	0.00		13 to 26	12.0	3.50	-0.83 (-1.4,-0.16)
Tauschmann comp	40	0.60	0.00		11 to 36	12.0	3.30	
Benhamou HCL	63	NR	NR		48.2 (±11.7)	12.0	NR	-2.4 (-3.0,-1.7)
Benhamou comp	63	NR	NR		48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-0.10	0.00		67	26.0	1.80	-0.1 (-0.3,0.2)
Boughton comp	17	0.10	0.00		67	26.0	1.60	
McAuley HCL	30	NR	NR		67.0	12.0	1.21	-0.47 (-1.05,-0.25)
McAuley comp	30	NR	NR		67.0	12.0	1.69	
Collyns HCL	59	NR	NR		7 to 80	16.0	NR	-0.4 (-1.1,0.28)
Collyns comp	59	NR	NR		7 to 80	16.0	NR	

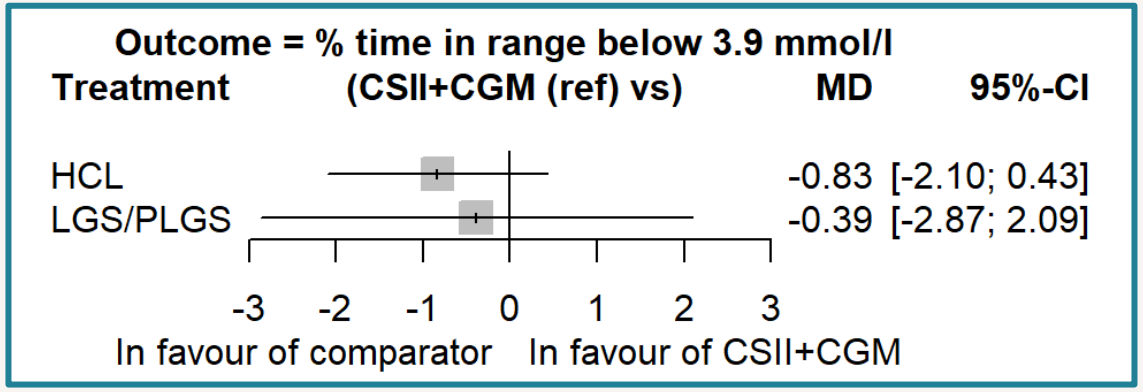
Percentage time below range (less than 3.9 mmol/litre): network meta-analysis

- NMA included 7 estimates
- Reference treatment class was continuous subcutaneous insulin infusion plus continuous glucose monitoring (**CSII plus CGM**) where estimates of less than 0 favoured HCL

Network map



NMA results

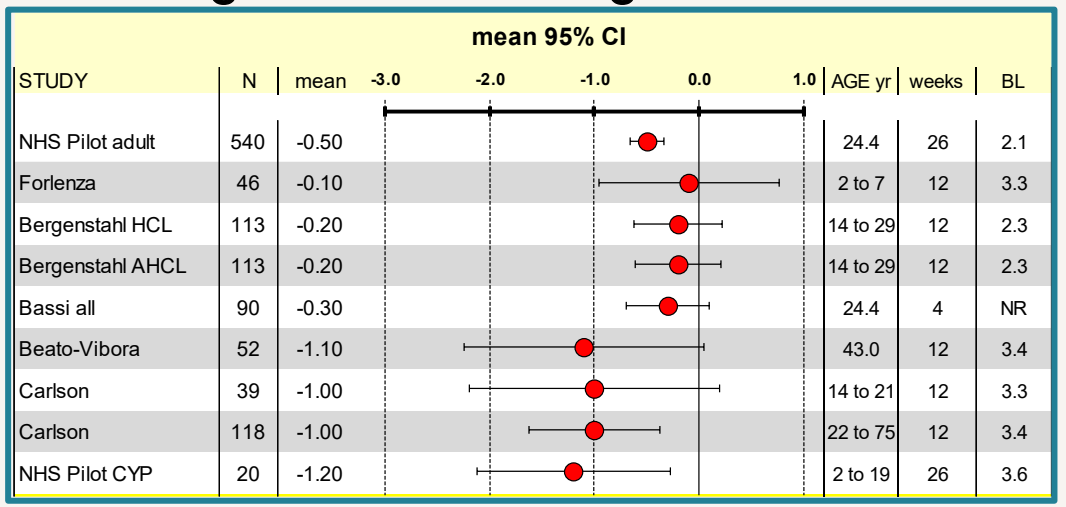


Mean difference of less than 0 (favours HCL), but no statistically significant difference between HCL and CSII plus CGM.

