

Guideline for the managed introduction of biosimilar basal insulin



summarising clinical guidelines for primary care

Guidelines identified a need for clinical guidance in a specific area and approached Mylan for an educational grant to support the development of a working party guideline. This working party guideline was developed by *Guidelines*, and the Chair and members of the group were chosen by and convened by *Guidelines*. The content is independent of and not influenced by Mylan, who checked the final document for technical accuracy and to ensure compliance with regulations. The views and opinions of the contributors are not necessarily those of Mylan, or of *Guidelines*, its publisher, advisers, or advertisers. No part of this publication may be reproduced in any form without the permission of the publisher.



Guideline for the managed introduction of biosimilar basal insulin

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Introduction

Diabetes mellitus is a group of metabolic disorders characterised by the inability to produce enough insulin or the inability to respond appropriately to the insulin produced. In time, this can lead to prolonged periods of hyperglycaemia, which can go on to cause serious complications such as cardiovascular disease, chronic kidney disease, foot ulcers, and blindness.¹ In the UK, about 3.8 million people have been diagnosed with type 1 or type 2 diabetes.²

About 10% of the NHS budget is currently funding diabetes-related care, with about 80% of this spent on complications. The current cost of direct care for those living with diabetes—including treatment, intervention, and complications—is estimated at £9.8 billion: £1 billion for type 1 and £8.8 billion for type 2 diabetes.³ The introduction of biosimilar alternatives to originator diabetes treatments offers the opportunity to make significant cost savings and support the NHS in meeting its affordability challenge while maintaining excellent diabetes care, as they are typically offered at a discount compared with the originators.⁴

What are biosimilars?

Biosimilars are biological medicines. Biological medicines ('biologics') contain active substances made in biological sources such as living cells or organisms.⁵ They are well established in clinical practice and indispensable for serious and chronic conditions such as diabetes.⁵ Table 1 summarises specific features of biosimilars.⁵

Unlike generics of small molecules, biologic copies cannot be identical to the originator, because tiny changes in the product structure and manufacturing process can change the way they work, which means they cannot be guaranteed to react in exactly the same way as the originator.^{4,6,7} Instead, biosimilars in the UK are required to show similarity to another biological medicine that is already approved in the EU.^{4,6,7} The development of biosimilars thus aims to show high similarity in terms of structure, biological activity and efficacy, safety, and immunogenicity profile through comprehensive non-clinical comparability studies designed to detect differences in responses.^{4,5,7} Once 'biosimilarity' with the originator is shown, biosimilars rely on the safety and efficacy experience with that originator, avoiding unnecessary repetition of clinical

Table 1: Specific features of biosimilar medicines⁵

Highly similar to the reference medicine ('originator')	<ul style="list-style-type: none"> Biosimilar has physical, chemical, and biological properties highly similar to those of the reference medicine There may be minor differences from the reference medicine, which are not clinically meaningful in terms of safety or efficacy.
No clinically meaningful differences compared with the reference medicine	<ul style="list-style-type: none"> No differences are expected in clinical performance Clinical studies that support approval of a biosimilar confirm that any differences will not affect safety or efficacy.
Variability of biosimilar kept within strict limits	<ul style="list-style-type: none"> Minor variability is only allowed when scientific evidence shows that it does not affect the biosimilar's safety and efficacy Range of variability allowed for a biosimilar is the same as that allowed between batches of the originator This is achieved with a robust manufacturing process to ensure that all batches of the medicine are of proven quality.
Same strict standards of quality, safety, and efficacy	<ul style="list-style-type: none"> Biosimilars are approved according to the same strict standards of quality, safety, and efficacy that apply to any other medicine.

trials and allowing safety and efficacy in one therapeutic indication to be extrapolated to other indications already approved for the originator.⁵ When NICE has already recommended an originator, the same guidance will normally apply to a biosimilar of that originator.⁷ Evidence acquired from 10 years of clinical experience shows that biosimilars approved through the European Medicines Agency can be used as safely and effectively in all approved indications as their originator.⁵

