Protocol I8R-MC-IGBM(a)
A Simulation Study Comparing Successful Administration, Time to Administer, and User Experience of Ready-to-Use Nasal Glucagon with Reconstitutable Injectable Glucagon

Nasal Glucagon (LY900018)

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1. Protocol Synopsis

Title of Study:
A Simulation Study Comparing Successful Administration, Time to Administer, and User Experience of Ready-to-Use Nasal Glucagon with Reconstitutable Injectable Glucagon

Rationale:
The aim of this study is to compare successful administration rates, time and experience of administering nasal glucagon (NG) with those of commercially available glucagon emergency kit (GEK) during a simulated severe hypoglycemia emergency. Two different groups of participants will undergo the simulations. One group will be trained to use each device, in a similar way to the training given to real-life caregivers, close friends or family members of a person with diabetes (PWD); the other group will not be given such training, to approximate the real-life experience of colleagues or acquaintances of a PWD. During the simulations, both types of participants will have to administer treatment to a manikin that represents a person with severe hypoglycemia.

The outcomes from these simulations will be measured quantitatively (the proportion of participants administering a successful dose of NG and GEK, and how long it takes) and qualitatively (via user-questionnaires that measure ease of use, confidence and other factors).

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
To test the hypothesis that more Trained Users can successfully administer NG than GEK when treating a simulated episode of severe hypoglycemia.	The percentage of Trained Users that perform a successful administration (complete dose delivered and all critical steps completed), both for NG and GEK.
Secondary	
To test the hypothesis that more Untrained Users can successfully administer NG than GEK when treating a simulated episode of severe hypoglycemia.	The percentage of Untrained Users that perform a successful administration (complete dose delivered and all critical steps completed), both for NG and GEK.
To compare the average time to successfully administer NG, compared with GEK.	The time taken by Trained Users and Untrained Users to successfully administer NG or GEK (complete dose delivered and all critical steps completed), as measured by study site staff.
To compare percentages of users who complete critical administration steps for both NG and GEK.	The percentages of Trained Users and Untrained Users who complete all of the critical steps for both NG and GEK, as assessed by site staff.
To assess the number of simulations that result in successful administration of NG.	The percentage of all simulations that result in a successful administration of NG, for all users combined.

Objectives	Endpoints
To assess whether, overall, one device (NG or GEK) is preferred over the other.	The percentage of participants (Trained Users, PWDs and Untrained Users) that prefer one device over the other, as recorded in a questionnaire.
To assess overall ease of use of both devices (NG and GEK).	The 'ease of use' questionnaire ratings given to NG and to GEK by Trained Users, PWDs and Untrained Users.

Summary of Study Design:

Study I8R-MC-IGBM is a single-center, crossover study assessing the use of NG and GEK during a simulation of a severe hypoglycemia episode, with 2 cohorts of participants: Trained Users (Part A) and Untrained Users (Part B).

Each participant will take part in 2 simulations, 1 with NG and 1 with GEK. Quantitative results (whether or not a dose is administered successfully, and how long it takes) will be recorded by site staff during each simulation. Qualitative results (the opinions of Trained Users, Untrained Users and PWDs) will be captured via questionnaires, both during and at the end of the study.

Study Arms and Planned Duration for an Individual Participant:
In **Part A**, each Trained User and the accompanying PWD will attend 3 one-day study visits, over the course of approximately 2 weeks:

- An initial training visit
- Two study visits, each involving a simulation of a severe hypoglycemia emergency, which the Trained User will attempt to treat with NG and GEK in turn (in randomized order).

In **Part B**, each Untrained User will attend 2 study visits over the course of approximately 1 week. Each visit will include 1 simulated severe hypoglycemia emergency, which the participant will attempt to treat with NG and GEK in turn (in randomized order).

Number of Participants:
Approximately 72 participants (39 Trained Users and 33 Untrained Users) will be recruited to ensure that 52 participants (26 Trained Users and 26 Untrained Users) complete the study.

Trained Users will be recruited such that, of the completers, half (i.e. at least 13) of the accompanying PWDs have type 1 diabetes mellitus (T1DM), and half (at least 13) have type 2 diabetes mellitus (T2DM).

Each Trained User will be accompanied at each visit by the PWD with whom they are recruited to the study.

Statistical Analysis:

The McNemar test will be used to assess the primary objective of the study (successful administration of doses in Part A of the study, with Trained Users). The exact-sign test will be used as a sensitivity analysis for the primary objective.

Successful administration will be assessed for each cohort:

- NG (Trained User) versus GEK (Trained User)
- NG (Untrained User) versus GEK (Untrained User)

For Part A (Trained Users), assessment of successful administration will also be stratified between those users who have an accompanying PWD with T1DM, and those who have an accompanying PWD with T2DM.

For baseline data, continuous variables will be presented using simple descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be presented as n/N and percentage.

Time to administer a dose will be assessed, making the following comparisons:

- NG (Trained User) versus GEK (Trained User)
- NG (Untrained User) versus GEK (Untrained User)
- NG (Trained User) versus NG (Untrained User)
- GEK (Trained User) versus GEK (Untrained User)

This analysis, using descriptive statistics, will be assessed for successful and unsuccessful administration combined, as well as successful administration only.