Observational studies: Percentage time below range

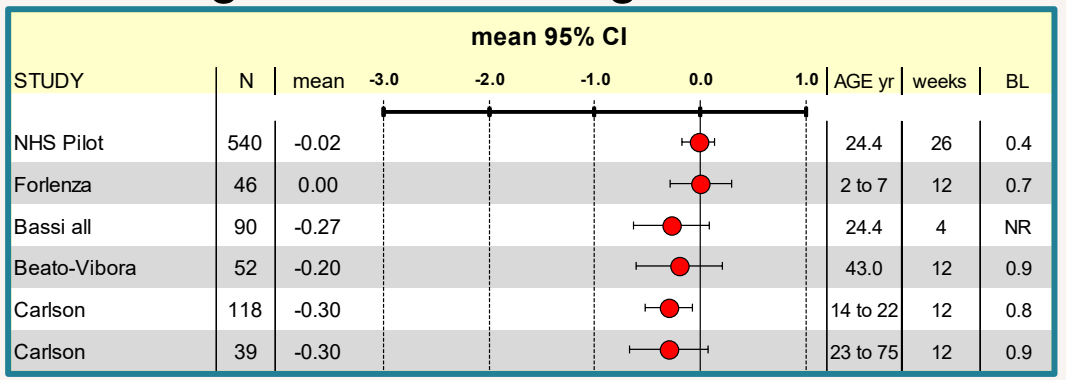
- Percentage time below range at baseline and after HCL intervention were small, with a resulting mean improvement of ~1% or less
- Baseline range: 2.1% in the NHS Pilot adult study to 3.4%
- NHS adult pilot reported a change of -0.5% ($p < 0.001$).
- NHSE CYP pilot study also reported a statistically significant improvement
- Some studies time below range less than 3.0 mmol/L

Percentage time below range 3.9 mmol/litre



STUDY	N	mean	AGE yr	weeks	BL
NHS Pilot adult	540	-0.50	24.4	26	2.1
Forlenza	46	-0.10	2 to 7	12	3.3
Bergenstahl HCL	113	-0.20	14 to 29	12	2.3
Bergenstahl AHCL	113	-0.20	14 to 29	12	2.3
Bassi all	90	-0.30	24.4	4	NR
Beato-Vibora	52	-1.10	43.0	12	3.4
Carlson	39	-1.00	14 to 21	12	3.3
Carlson	118	-1.00	22 to 75	12	3.4
NHS Pilot CYP	20	-1.20	2 to 19	26	3.6

Percentage time below range 3.0 mmol/litre



STUDY	N	mean	AGE yr	weeks	BL
NHS Pilot	540	-0.02	24.4	26	0.4
Forlenza	46	0.00	2 to 7	12	0.7
Bassi all	90	-0.27	24.4	4	NR
Beato-Vibora	52	-0.20	43.0	12	0.9
Carlson	118	-0.30	14 to 22	12	0.8
Carlson	39	-0.30	23 to 75	12	0.9

Subgroup and sensitivity analyses

- EAG did a subgroup analysis using mean or median age of participants at baseline
    - Compared children and young adults (<18 years) with adults (≥18 years)
    - NMA results in subgroups similar to whole population
        - Change in HbA1c percentage for HCL -0.31 (-0.43, -0.20) in children and young adults and -0.24 (-0.32, -0.15) in adults
- No significant effect from removing Stewart et al. 2018 (only pregnant women), or Benhamou et al. 2019 (potential outlier)

Adverse events and patient reported outcomes

Adverse events:

- RCTs reported a small number of adverse events for both treatment groups
- No clear trends and differences between HCL and the comparator

Patient reported outcomes:

- 1 study (Benhamou et al. 2022), comparing an open loop to a closed loop system, found that user satisfaction had increased significantly after the closed loop period.
- Other studies did not observe any significant changes.

Summary (1)

- RCTs heterogeneous and relatively small
- Relatively narrow inclusion criteria
    - Most participants had reasonably good glycaemic control: baseline HbA1c between 7% and 8%, time in range over 50% (range 47% to 62%)
- In NMA of RCTs HCL arm versus CSII plus CGM improved significantly for
    - HbA1c: -0.29 (95% CI: -0.37 to -0.21)%
    - Percentage time in range (3.9 to 10 mmol/L): +8.62 (95% CI: 7.03 to 10.22)%
    - Percentage time above range (>10.0 mmol/L): -7.20 (95% CI: -8.89 to -5.51)%

Summary (2)

- Outcome estimates for observational studies quantitatively broadly in line with those from RCTs
- NHSE adult pilot study included a broader spectrum of patients with worse glycaemic control at baseline (HbA1c around 9.4%)
    - HCL associated with change in HbA1c of -1.5%
- Data from RCTs and NHSE pilot suggests no increase in risk of hypoglycaemia.

Points for committee consideration

1. Differences in baseline characteristics between RCTs and NHSE pilot led to different estimated HbA1c percentage changes
2. Issues around the RCT and NHSE pilot evidence and generalisability
3. Population subgroup evidence (children and pregnant women)

Points for committee consideration (1): Baseline differences between RCTs and NHSE pilot

- Differences in baseline characteristics between RCTs and NHSE pilot led to different estimated HbA1c percentage changes

Clinical experts:

- People with higher HbA1c levels at baseline expected to have a greater reduction.
  - Participants in RCTs had a lower HbA1c (**7% to 8%**) than in NHSE adult pilot (around **9.4%**).
- Expected change in HbA1c: some experts preferred NHSE pilot estimate of **-1.5%** while others preferred RCT NMA estimate of **-0.29%**
- Experts also highlighted the recent ADAPT study

Points for committee consideration (2a): RCT evidence and generalisability

- Clinical effectiveness analysis prioritised RCT evidence
- RCTs were small (numbers of participants ranged from less than 20 to 135) and heterogeneous

Clinical experts:

- Some concern about recruitment of patients in RCTs. Participants in RCTs usually have higher levels of motivation and better ability to self-manage than NHS populations
- Baseline T1DM management is likely to be good and percentage improvements likely to be less
- RCTs include a mix of 1st and later generation HCL systems
- “[RCTs] consist of small numbers… are of short duration and often have affiliated links to device companies”
- “[Most] look at children and younger adults whereas most pump users in our adult clinics are not in either of these groups.”