The safety of biosimilars is monitored through pharmacovigilance, just as for any other medicine.⁵ Over the past decade, the EU monitoring system has not identified any relevant difference in the nature, severity, or frequency of adverse events between biosimilars and their reference medicines.⁵ However, as with any drug, biosimilars are labelled with a black triangle for the first few years after approval to signal to clinicians that they are subject to additional monitoring, and all adverse events with these medications need to be reported.^{4,5}

Brand name prescribing for all insulins, including biosimilars, is important; biosimilars should only be switched by the prescriber after careful consideration of the options available, but they should not be substituted at the dispensing level. Biosimilar insulin devices may be different from originator insulin devices, and this should be considered when prescribing a biosimilar insulin. End-user familiarity with the product is essential to ensure they are able to give themselves the medication and that the correct dosage is administered.^{6,8}

Rationale for this guideline

Insulin is classified as a high-risk medication, as it can cause severe side-effects such as hypoglycaemia, and its use is more complex than with most other drugs. This complexity can lead to clinical inertia from healthcare professionals in progressing with insulin therapy, e.g. increasing the dose or switching to a 'new' insulin such as a biosimilar.⁹ Lack of awareness of, familiarity with, and confidence in biosimilars can also lead to reluctance to use these products. Clinicians may also anticipate that individuals will be reluctant to take biosimilars, but they are often more receptive than might be anticipated—especially if they feel they are helping the NHS to get value for money.¹⁰

At the time of writing, national guidance for biosimilar insulin use in the UK is restricted to a position statement from Diabetes UK⁴ and an evidence review from NICE on Abasaglar (biosimilar insulin glargine).¹¹

The NICE review concluded that evidence from two phase 3 studies in type 1 and type 2 diabetes—ELEMENT 1 and ELEMENT 2, respectively—showed that biosimilar insulin glargine was as effective as the originator insulin glargine (Lantus) at reducing HbA_{1c} levels in people with type 1 and type 2 diabetes, and with a safety profile comparable to that of the originator.¹¹ The same results were later obtained in two additional studies, INSTRIDE 1 and INSTRIDE 2 for Semglee▼ (biosimilar insulin glargine) compared to the originator.^{12,13}

Setting a precedent, a NICE review of the use of human growth hormone when a biosimilar is available recommends that 'the choice of product should be made on an individual basis after informed discussion between the responsible clinician and the patient and/or their carer about the advantages and disadvantages of the products available, taking into consideration therapeutic need and the likelihood of adherence to treatment. If, after that discussion, more than one product is suitable, the least costly product should be chosen'.¹⁴

With this in mind, there is a clear need to support primary care clinicians with practice guidance on when and how to use biosimilar basal insulins.

Guideline for the managed introduction of biosimilar insulin

Figure 1 (p. 4) provides an algorithm summarising the working party group's consensus guideline for the managed introduction of biosimilar basal insulin. It is intended to offer concise, easy-to-follow, practical guidance to inform and support primary care clinicians to initiate or transfer suitable individuals to biosimilar insulin glargine. It is intended to be used for people with type 2 diabetes who are deemed suitable for analogue basal insulin initiation; although biosimilar insulins are suitable for people with type 1 diabetes, this guideline is not intended for use in this population, whose insulin should be managed by their specialist.

In its position statement, Diabetes UK recommends against switching people well controlled on an insulin to a biosimilar;⁴ however, given the equivalent efficacy and safety demonstrated by biosimilar insulins in comparison to the originator, the working party group believes that appropriately selected individuals in this cohort may be suitable from switching to a biosimilar insulin glargine.