2. Schedule of Activities

Study Schedule Protocol I8R-MC-IGBM: Part A (Trained Users)

Procedure	Study Visits			Comments
	Visit 1	Visit 2	Visit 3	
	Day 1	Days 8-9	Days 15-17	There must be a gap of at least 7 days between visits.
Evaluation of Eligibility	X			Prescreening will be conducted by telephone before Visit 1. For details on evaluation of eligibility, see Section 6.
Informed Consent	X			
Randomization	X			Randomization will be stratified by diabetes type of PWD (T1DM, T2DM).
PWD Trained on Device 1 by Staff	X			This training should take no longer than 30 minutes, including questions.
"Memory Decay" Period	X			The "memory decay" period will last 55 to 60 minutes and include a short distractor task. See Section 5.1.3.5.
Participant Trained on Device 1 by PWD	X			Site staff should allow up to 30 minutes for the PWD to train the participant.
Simulation		X	X	The simulation at Visit 2 is with Device 1. The simulation at Visit 3 is with Device 2. See Table IGBM.2 for randomization schedule and Section 5.1.3.3 for details of simulations.
Participant completes NASA TLX		X	X	
PWD Trained on Second Device by Staff		X		This training should take no longer than 30 minutes, including questions.
"Memory Decay" Period		X		The "memory decay" period will last 55 to 60 minutes and include a short distractor task. See Section 5.1.3.5.
Participant Trained on Second Device by PWD		X		Site staff should allow up to 30 minutes for the PWD to train the participant.
Questionnaires			X	After the simulation at Visit 3, each PWD and Trained User will watch a video showing both simulations. Then, after a delay of 55 to 60 minutes, each PWD and Trained User will answer the comparative and individual-device questionnaires. See Section 5.1.3 for the order of questionnaires and Section 9.10 for detail of questions.
Safety Assessment/ Follow-up/Early Discontinuation	X	X	X	The safety assessment covers any accidents during training or simulations (see Section 9.4), or significant errors (e.g. insulin was administered during the simulation instead of glucagon). For follow-up of discontinued participants see Section 8.

Abbreviations: NASA = National Aeronautics and Space Administration; PWD = person with diabetes; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TLX = Task Load Index.

Study Schedule Protocol I8R-MC-IGBM: Part B (Untrained Users)

Procedure	Visit 1	Visit 2	Comments
	Day 1	Days 8-9	
Evaluation of Eligibility	X		Prescreening to be conducted by telephone. For details on evaluation of eligibility, see Section 6.
Informed Consent	X		
Randomization	X		
Simulation with Device 1	X		
NASA TLX on Device 1	X		
Simulation with Device 2		X	
NASA TLX on Device 2		X	
Questionnaires		X	After the simulation at Visit 2, each Untrained User will watch a video showing both simulations. Then, after a delay of 55 to 60 minutes, each Untrained User will answer the comparative and individual-device questionnaires (Section 9.10).
Safety Assessment/ Follow-up/Early Discontinuation	X	X	The safety assessment covers any accidents during simulations (see Section 9.4), or significant errors (e.g. insulin was administered during the simulation instead of glucagon). For follow-up of discontinued participants, see Section 8.

Abbreviations: NASA = National Aeronautics and Space Administration; TLX = Task Load Index.

3. Introduction

3.1. Study Rationale

The aim of this study is to assess how well different groups of people – those who have received training and those who have not – are able to use nasal glucagon (NG), compared with a commercially available glucagon emergency kit (GEK) delivered via the intramuscular route, during simulations of severe hypoglycemia emergencies. Assessment of the participants' performance will take 2 forms:

- Quantitative: The proportion of participants who deliver complete doses, and follow all critical steps for dose administration, and the time it takes to deliver a dose, as recorded by study site staff;
- Qualitative: the user experience, as recorded in questionnaires. Questions include preference for either device, confidence using each device, and ease of use.

In this protocol, participants who are given instructions on each device prior to the simulations are referred to as "Trained Users". They will be caregivers, family members or people otherwise close to a person with diabetes (PWD). Before each simulation, they will receive training from their accompanying PWD in the use of the glucagon rescue devices; this is intended to approximate the training that caregivers and relatives are likely to receive from PWDs in real life.

Study participants who are not given instructions on each device prior to the simulations are referred to as "Untrained Users". These are intended to approximate the real-life colleagues or acquaintances of a PWD, who may be present during a severe hypoglycemia emergency and willing to step in, but are not likely to have received training on the rescue device.

The study involves simulations of severe hypoglycemia emergencies using manikins. No drug will be administered to people.

3.2. Background

Hypoglycemia, one of the most serious acute complications of diabetes treatment, is defined as an abnormally low blood glucose level that exposes the individual to potential harm. The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth, according to American Diabetes Association (ADA) guidance (ADA 2018). ADA guidance identifies a 3-stage classification of hypoglycemia:

Level	Glycemic criteria	Description
Hypoglycemia alert value (level 1)	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	≤54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

Source: ADA Standards of Medical Care in Diabetes – 2018.

Based on this classification, the ADA recommends that glucagon should be prescribed for all individuals at increased risk of clinically significant hypoglycemia (level 2), so that glucagon is available should it be needed. Furthermore, an individual does not need to be a healthcare professional to safely administer glucagon.

Nasal glucagon, also known as LY900018, is an investigational drug-device combination product intended for the treatment of severe hypoglycemia (level 3 in the ADA guidance), in adult and pediatric PWDs. Nasal glucagon consists of a single-use nasal dosing device that delivers a fixed 3-mg dose of glucagon powder, absorbed passively through the nasal mucosa.