Points for committee consideration (2b): NHSE pilot evidence and generalisability

- NHSE pilots were non-randomised, with no control group and with a before-after study design

Clinical experts:

- NHSE pilot mirrors real-world NHS practice better and eliminates some of the biases in RCTs
    - Shows that groups with higher HbA1c, in a real-world practice situation can achieve improvements in glycaemia and hypoglycaemia, as well as reduction in diabetes burden
- "…the advantage of these studies is they were based on 'real world' scenarios with a broad selection of people living with diabetes."
- Included a broader range of patients than usually recruited to RCTs
- "These are the patients that we see daily in clinic that struggle to achieve glycaemic targets and who experience the physical and psychological impacts of type 1 diabetes."
- "…before/after design and lack of control group leaves little protection against confounding variables and limits the ability of the research to draw conclusions from their data."

Points for committee consideration (3): Population subgroup data - paediatric

- RCT children and young adults subgroup (under 18 years), the change in HbA1c percentage for HCL was greater (-0.31 [-0.43, -0.20]) than the adult subgroup (-0.24 [-0.32, -0.15]).
- NHSE CYP pilot net HbA1c change was –0.7%
- Data was not presented on specific child age groups as were included in the scope (that is, 5 years and under, 6 to 11 years and 12 to 19 years).

Clinical experts:

- Highlighted differences between children and adults with diabetes and noted that children:
  - Tend to have less predictable behaviour and activity
  - May also be more insulin sensitive. Children may require smaller insulin doses
  - Issues around having injections at school; hence pump accessibility is better
  - Less proficiency in self management
  - Growth and hormonal changes have an impact on diabetes control/insulin requirements

Points for committee consideration (3): Population subgroup data - pregnancy

- There was very limited evidence on pregnancy and the effectiveness of HCL in pregnant women remains unclear

Clinical experts:

- "Diabetes in pregnancy requires much tighter diabetes management to prevent complications within pregnancy, and harm to the unborn child."
- "HbA1c is a less effective clinical measure (or study outcome) of diabetes control in pregnant women. The evidence for improvements in time in range is increasing but limited at present."
- "Different licensing requirements and lower targets are needed in pregnancy."

NICE National Institute for Health and Care Excellence

No ACIC – for projector, committee and observers

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Cost effectiveness considerations