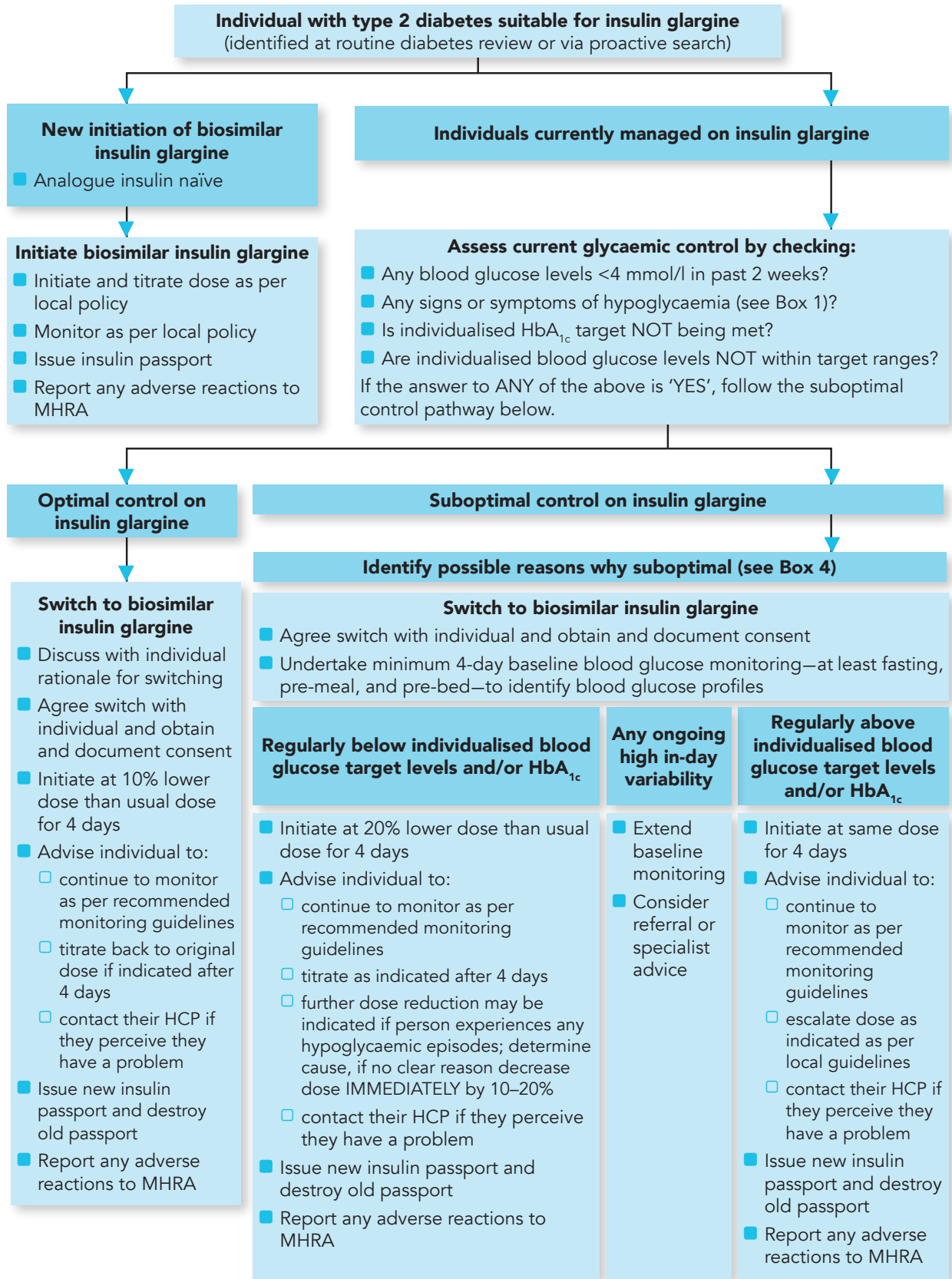
Switching stable individuals with diabetes to a biosimilar insulin would also support the NHS England commissioning framework, which aims to achieve savings by switching at least 80% of existing patients to a biosimilar within 12 months from launch, in a proactive, systematic and safe way.¹⁵ To avoid increasing costs by scheduling extra consultations, healthcare professionals can discuss the switch during the individual's annual review or during group consultations of suitable individuals.