Nasal glucagon is being developed as an alternative to commercially available GEKs for treatment of severe hypoglycemia, with a needle-free device and fewer steps for administration.

3.3. Benefit/Risk Assessment

This study does not involve the dosing of study drug to humans. As such, there is no expected benefit to study participants. During each simulation with a GEK, there is a risk that participants may suffer a needle-stick injury, which may also result in accidental administration of the marketed comparator product. Site staff will closely monitor simulations and respond to any such safety issues that arise.

4. Objectives and Endpoints

Table IGBM.1 shows the objectives and endpoints of the study.

Table IGBM.1. Objectives and Endpoints

Objectives	Endpoints
Primary To test the hypothesis that more Trained Users can successfully administer NG than GEK when treating a simulated episode of severe hypoglycemia.	The percentage of Trained Users that perform a successful administration (complete dose delivered and all critical steps completed), both for NG and GEK. See Section 5.1.3.4 for definitions of complete dose and critical steps.
Secondary To test the hypothesis that more Untrained Users can successfully administer NG than GEK when treating a simulated episode of severe hypoglycemia.	The percentage of Untrained Users that perform a successful administration (complete dose delivered and all critical steps completed), both for NG and GEK. See Section 5.1.3.4 for definitions of complete dose and critical steps.
To compare the average time to successfully administer NG, compared with GEK.	The time taken by Trained Users and Untrained Users to successfully administer NG or GEK (complete dose delivered and all critical steps completed), as measured by site staff.
To compare percentages of users who complete critical administration steps for both NG and GEK.	The percentages of Trained Users and Untrained Users who complete all of the critical steps for both NG and GEK, as assessed by site staff.
To assess the number of simulations that result in successful administration of NG.	The percentage of all simulations that result in a successful administration of NG, for all users combined.
To assess whether, overall, one device (NG or GEK) is preferred over the other.	The percentage of participants (Trained Users, PWDs and Untrained Users) that prefer one device over the other, as recorded in a questionnaire.
To assess overall ease of use of both devices (NG and GEK).	The ‘ease of use’ questionnaire ratings given to NG and to GEK by Trained Users, PWDs and Untrained Users.

Objectives	Endpoints
Exploratory	
To assess participants' overall confidence in the use of NG and GEK devices.	The 'confidence' questionnaire ratings given to NG and to GEK by Trained Users, Untrained Users and PWDs.
To compare the time it takes a PWD to teach the use of NG and GEK devices.	The average length of time taken by PWDs to teach the use of NG and GEK to their associated Trained User, as measured by site staff.
To compare participants' experience of Mental Demand, Effort, Frustration and other elements of the NASA Task Load Index, following NG and GEK simulations.	Ratings given by Trained Users and Untrained Users in the NASA Task Load Index to describe their experiences with NG and GEK.

Abbreviations: GEK = glucagon emergency kit; NASA = National Aeronautics and Space Administration; NG = nasal glucagon; PWD = person with diabetes.

5. Study Design

5.1. Overall Design

This is a single-center, randomized, crossover study assessing the percentage of successful doses, speed, and experience of administering both NG and a commercially available GEK during simulations of severe hypoglycemia emergencies. Participants in the study will administer nasal and injectable glucagon devices to manikins.

Study I8R-MC-IGBM (IGBM) is divided into 2 parts, with different types of participants: Part A (Trained Users, who will attend all study visits with a PWD) and Part B (Untrained Users). Both parts of the study may be run at the same time.

The study is intended to simulate real-life conditions to capture and document, in a controlled setting, any differences in how Trained Users and Untrained Users use NG and GEK, and their experience of doing so.

5.1.1. Types of Participants

Participants are defined as follows:

- **Trained User:** A participant who, during the study, will be given a level of training intended to mimic that of a real-life caregiver, relative, or close friend of a PWD.
    - "Trained User" participants must be either related to, or a close friend of, a PWD, and therefore already familiar with diabetes and the risk of severe hypoglycemia. Each Trained User must be recruited alongside the PWD with whom they are familiar, as a "dyad" (a pair of people who have a pre-existing relationship).
    - The Trained User will receive instruction on the use of each device, from the PWD, before taking part in the simulation using that device.
    - Trained Users must not have actually administered injectable glucagon (or another rescue medication) in the past. However, they may own a glucagon rescue kit, and may have been instructed in its use, as long as such instruction occurred at least 2 years before screening.
- **PWD:** The PWD who is the close friend or relative of the Trained User.
    - During the study, the PWD will be trained by site staff on the use of each device, and before each simulation, will relay these instructions to the Trained User.
    - The PWD previously may have been instructed in the use of a glucagon rescue kit, as long as such instruction occurred at least 2 years before screening.
- **Untrained User:** A participant who will not be given training during the study on either device, and who has limited knowledge of severe hypoglycemia and how to treat it.
    - These participants are intended to approximate a real-life colleague or acquaintance of a PWD: someone who is aware of the PWD's condition and is

willing to intervene in an episode of severe hypoglycemia, but has not received instructions. Untrained Users in this study may or may not know a PWD in real life. In any case, they must not have caregiving responsibilities toward a PWD.

- Untrained Users will participate in the study alone (not as part of a dyad).
- Prior to the simulations in this study, Untrained Users will be given basic information about severe hypoglycemia and briefly shown an example of each rescue device.