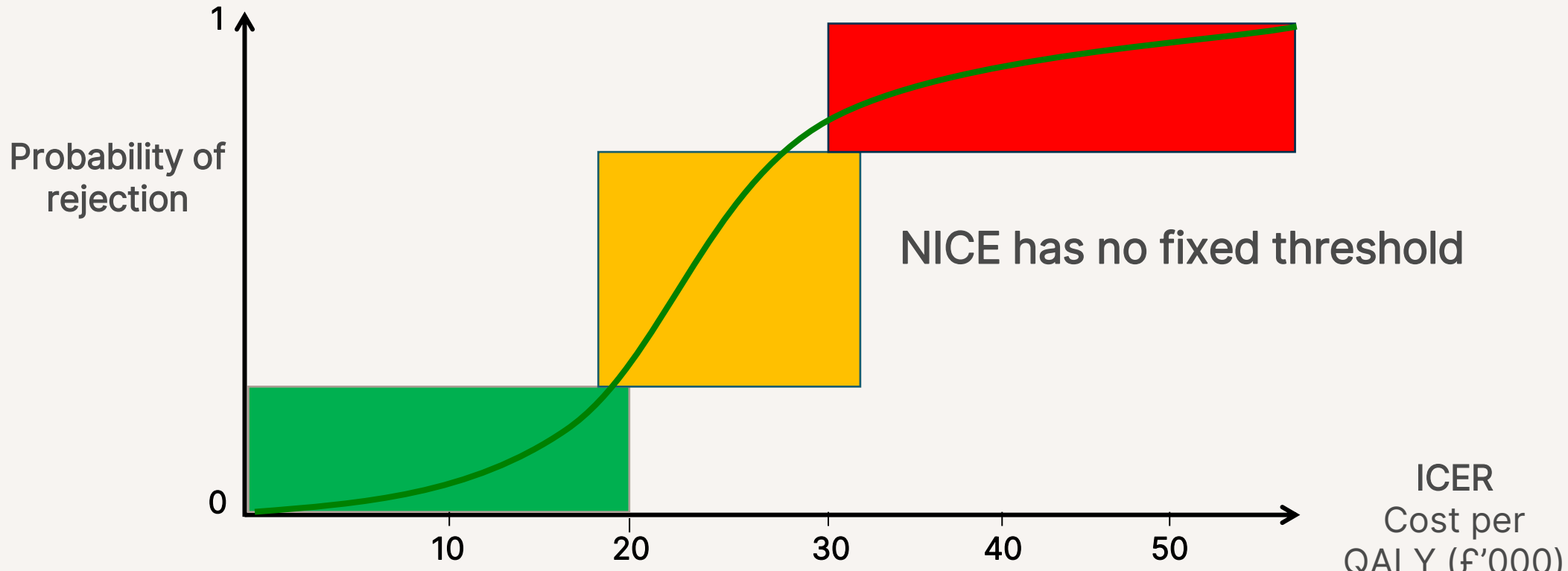
John Cairns

Professor of Health Economics &
DAC standing committee member

29 November 2022

NICE National Institute for Health and Care Excellence

Recap cost-effectiveness



Probably cost effective

Make explicit reference to:
- certainty
- HRQoL adequately captured?
- Innovative nature of technology

Need to identify an increasingly strong case with regard to same factors

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Decision question(s)

Cost effectiveness review objective: To assess the cost effectiveness of using hybrid closed loop (HCL) systems for managing glucose levels in type 1 diabetes

Population: People with type 1 diabetes who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion or real time continuous glucose monitoring or intermittently scanned glucose monitoring.

Subgroups:

- Pregnant women and those planning pregnancies (excluding gestational diabetes).
- Children (5 years and under, 6 – 11 years, 12 - 19 years).

Comparators:

- Real time continuous glucose monitoring (rtCGM) with continuous subcutaneous insulin infusion (non-integrated)
- Intermittently scanned glucose monitoring (isCGM) with continuous subcutaneous insulin infusion

Other models found

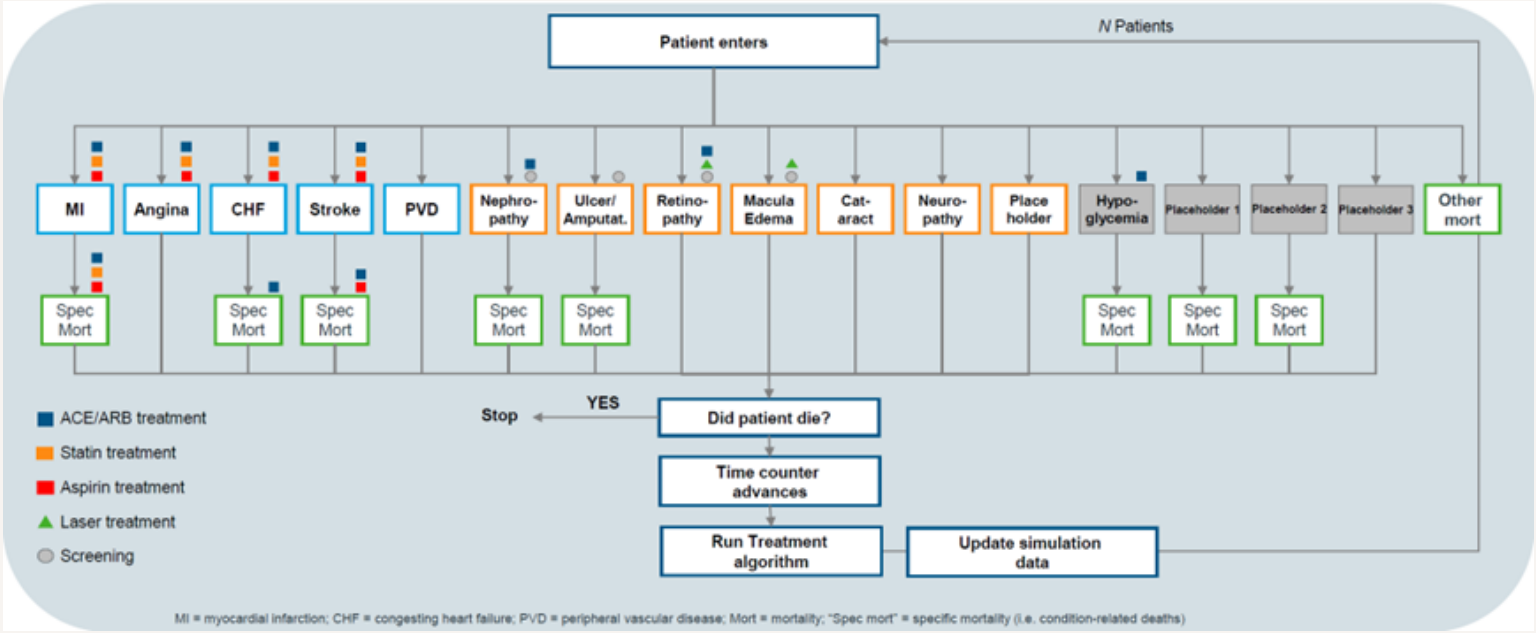
The EAG did a systematic review for previous relevant publications:

- **6 studies** were included in the review
    - **5** economic evaluations of HCL systems and **1** budget impact analysis
- 4 of the economic evaluations used the **IQVIA core diabetes model (CDM)** and 1 used the Sheffield type 1 diabetes model.
- In 4 of the cost effectiveness studies, base case results were very sensitive to severe hypoglycaemic rates (SHE) and changes in the assumptions relating to the quality-of-life benefit associated with reduced fear of hypoglycaemia (FOH).
- EAG: cost effectiveness acceptability curves from these studies showed that HCL systems are expected to be cost effective compared with the comparator technologies at various hypothetical maximum acceptable thresholds

Description of model (1)

- The modelled treatment pathway assumes that people remain on a single treatment option throughout: either CSII plus CGM (base case: 90% isCGM and 10% rtCGM), PLGS or HCL
- In line with DG21 and NG17 the EAG used the IQVIA CDM to model the micro and macro vascular complications of diabetes and patients' overall survival.