Current guidelines recommend switching individuals with poor control on their current insulin, and the group feels that a straightforward switch to a biosimilar of that insulin is reasonable, as long as reasons for suboptimal control are identified and addressed as part of the switch.

Who should be prescribing biosimilar insulins?

The guideline aims to support initiation of and switches to biosimilar basal insulins by primary care clinicians who usually prescribe basal insulins, including physicians, nurses, pharmacists, non-medical prescribers, and medicine optimisation teams. All prescribers should also have the

Figure 1: Algorithm for the managed introduction of biosimilar basal insulin.



HbA_{1c}= individualised glycosylated haemoglobin; HCP=healthcare professional; MHRA=Medicines and Health Regulatory Authority.

competencies defined in Diabetes UK's competency framework for healthcare professionals working with people with diabetes,¹⁶ as determined by the local lead.

Who should be receiving biosimilar insulins?

Biosimilar insulins should never be introduced as part of a whole-population switch. Insulin prescribing should be tailored to each individual. This position is supported by Diabetes UK.⁴ The working party group therefore recommends a phased introduction of biosimilar insulins:

1. New starters who are naïve to basal insulin analogue
2. Individuals who are 'optimised' on basal insulin (no blood glucose levels <4 mmol/l in past 2 weeks; no signs or symptoms of hypoglycaemia [see Box 1], individualised glycosylated haemoglobin [HbA_{1c}] target met, and individualised blood glucose levels within target ranges)
3. Individuals with suboptimal control (blood glucose levels <4 mmol/l in past 2 weeks, signs or symptoms of hypoglycaemia [see Box 1], individualised HbA_{1c} target not met, or individualised blood glucose levels not within target ranges).

Switching could include people currently on neutral protamine Hagedorn (NPH) with increasing frailty in whom de-escalation of therapy to relax HbA_{1c} targets is appropriate, as well as individuals on twice-daily NPH administered by district nurses. Indeed, the latter is an important easy target for cost savings, as an audit of district nurse visits in one trust found that nurses were making more than 300 visits per day to administer insulin twice daily in individuals who had been historically receiving this formulation for years without review and whose circumstances had changed to require district nurse administration. In this trust, the systematic review of this patient cohort and switching to a biosimilar where clinically indicated, from either a twice daily NPH or glargine, produced a saving of £473,000 simply by reducing the number of district nurse visits to 166 per day.¹⁷

New initiation of biosimilar glargine

- In individuals naïve to analogue insulin, initiate and titrate biosimilar insulin glargine as per local policy
- Monitor as per local policy
- Issue an insulin passport
- Report any adverse reactions to the MHRA.

Switching to biosimilar glargine

- Individuals currently taking insulin glargine who may be suitable for a switch to biosimilar insulin glargine may be identified during their next diabetes review or during a proactive search to identify those suited to a switch

Box 1: Most common symptoms of hypoglycaemia

- Sweating
- Trembling
- Hunger
- Palpitations
- Confusion
- Drowsiness
- Lack of coordination
- Difficulty speaking.

NB Elderly people, frail individuals, or people with longstanding diabetes or frequent hypoglycaemia may not experience or recognise these symptoms.¹⁸

- The working party group feels it is important to minimise additional work involved in switching, which may mean identifying multiple individuals suitable for switching and arranging group consultations to discuss and implement the switch
- Once individuals suitable for switching have been identified, it is important to determine whether current glycaemic control is optimal, as the steps for those with optimal and suboptimal control differ; optimal control is defined as:
 - no blood glucose levels <4 mmol/l in past 2 weeks
 - no signs or symptoms of hypoglycaemia (see Box 1)
 - individualised HbA_{1c} target met
 - individualised blood glucose within target ranges
- The biosimilar delivery device should be considered as part of the decision, as switching to a different type of device can cause problems, although reteaching is often straightforward
- A new insulin passport should be issued and the previous passport should be destroyed
- Box 2 provides practical tips for making the switch; Box 3 provides points to discuss with individuals before a switch is agreed and after the switch; and Box 4 provides suggestions on how to position the switch with individuals.