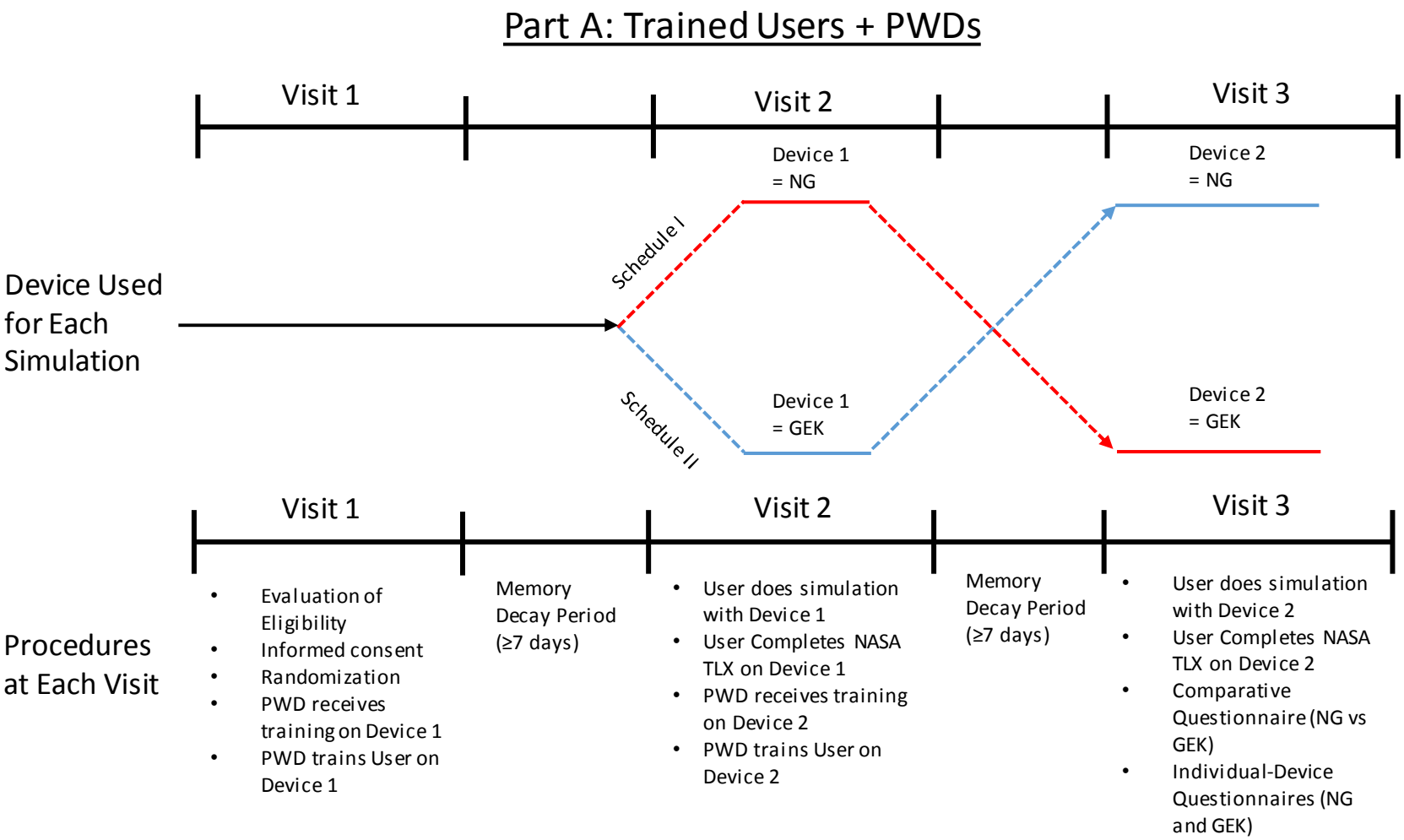
5.1.2. Device Assessment Criteria

The criteria for assessing each device include the following:

- **Dose:** Are Trained Users and Untrained Users able to administer a successful dose more often in an emergency with one device than the other?
- **Speed:** Are Trained Users and Untrained Users able to deliver a dose faster in an emergency with one device than the other?
- **Accuracy:** Do Trained Users and Untrained Users use one device more correctly, i.e. perform the critical steps for dose administration, with fewer errors?
- **Preference:** Overall, do Trained Users, PWDs, and Untrained Users prefer one device over the other?
- **Confidence:** How confident are Trained Users and Untrained Users in their ability to successfully deliver a dose? How confident are PWDs in the ability of Trained Users to successfully deliver a dose?
- **Ease of Use:** How easy do Trained Users and Untrained Users find each device to use? How easy do PWDs think Trained Users find each device?
- **Task Load:** How do Trained Users and Untrained Users rate each simulation in terms of the mental demand, frustration, and other aspects measured using the NASA Task Load Index (TLX)?