- The model predicts progress of people with T1DM over their lifetime, modelling the incidences of the 11 macro and micro vascular complications, the likelihoods of which are affected by T1DM



Description of model (2): Paediatric modelling

- The EAG said it had concerns about the reliability of using the IQVIA CDM to model a paediatric population due to key sources using data that relates primarily to an adult population.
- The model is affected by both the longer duration that is required for a lifetime horizon and the degree to which the risk equations of the model relate to a paediatric population
- The EAG did an exploratory analysis using the NMA results for the subset of paediatric studies and a scenario analysis that applies the NHSE paediatric pilot results

Description of model (3)

Population: EAG used data from the 2019 to 2020 National Diabetes Audit subgroup of those on pump therapy for the key baseline characteristics

Population characteristic	National Diabetes Audit Mean	National Diabetes Audit SD	NHSE adult pilot mean (scenario)	NHSE adult pilot SD
Age	43.4	17.8	40	16.3
Duration diabetes	24.8	15.6	21	11.8
HbA1c	8.0	1.1	9.4	2.0
Male	42%	n.a.	33%	n.a.
White	97%	n.a.	96%	n.a.
Black	1%	n.a.	1%	n.a.
Asian	2%	n.a.	3%	n.a.

Other baseline characteristics needed as inputs to the IQVIA CDM were from NG17 (see appendix 7 of the updated external assessment report).

Description of model (4)

Comparators: In addition to the intervention (HCL), the cost effectiveness analysis considered the 2 comparators in the EAG's network meta-analysis:

1. CSII plus CGM non-integrated
2. LGS/PLGS (no longer available to purchase and therefore not discussed further)

- The EAG did not evaluate CSII plus CGM separately as CSII plus real time CGM (rtCGM) and CSII plus intermittently scanned CGM (isCGM). It assumed the balance to be 10% CSII plus rtCGM and 90% CSII plus isCGM for adult patients based upon advice from the Diabetes Technical Network.
- In the scenario analysis that uses the NHSE adult pilot data, the EAG retained the assumption of 10% CSII plus rtCGM and 90% CSII plus isCGM

Description of model (5)

Modelling of HbA1c effects: HbA1c progression: Base case assumed no annual worsening of HbA1c over time. An annual worsening of 0.045% was applied in a scenario analysis.

HbA1c effects:

Intervention/ comparator	NMA (base case)	NMA adult only (scenario analysis)	NHSE adult pilot (scenario analysis)
HCL	-0.29% (0.033%)	-0.24% (0.043%)	-1.50% (0.051%)
CSII plus CGM	0.00%	0.00%	-

Base case assumes that the **HbA1c effect endures for the model time horizon of 60 years.** Scenario analyses that use durations of 5, 10 and 20 years were also done.

NSHE and SHE rates: EAG did not include NSHE or SHE effects in its base case. Different sources were used for rates in scenario analyses.

Description of model (6): Costs

Training costs: Base case does not include training costs involved from moving from MDI plus CGM to CSII plus CGM or to HCL. Estimates of staff time and outpatient visits were the same for these.

- A scenario applied a cost of £1,132 for people moving from CSII plus CGM to HCL

Treatment costs: EAG used current list prices for the technologies provided by the NHS Supply Chain

- EAG: the costs of HCL pumps and consumables differ slightly between systems but the total 4 year costs are similar.
- EAG used the unweighted averages for year 1 and years 2, 3 and 4. To account for potential reductions in CGM sensor durations, the EAG increased the cost of all CGM sensors by 5% in the base case based upon company data.

Intervention/comparator	Year 1	Years 2 to 4	4 year total	Average
HCL	£7,931	£5,015	£22,975	£5,744
CSII plus CGM (is and rt)	£5,480	£3,751	£16,734	£4,184

Costs and health related quality of life (1)

Ongoing visits and costs of micro and macro vascular complications:

- EAG assumed that that without complications the average patient once established on treatment is seen in an outpatient clinic once per quarter, at an annual routine outpatient cost of £640
- Other ongoing routine management costs and costs of micro and macro vascular complications are taken from NG17 and inflated to 2019 to 2020 prices (see tables 27 and 28 on updated external assessment report).

Disutilities of micro and macro vascular complications:

- EAG used default values of the IQVIA CDM, in line with NG17 (see table 23 in the updated external assessment report)

Costs and health related quality of life (2)

NSHE and SHE costs:

- In scenario analyses, the EAG applied a cost of £1.83 for SHEs not requiring outside medical attention and £542 for those requiring medical attention
- Assumed that 37.9% of SHEs require medical attention

Disutilities of hypoglycaemic events (scenario analyses): EAG used estimates from Gordon et al. and Currie et al.