Switching to biosimilar glargine in individuals with optimal control on insulin glargine

- Agree the switch with the individual and obtain and document consent
- Initiate at a 10% lower dose than usual dose for 4 days
- Advise the individual to:
 - continue to monitor as per recommended monitoring guidelines
 - titrate back to the original dose if indicated after 4 days
 - contact their HCP if they perceive they have a problem

Box 2: Practical tips

- › Give the individual an information sheet (e.g. Semglee▼ patient information leaflet: www.medicines.org.uk/emc/files/pil.9815.pdf; Abasaglar patient information leaflet: www.medicines.org.uk/emc/files/pil.6901.pdf)
- › Tell the person what to look out for
- › Tell the person what to do if there is a problem
 - avoid initiating any new drug just before or over a weekend, so they can access help if they have any problems or questions
- › Ensure the person can visually recognise their insulin and device.

Box 3: Discussion points for individuals

The switch should be discussed in a way that gives the individual confidence in the new drug.

Pre-decision

- › Explain the rationale for the switch, as relevant:
 - offer information on biosimilars that is appropriate to the individual
 - explain that the switch will allow cost savings with no anticipated difference in day-to-day control, without compromising efficacy or safety
- › Allow the individual to raise and address their concerns.

Post-switch

- › Emphasise that it is good practice to be vigilant after any change in medication.

Box 4: Reasons for suboptimal control on insulin

- › Poor or suboptimal adherence
- › Poor injection technique (e.g. storage, site selection, site rotation, injection process)
- › Injection timing
- › Psychological causes
- › Presence of lipohypertrophy
- › Diet and lifestyle
- › Intercurrent or concurrent illness
- › Interacting drugs, e.g. recent steroid therapy or antipsychotic drugs.

- › Issue a new insulin passport and destroy the old passport
- › Report any adverse reactions to the MHRA.

Switching to biosimilar glargine in individuals with suboptimal control on insulin glargine

- › Identify reasons why control is suboptimal (see Box 4) and address as appropriate

- › Agree the switch with the individual and obtain and document consent
- › Undertake minimum 4-day baseline blood glucose monitoring—at least fasting, pre-meal and pre-bed—to identify blood glucose profiles
- › If an individual is regularly below individualised blood glucose target levels and/or HbA_{1c}:
 - initiate at a 20% lower dose than usual dose for 4 days
 - advise the individual to:
 - continue to monitor as per recommended monitoring
 - titrate as indicated after 4 days
 - contact their HCP if they perceive they have a problem
- › Further dose reductions may be indicated if the person experiences hypoglycaemic episodes; if there is no clear reason for these, decrease the dose immediately by 10–20%¹⁹
- › Issue a new insulin passport and destroy the old passport
- › If an individual has any ongoing high in-day variability
 - extend baseline monitoring
 - consider referral for specialist advice
- › If an individual is regularly above their individualised blood glucose target levels and/or HbA_{1c}:
 - initiate at the same dose for 4 days
 - advise the individual to:
 - continue to monitor as per recommended monitoring guidelines
 - escalate their dose as indicated per local guidelines
 - contact their healthcare professional if they perceive they have a problem
- › Issue a new insulin passport and destroy the old passport
- › Report any adverse reactions to the MHRA.