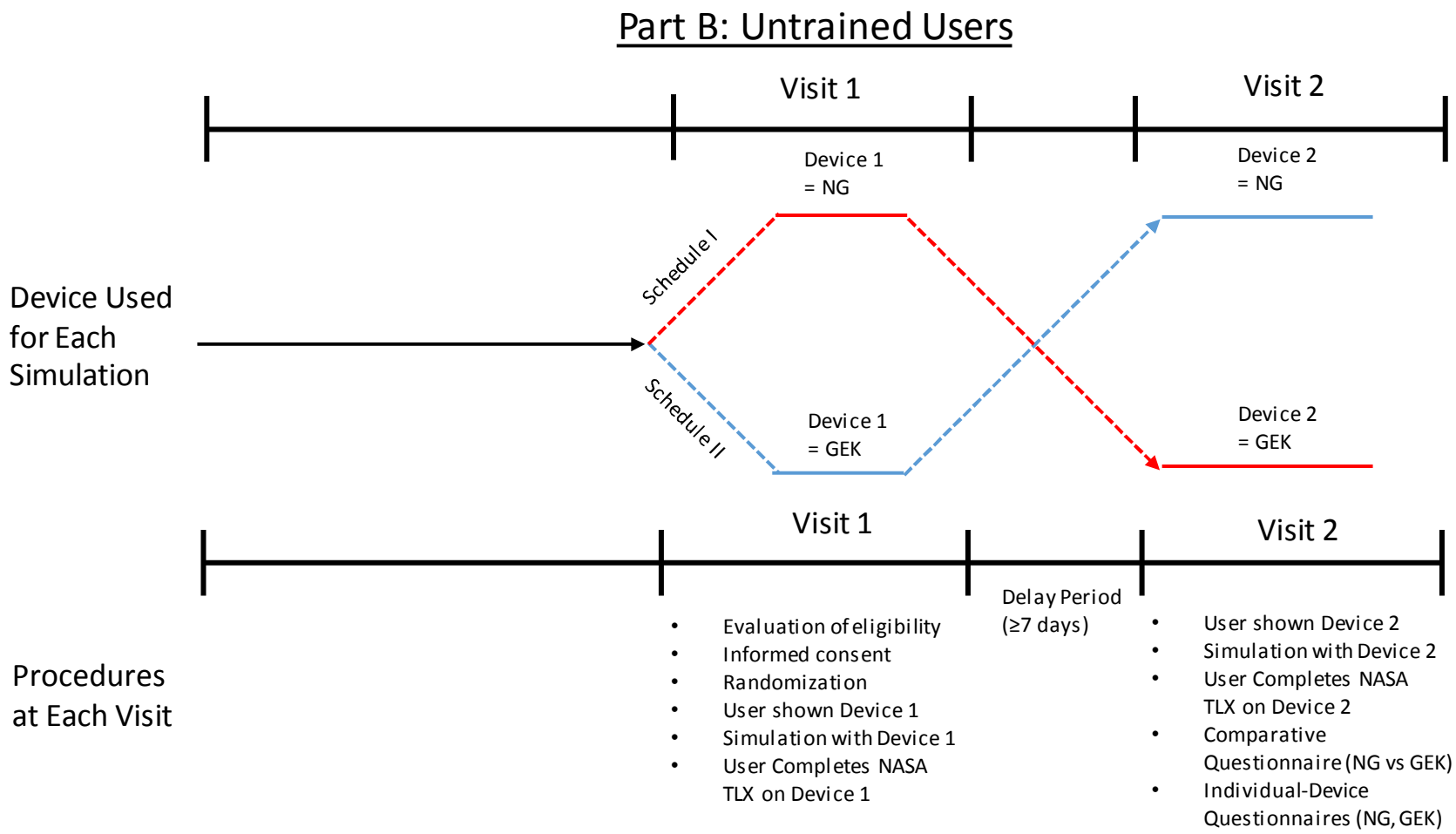
Study governance considerations are described in detail in Appendix 2.

Figure IGBM.1 (Part A) and Figure IGBM.2 (Part B) illustrate the study design.



Abbreviations: GEK = glucagon emergency kit; NASA = National Aeronautics and Space Administration; NG = nasal glucagon; PWD = person with diabetes; TLX = Task Load Index.

Figure IGBM.1. Illustration of study design for Protocol I8R-MC-IGBM: Part A.



Abbreviations: GEK = glucagon emergency kit; NASA = National Aeronautics and Space Administration; NG = nasal glucagon; TLX = Task Load Index.

Figure IGBM.2. Illustration of study design for Protocol I8R-MC-IGBM: Part B.

5.1.3. Detailed Description of Study Procedures

As shown in Figure IGBM.1 and Figure IGBM.2, study procedures will vary between Part A (Trained Users) and Part B (Untrained Users).

Details of each simulation are intended to be included in a study operations manual. Site staff will make a video recording of each simulation, for study participants to review later, before they complete questionnaires. The videos may also be used to validate the site's evaluation of critical steps and other aspects of the simulation.

5.1.3.1. Part A (Trained Users)

Trained Users will be required to attend the study site on 3 occasions, each time accompanied by the PWD with whom they are associated.

At **Visit 1**, each Trained User and their associated PWD will be evaluated for eligibility, give informed consent, and be randomized to 1 of 2 schedules (Table IGBM.2).

Randomization will be stratified by the type of diabetes, i.e. randomization will be performed separately for PWDs with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), and their accompanying Trained User.

Following randomization, site staff will instruct the PWD how to use Device 1 (i.e. either NG or GEK, depending on the randomization). This instruction will include a mock administration, during which the PWD will actuate the device. After a "memory decay" period including a distractor task (see Section 5.1.3.5), the PWD will relay instructions on how to use Device 1 to the Trained User.

At **Visit 2**, approximately 7 days after Visit 1, each Trained User will take part in a simulation of a severe hypoglycemia emergency with a manikin (see Section 5.1.3.3). The gender of the manikin will match the gender of the PWD. The PWD will not be in the room and will not observe the simulation. Site staff will assess dose administration (successful/unsuccessful; see Section 5.1.3.4), and the time taken to administer a dose.