Hypoglycaemia events and carer disutilities: EAG did not identify any data that quantified disutilities associated with impact of hypoglycaemic events on parents and carers. A scenario analysis doubles the disutilities associated with hypoglycaemia events to reflect possible effects on carers.

Health related quality of life: EAG used a value of 0.839 for quality of life without complications for patients with T1DM, based on the EQ-5D baseline average (Peasgood et al. 2016)

Results – base case

- Compared with CSII plus CGM, HCL is estimated to increase undiscounted survival by 0.458 years
- Discounting reduces the net survival gain to 0.149 years, giving a patient gain of 0.160 QALYs.
- Net treatment cost of £31,185 is partly offset by renal savings of £421 and eye savings of £3,085, resulting in a net cost of £28,628.
- Results in an ICER of £179k per QALY gained

Technology	Life Years Undiscounted	Total QALYs	Total Costs	ICER compared with CSII
CSII	32.499	14.232	£134,661	-
HCL	32.957	14.392	£163,289	£178,925

Results –Scenario analyses (1)

Scenario	Change in costs	Change in QALYs	ICER compared with CSII plus CGM
Base case	£28,628	0.160	£179k
SA01a: Only adult studies	£28,734	0.141	£204k
SA01b: Benhamou et al. excluded	£28,096	0.169	£166k
SA02a: NHS adult pilot baseline characteristics	£25,775	0.205	£126k
SA02b: NHS adult pilot characteristics and effect	**£12,447**	**1.004**	**£12,398**
SA02c: SA02b + reduced complication costs	£21,669	1.004	£21,583
SA03a: 8 year time horizon	£12,740	0.014	£910k
SA03b: 12 year time horizon	£16,601	0.025	£664k
SA03c: 24 year time horizon	£23,975	0.073	£328k
SA04a: 5 year HbA1c effect	£29,571	0.045	£657k
SA04b: 10 year HbA1c effect	£28,887	0.068	£425k
SA04c: 20 year HbA1c effect	£28,369	0.115	£247k

Results –Scenario analyses (2)

Scenario	Change in costs	Change in QALYs	ICER compared with CSII plus CGM
SA05a: NSHEs with HCL 20.8 annual	£28,628	0.170	£169k
SA05b: NSHEs with HCL 57.2 annual	£28,628	0.173	£166k
SA05c: NSHEs with HCL 13.0 annual	£28,628	0.168	£170k
SA06: HEs: NSHEs and SHEs	£28,325	0.174	£163k
SA07a: SA06 + SHEs Currie values	£28,325	0.235	£121k
SA07b: SA06 + SHEs Nauck values	£28,325	0.170	£169k
SA08a: SA06 + £36/£628 SHE cost	£28,246	0.174	£162k
SA08b: SA06 + £381 SHE cost	£28,069	0.174	£161k
SA09: SA06 + HEs double quality of life effect	£28,325	0.188	£151k
SA10a: CSII 85% isCGM 15% rtCGM	£27,117	0.160	£169k
SA10b: CSII 95% isCGM 5% rtCGM	£30,139	0.160	£188k

Results –Scenario analyses (3)

Scenario	Change in costs	Change in QALYs	ICER compared with CSII plus CGM
SA11: HCL/PLGS annual cost £500 more	£38,244	0.160	£239k
SA12: CSII to HCL training cost £1,132	£29,760	0.160	£186k
SA13a: All-cause mortality	£27,846	0.139	£200k
SA13b: Non-specific mortality excluding hypertension	£28,556	0.171	£167k
SA14: Annual 0.045% HbA1c worsening	£27,694	0.181	£153k

Exploratory paediatric modelling inputs

Baseline characteristics

Population characteristic	NHSE paediatric pilot mean
Age	12
Duration diabetes	6.6
HbA1c	7.9%
Male	58%
White	94%
Black	3%
Asian	3%

Time horizon was extended to 80 years and the EAG assumed paediatric patients had not developed any of the complications associated with diabetes

HbA1c percentage changes

Population characteristic	NMA (base case)	NMA paediatric studies	NHSE paediatric pilot (scenario analysis)
HCL	-0.29% (0.033%)	-0.31% (0.059%)	-0.70% (0.019%)
CSII plus CGM	0.00%	0.00%	-

Exploratory paediatric modelling – base case results

- Compared with CSII plus CGM, HCL is estimated to increase undiscounted survival by 0.819 years.
- Additional treatment costs of £40,606 are partially offset by savings in renal complications of £2,459 and eye diseases of £5,143 resulting in total net costs of £32,966
- Coupled with the gain of 0.196 QALYs gives an ICER of £168,196 per QALY gained

Technology	Life Years Undiscounted	Total QALYs	Total Costs	ICER compared with CSII
CSII	60.123	19.252	£176,628	-
HCL	60.942	19.448	£209,595	£168,196