Future switches

- › Although there is currently no target for use of biosimilar insulins, switches to biosimilars are likely to be encouraged by the NHS across the UK because of the potential for savings, particularly as new biosimilars come to market
- › Steps can be taken to minimise additional work involved in switching, but other services will always be impacted to some degree because of, for example, additional monitoring,⁴ training on new devices, and onwards referrals
 - The cost benefit from switching to biosimilars must be enough not to be counteracted by the time involved in switching

- Biosimilar insulin switches should be discussed face to face with the individual rather than by letter
 - this can be done individually during their annual diabetes review or at group consultations of individuals identified to be suitable for switching through a proactive search
 - the switch should be discussed by the usual healthcare professional, who will already have built up trust with the individuals
- An individual should not be switched more than once within a 12-month period
 - switches should not be made purely for costs between annual reviews unless the individual has problems with efficacy, safety or delivery with their current insulin glargine
- Be confident about pushing back against switches in individual cases when not appropriate.

Prescribing practicalities

- Consider changing the position of biosimilars in the electronic system so they are higher up the list and easier to access
- All electronic prescribing systems should have insulins listed by brand names, so no generic prescribing should occur
- Avoid initiating any new drug just before or over a weekend so the individual can access help if they have any problems or questions.

Conflicts of interest

Su Down is Editor in Chief of the *Journal of Diabetes Nursing* and Co-Vice Chair of the Primary Care Diabetes Society. She has received funding from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Mylan, MSD, Napp, Novo Nordisk, and Sanofi for providing educational sessions and/or attending advisory boards.

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Pam Brown is Editor in Chief of *Diabetes and Primary Care* journal. She has received funding from Abbott, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Mylan, MSD, Napp, and Novo Nordisk for providing education sessions and resources, attending advisory boards, and travel to conferences.

Jane Diggle is Co Vice-Chair of the Primary Care Diabetes Society, Associate Editor in Chief for *Diabetes and Primary Care* journal, a Board Member of Injection Technique Matters, and Associate Member of TREND-UK. She has received funding from BD, Boehringer Ingelheim, Bristol Myers Squibb/Astra

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Useful resources

For healthcare professionals

- NHS England biosimilar statement: www.england.nhs.uk/medicines/biosimilar-medicines/
- NICE biosimilar statement: www.nice.org.uk/advice/ktt15
- MRHA guidance on prescribing by brand name for biosimilars: www.gov.uk/drug-safety-update/biosimilar-products
- Yellow Card Scheme: <https://yellowcard.mhra.gov.uk/>
- Six steps to insulin safety: www.diabetesonthenet.com/course/the-six-steps-to-insulin-safety/details
- Diabetes UK's healthcare professional competency frameworks in diabetes: www.diabetes.org.uk/professionals/position-statements-reports/healthcare-professional-staffing-competency/healthcare-professional-competency-frameworks-in-diabetes
- EASD/ADA consensus guidelines on managing hyperglycaemia in type 2 diabetes: diabetologia-journal.org/2018/10/05/new-easd-ada-consensus-guidelines-on-managing-hyperglycaemia-in-type-2-diabetes-launched-at-easd-meeting-new-recommendations-include-specific-drug-classes-for-some-patients-and-enhancing-medication-a/
- Hypoglycaemia in adults in the community: recognition, management and prevention: https://trend-uk.org/wp-content/uploads/2018/09/HCP_Hypo_TREND_FINAL.pdf
- Monitoring and DVLA: www.gov.uk/diabetes-driving
- Injection Technique Matters: <https://trend-uk.org/injection-technique-matters/>
- Insulin passports: www.yourdiabetes.org.uk/your-diabetes/guide-to-your-diabetes/the-adult-insulin-passport/
- NICE frailty guideline: <https://stpsupport.nice.org.uk/frailty/index.html>
- ELEMENT studies:
 - ELEMENT 1—T1DM: www.ncbi.nlm.nih.gov/pubmed/25974640
 - ELEMENT 2—T2DM: www.ncbi.nlm.nih.gov/pubmed/25931141

For individuals with diabetes

- Diabetes UK—support for individuals with diabetes: www.diabetes.org.uk

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