After a short rest period, the Trained User will complete the NASA TLX questionnaire about their experience with Device 1. At around the same time, site staff will instruct the PWD how to use Device 2. After a "memory decay" period including a distractor task (see Section 5.1.3.5), the PWD will relay instructions on how to use Device 2 to the Trained User.

At **Visit 3**, approximately 7 days after Visit 2, each Trained User will take part in a second simulation, similar to the first. They will be asked to treat the manikin with Device 2, again observed by site staff only. The gender of the manikin will again match the gender of the PWD. After a short rest period, the Trained User will complete the NASA TLX questionnaire about their experience with Device 2. At around the same time, site staff will assemble a video of both simulations (from Visits 2 and 3). Then both PWD and Trained User will watch the video. After a delay of 55 to 60 minutes, the PWD and Trained User will each complete a questionnaire comparing both devices; later they will complete individual questionnaires for both NG and GEK, in randomized order (Table IGBM.2). Details of the questionnaires are in Section 9.10.

Participants will be given a device-specific questionnaire only if the Trained User attempted to administer that device. For example, there will be no questionnaire for a simulation if insulin was wrongly administered instead of the glucagon device, or if no attempt was made to administer a device. Similarly, participants will be given the comparative questionnaire only if the Trained User attempted to administer both NG and GEK during the respective simulations.

5.1.3.2. Part B (Untrained Users)

Untrained Users will attend the site for 2 visits (Figure IGBM.2).

At **Visit 1**, after being evaluated for eligibility and giving informed consent, each Untrained User will be randomized to 1 of 2 schedules (Table IGBM.2), which will determine the device used at each simulation. Male manikins will be used in each case.

Each Untrained User will be given a brief explanation of diabetes and severe hypoglycemia, and briefly shown an example of Device 1 (NG or GEK depending on randomization). No instruction will be given on how to use the device; nor will the Untrained User be allowed time to read any instructions for using the device.

Each Untrained User will then take part in a simulation (see Section 5.1.3.3) using Device 1. Staff will assess successful or unsuccessful treatment (Section 5.1.3.4), and time to successful administration (if this occurred within the allotted time). After a short rest period, the Untrained User will complete the NASA TLX questionnaire about their experience.

At **Visit 2**, approximately 7 days after Visit 1, each Untrained User will be shown an example of Device 2. As at Visit 1, no instruction will be given on how to use the device. The Untrained User will take part in a simulation using Device 2, and then complete the NASA TLX. Site staff will assemble a video of both simulations, and the Untrained User will watch it. After a delay of 55 to 60 minutes, the Untrained User will fill in a questionnaire comparing both devices, and then individual-device questionnaires in randomized order (Table IGBM.2). Details of the questionnaires are in Section 9.10. The Untrained User will be given a device-specific questionnaire only if they attempted to administer that device. For example, there will be no questionnaire for a simulation if insulin was wrongly administered instead of the glucagon device, or if no attempt was made to administer a device. Similarly, Untrained Users will be given the comparative questionnaire only if they attempted to administer both NG and GEK devices during the respective simulations.

5.1.3.3. Example Simulation

The participant in the simulation (Trained User or Untrained User) will be taken into a room where a fully clothed adult manikin is present (e.g. lying face-up on the ground, on a bed, or in a chair). The participant will be told that the manikin represents a PWD experiencing severe hypoglycemia. For Part A, site staff will refer to the manikin using the PWD's name during the simulation.

Near to the manikin will be a backpack, chest of drawers, or other receptacle, appropriate to the simulated location (bedroom, office, etc.). This will contain diabetes supplies (glucometer and

strips, alcohol swabs, lancing device, insulin syringe and a vial of insulin) and the glucagon device (NG or GEK depending on randomization); it may also contain other everyday items.

The participant will be told to find the PWD's glucagon device and administer rescue glucagon as quickly as possible. Once the participant finds the device, the timing of the simulation will start. While the participant attempts to administer glucagon, site staff will emphasize the urgency of the situation, e.g. by telling the participant that it will be some time before an ambulance arrives. Distracting sounds and events will be incorporated to simulate the stress of a real-life situation. After approximately 15 minutes, site staff will tell the participant that the ambulance has arrived, ending the simulation.

5.1.3.4. Assessment of Successful Administration

The study objectives (Section 4) include an assessment of whether participants are able to successfully administer a dose of glucagon to the manikin. To successfully administer either NG or GEK, a participant must complete all of the critical steps for each device, AND administer a complete dose, as defined below:

1. Complete All Critical Steps

Device	Critical Steps
NG	• Remove device from packaging • Do not test before use • Insert the device tip into one of the manikin's nostrils • Push the plunger, keeping the tip inside the nostril, until the green line no longer shows
GEK	• Remove device from packaging • Inject the diluent from the syringe into the vial containing the drug powder • Ensure drug powder is dissolved (by shaking/swirling) • Draw the dissolved drug into the syringe • Inject the drug into the manikin at an appropriate site for intramuscular administration (e.g. thigh/buttock/upper arm)

AND

2. Administer a Complete Dose

Device	Complete Dose
NG	Device plunger is pushed until the green line on the plunger is no longer visible.
GEK	90% or more of the glucagon drug solution is administered.