Exploratory paediatric modelling – scenario analyses results

Scenario	Change in costs	Change in QALYs	ICER compared with CSII plus CGM
Base case	£32,966	0.196	£168k
SA01a: Only paediatric studies	£30,924	0.266	£116k
SA02a: NHSE paediatric pilot	£25,448	0.465	£54,727
SA02b: SA2a + HFS2-ws quality of life	£25,448	0.722	£35,259
SA02c: SA2a + triple HFS2-ws quality of life (both parents have similar quality of life improvement for 15 years)	£25,448	0.984	£25,868
SA02d: SA02a + reduced complications costs	£32,091	0.465	£69,013
SA03: Pittsburgh CVD modelling	£32,245	0.169	£191k
SA04: CSII 75% isCGM and 25% rtCGM	£26,961	0.196	£138k

HFS2-ws: hypoglycaemia fear survey – worry subscale

Results – summary (1)

The key model inputs that impacted on results were:

- The net effect upon HbA1c
- The duration of the net effect upon HbA1c
- The model time horizon
- Treatment costs

- Using NMA estimated HCL effect on **HbA1c of -0.29%** resulted in an ICER of **£179k** per QALY
- The ICER was reduced to **£126k** per QALY gained if the NHSE adult pilot baseline patient characteristics were used. When the NHSE adult pilot change in **HbA1c of -1.5%** was used this resulted in an ICER of **£12,398** per QALY gained.

Results – summary (2)

- Modelling of longer term effects was uncertain
- Duration of the HbA1c effect was also uncertain
- There was high uncertainty around NSHE and SHE annual event rates. There was also a lack of evidence that HCL had an effect on these.
- Exploratory modelling of a paediatric population very broadly mirrored the adult results, but the EAG had reservations about the reliability the IQVIA CDM for modelling a paediatric population

Points for committee consideration

1. Using the NHSE adult pilot data and HbA1c change (-1.5%) results in a large decrease in the ICER
2. In most of the clinical evidence the comparator used rtCGM, but the model base case assumed 90% of people had cheaper isCGM and only 10% rtCGM which is more expensive.
3. The time horizon is a key driver of model results
4. Duration of the HbA1c effect is another key driver of the model results
5. Disutilities in the model:
    - lack of data on the effect of HCL on NSHEs and SHEs
    - reduction in mental burden and parental or carer anxiety provided by HCL systems may not be captured in the model
6. Subgroups: Uncertainty in exploratory paediatric modelling. There was also a lack of evidence on HCL for pregnant women

Points for committee consideration (1): NHSE adult pilot data

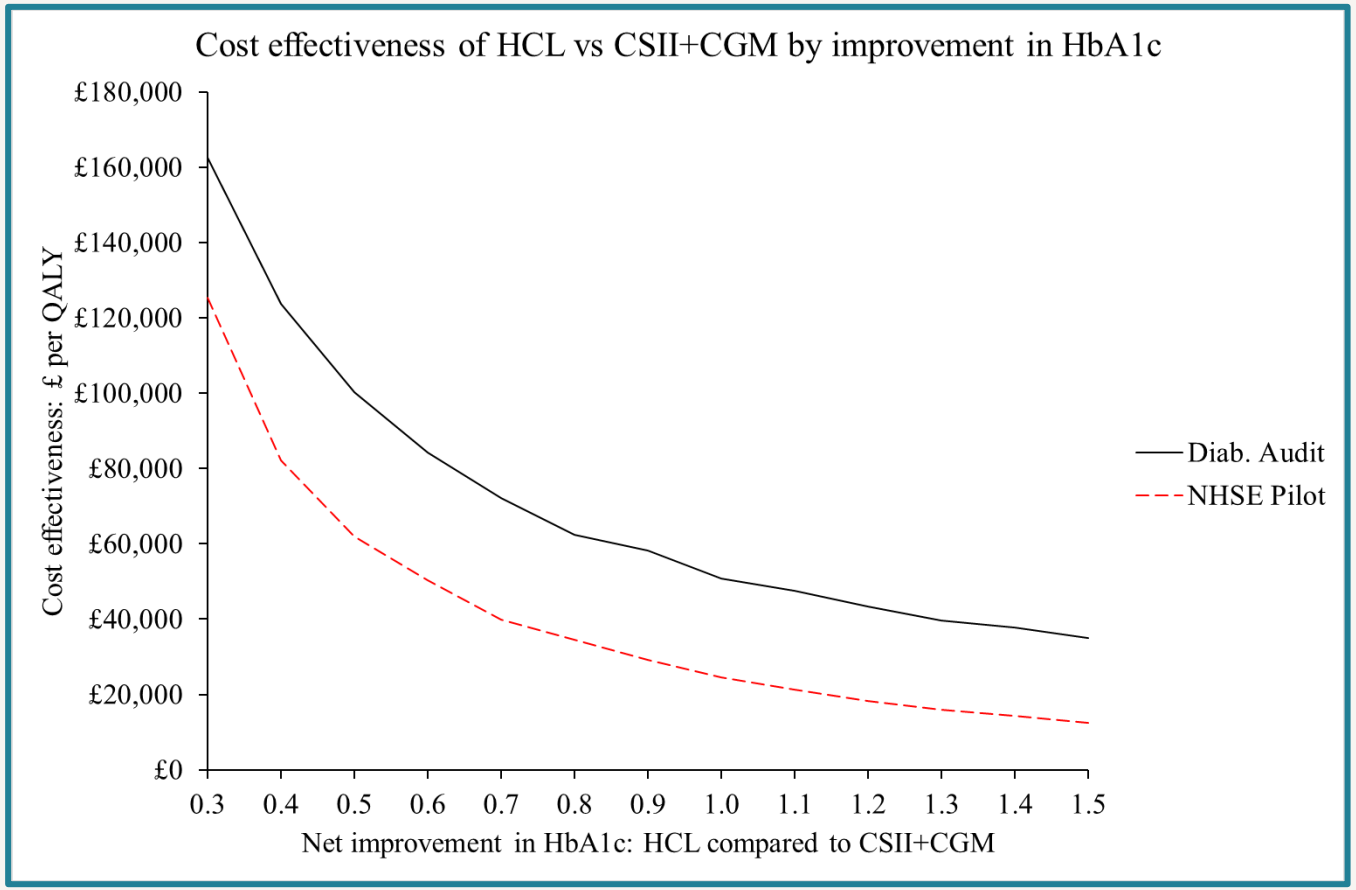
- Using the NHSE adult pilot baseline characteristics data and HbA1c change (-1.5%) results in a large decrease in the ICER from the base case (£12,398 compared with £179k per QALY gained)