5.1.3.5. "Memory Decay" Period

In Part A, there will be a gap of 55 to 60 minutes between PWDs receiving instruction from site staff on the use of the device for the next simulation, and the PWDs relaying instructions to their accompanying Trained User. During this "memory decay" period, PWDs will be given a short "distractor task", such as a questionnaire about a topic unrelated to the device or simulation.

5.2. Number of Participants

Approximately 72 participants (39 Trained Users and 33 Untrained Users) may be enrolled so that approximately 52 participants (26 Trained Users and 26 Untrained Users) complete the study.

Each Trained User must be accompanied during each visit by the PWD with whom they are associated (see Section 6.1). Trained Users will be recruited such that, of completers, half (i.e. at least 13) of the accompanying PWDs have T1DM, and half (at least 13) have T2DM.

For purposes of this study, a participant completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been completed.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last participant.

5.4. Scientific Rationale for Study Design

The use of a crossover design allows a within-participant comparison of NG with GEK.

The use of 2 groups of participants, Trained User and Untrained User, is intended to simulate the types of people in the real world who are typically required to administer glucagon in an emergency: caregivers/relatives/close friends of PWDs who have received instruction in how to administer glucagon; and colleagues or acquaintances who have not received instruction, but still may be willing to step in.

The process of a PWD relaying instructions to the Trained User – rather than the Trained User receiving instruction first-hand from site staff – is intended to simulate the real-life tendency for PWDs to learn from a medical professional how to use a GEK, and to later relay this information to caregivers, relatives and/or close friends. The "memory decay" period is intended to simulate the delay that occurs in relaying these instructions.

A manikin will represent a person experiencing severe hypoglycemia; this allows for better control of the variables of each simulation, and avoids ethical issues related to the induction of severe hypoglycemia in people.

The PWD will not observe simulations in real time, so as to minimize the risk of their intervening or otherwise influencing the Trained User. This is intended to ensure simulations are like-for-like between participants and between devices, which will aid comparison.

In Part A, the manikin will appear to have the same gender as the PWD, and will be referred to with the PWD's name, to simulate the increased stress and pressure of treating a relative or close

friend. In Part B, this is not a pertinent factor, and manikins will default to being male in appearance.

5.5. Justification for Dose

Not applicable.

6. Study Population

A generic prescreening by telephone may occur prior to Visit 1 to arrange scheduling of visits for both parts. For Part A (Trained Users), the PWD must declare willingness to attend all study visits along with the Trained User.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible for inclusion in the study only if they meet all of the following criteria at screening:

For all participants (Trained Users, PWDs and Untrained Users):

[1] are at least 18 years old at the time of informed consent

[2] are able to understand the purpose and procedure of the study and to give written informed consent to show their own willingness to participate in the study

Trained Users only:

[3] are persons who are not diagnosed with T1DM or T2DM

[4] are close friends/relatives of a patient who has been diagnosed with T1DM or T2DM and is being treated with insulin

[5] have not previously administered any rescue medications (e.g. epinephrine, glucagon, narcan or seizure medications)

[6] agree to not seek out information, or take any training, on how to administer either NG or injectable glucagon through the end of the study, except the training given as a part of the study

Untrained Users only:

[7] have not been diagnosed with T1DM or T2DM, and are not a Trained User of a person with T1DM or T2DM

[8] have not previously administered any rescue medications (e.g. epinephrine, glucagon, narcan or seizure medications); have not received training to administer any such medication; and agree not to take any such training through to the end of the study

6.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

All participants (Trained Users, PWDs and Untrained Users):

[9] are study site staff directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child or sibling

[10] are Lilly employees or employees of High Point Clinical Trials Center

[11] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

Trained Users and Untrained Users only (i.e. the participants involved in the simulations):

[12] are currently enrolled in a clinical study involving any type of medical research judged not to be scientifically or medically compatible with this study

[13] have a history of pheochromocytoma, insulinoma or glucagonoma

[14] are judged by the investigator as being likely to have difficulty performing the administration due to physical, cognitive and/or severe psychiatric disorder, etc.

[15] are judged by the investigator as being trained or experienced in performing rescue drug administration

[16] are judged by the investigator as being trained or experienced in performing high-fidelity simulations of drug administration

[17] have used a GEK, attempted to use a GEK, or received instruction in using a GEK in the past 2 years

[18] have received formal training in a medical field, and/or worked in this field within the prior 5 years; or otherwise are judged by the investigator as being trained or experienced as a first responder

PWDs only:

[19] have received instruction in using a glucagon rescue kit in the past 2 years

[20] have experienced severe hypoglycemia and been treated with a rescue device in the past 2 years.

6.3. Lifestyle and/or Dietary Requirements

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, after consultation with the Sponsor.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of NG with a commercially available glucagon injection kit, administered to a manikin as part of a simulated severe hypoglycemia emergency. No treatment will be administered to humans.

The investigator or designee is responsible for

- explaining the correct use of the devices to PWDs
- verifying that the simulations are conducted properly
- maintaining accurate records of NG and GEK device dispensing and collection
- ensuring all devices are destroyed at the end of the study

7.1.1. Packaging and Labeling

Investigational NG devices will be provided empty of drug product, with a mock label, in shrink-wrap, and labeled per local regulations. Commercially available glucagon injection kits are labeled according to the country's regulatory requirements.

In Part A, during the demonstration given by site staff to PWDs, and the demonstrations by PWDs to their accompanying Trained User, written Instructions for Use (IFU) will be provided for both devices.