EAG:

- Provided HbA1c net improvement threshold analyses using both the national diabetes audit CSII patient baseline characteristics (HbA1c 8.0%) and the NHSE adult pilot baseline characteristics (HbA1c 9.4%)

Clinical experts:

- People with higher HbA1c levels at baseline will have the greatest reduction.



Points for committee consideration (2): Differences between rtCGM and isCGM

- All of the clinical evidence had a comparator that used rtCGM. No studies specified use of isCGM
- Model base case assumed 90% isCGM and only 10% rtCGM.
- Therefore, for the comparator the model is using the clinical effectiveness of rtCGM with the lower cost of isCGM and so may be underestimating the cost effectiveness of HCL

Clinical experts:

- Is-CGM and rt-CGM are not the same cost wise or clinically
- Cost of HCL for those on rtCGM/CSII already are over-estimated - most CSII's currently have an algorithm at no extra cost

Points for committee consideration (3): Time horizon

- Time horizon is a key driver of model results
- In the base case the time horizon was 60 years
- Modelling of longer term effects is uncertain
- Shorter time horizons explored in scenario analyses resulted in larger ICERs

Clinical experts:

- Agreed with the base case 60 year time horizon, although may not be realistic in older adults

Points for committee consideration (4): Duration of the HbA1c effect

- Duration of the HbA1c effect is another key driver of the model results
- Base case assumes that the effect lasts for the lifetime of the model
- This is uncertain and reducing the duration in scenario analyses results in higher ICERs

Clinical experts:

- Agreed with the base case assumption. “There may be some change but largely our clinical experience is [that] improvements persist”.
- “Most clinical interventions are associated with an initial fall in HbA1c, over time, HbA1c and other measures of glycaemic control drift up. NHSE pilot studies showed a more sustained fall in HbA1c (but still only over 12 months)”.
- “Data from paediatrics using pump therapy alone indicates that once a HbA1c [level] is achieved it is maintained”.

Points for committee consideration (5a): Disutilities in the model

- Lack of data on effect of HCL on NSHEs and SHEs. Also high uncertainty around annual event rates
- Reduction in mental burden and parental or carer anxiety provided by HCL systems may not be captured adequately in the model

Clinical experts:

- "reduction in mental burden, especially from newer versions of HCL systems that are testing free and lower alarm burden, with improved algorithms have not been fully demonstrated in the evidence. Hence the QALY calculation underscores this".
- "SA07b gives a better estimation of the cost from SHE / NSHE"
- "SA09 is also important – mental health effects of SHE and NSHE are important including depression and anxiety which is higher in this group"
- Agreed with the scenario that doubled quality-of-life effect of hypoglycaemia events to reflect possible effects on carers

Points for committee consideration (5b): Disutilities in the model

Clinical experts:

- “[SA09] does not also take into account other carer impacts in relation to helping/managing Type 1 Diabetes. Such as intervention due to hyperglycaemia which would be less on a HCL but is still required in the event of pump failure, illness, growth etc”.
- “I feel it is essential to look at the impact of these technologies on quality of life of people living with diabetes and their carers.”
- “As a long-term health condition type 1 diabetes is associated with significant psychological issues and ‘diabetes distress’ has an enormous impact on quality of life as well as diabetes outcomes in such patients.”
- “We know already from clinic comments and the NHS Pilot that family quality of life is improved”
- “Ease of use of the technology is not captured nor is fear of hypoglycaemia”
- “In paediatric practice parents report improved quality of life and sleep”

Points for committee consideration (6): Subgroups –paediatrics and pregnancy

- Uncertainty in the exploratory paediatric modelling results due to uncertainty around the modelled long term survival and about how much of the clinical data used in the IQVIA CDM construction was from a paediatric population
- Cost effectiveness of HCL for pregnant women not considered due to the lack of evidence

Clinical experts:

- Modelling tends to focus on only life expectancy, quality adjusted life expectancy, cumulative incidence and time to onset of long-term complications as the outcomes of interest. Such data are usually unavailable for paediatric assessment".

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