For each simulation, GEK devices will be provided sealed, and NG devices provided in shrink-wrap.

7.2. Method of Treatment Assignment

Randomization will be performed using a computer-generated randomization schedule, stratified by type of participant (Trained Users and Untrained Users). The randomization of Trained Users will be further stratified by whether their accompanying PWDs have either T1DM or T2DM. Table IGBM.2 shows the randomization scheme that will be used for both parts of the study, and for the order of device-specific questionnaires given after the last simulation.

Table IGBM.2. Example Randomization Schedule - Study IGBM

	Device for Simulation 1 ("Device 1"); and Device Specified in Questionnaire 1	Device for Simulation 2 ("Device 2"); and Device Specified in Questionnaire 2
Schedule I	GEK	NG
Schedule II	NG	GEK

Abbreviations: GEK = glucagon emergency kit; NG = nasal glucagon.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all study products received and any discrepancies are reported and resolved before use of the study product.

NG shrink-wrap, and GEK container seals, should not be removed prior to simulations. NG shink-wrap should not be removed prior to the device demonstrations given by site staff to PWDs.

Only participants enrolled in the study may receive NG and GEK devices and these must only be provided by authorized site staff. All study devices should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions, where applicable, with access limited to the investigator and authorized site staff.

7.6. Treatment Compliance

Nasal glucagon and injectable glucagon will be stored at the site throughout the study. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study product accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.7. Concomitant Therapy

Not applicable.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Site staff will attempt to contact participants who discontinue from the study prematurely for any reason, for follow up (for safety assessment and/or to determine why they discontinued).

8.1. Discontinuation from Study Treatment

Not applicable.

8.1.1. Discontinuation of Inadvertently Enrolled Participants

Not applicable for this study.

8.2. Discontinuation from the Study

Participants will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the participant should be discontinued from the study
- Participant Decision
    - the participant requests to be withdrawn from the study.

8.3. Participants Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site. Site staff are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

Because this study involves simulations where participants will handle an injectable kit (the GEK), there is a risk of needle-stick injury.

In the event of an accidental needle-stick injury, subjects will be medically managed as appropriate, including any laboratory sampling that may be required to manage their safety.

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report, if applicable.

The investigator remains responsible for following, through an appropriate health care option, adverse events (AEs) that are serious or otherwise medically important, considered related to the study or that caused the participant to discontinue before completing the study. The participant should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form (ICF) is signed, study site personnel will record, via case report form (CRF), the occurrence and nature of each participant's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device or a study procedure, taking into account the disease, concomitant treatment or pathologies.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

9.2.1. Serious Adverse Events

A serious adverse event (SAE) is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e. immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above
- when a condition related to the investigational device (e.g. drug delivery system) necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Study site personnel must alert the Lilly clinical research physician (CRP)/clinical pharmacologist, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the CRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and handled a device. However, if an SAE occurs after signing informed consent, but prior to handling a device, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued from and/or completed the study (the participant summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to drug product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the label for the GEK, and that the investigator reports as related to this product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality and to facilitate process and product improvements.

Participants should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

Not applicable.

9.4. Safety

During each simulation with GEK, there is a risk that participants (Trained Users and Untrained Users) may suffer a needle-stick injury. Site staff will closely monitor simulations and respond to any such safety issues that arise.

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. When appropriate, the Lilly clinical pharmacologist or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Economics

Not applicable.

9.10. Questionnaires

As detailed in Section 5.1.3, Trained Users and Untrained Users will complete NASA TLX questionnaires soon after each simulation, and all participants (Trained Users, Untrained Users and PWDs) will complete further questionnaires at the end of the study.

As detailed in Sections 5.1.3.1 and 5.1.3.2, the individual (device-specific) and comparative questionnaires will be given only for devices that participants actually attempted to administer during the simulations. The NASA TLX will be administered for all participants, whether they attempted to administer a glucagon device or not.

Assuming the comparative questionnaire is given, it will always be given before the device-specific questionnaires. The order of the NG- and GEK-specific questionnaires will be randomized (Table IGBM.2).

9.10.1. NASA Task Load Index

Following each simulation, Trained Users and Untrained Users (but not PWDs) will be asked to complete Hart and Staveland's NASA TLX to gauge their experience during that simulation. The NASA TLX is a series of 21-point scales that measure various aspects of carrying out a task. Example questions include Mental Demand ("How mentally demanding was the task?"), Effort ("How hard did you have to work to accomplish your level of performance?") and Frustration ("How insecure, discouraged, irritated, stressed, and annoyed were you?").

9.10.2. Questionnaire Comparing Both Devices

For Trained Users and Untrained Users, the comparative questionnaire will include questions on preference, ease of use and confidence using each device.

Person with diabetes will receive a differently worded questionnaire that will include questions on their preference of device, and their impression of the user experience for ease of use and confidence.

9.10.3. Device-Specific Questionnaires (NG and GEK)

All participants (Trained Users, Untrained Users and PWDs) will be given a device-specific questionnaire for each device (NG and/or GEK) that the participant attempted to administer. The questionnaires will include questions related to ease of use and confidence in using each device, without comparing to the other device.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size is 26 in each of the 2 cohorts (Trained Users and Untrained Users). It is assumed that the percentages of successful dosing of NG and GEK will be 90% and 50%, respectively. Additionally, a proportion of discordant pairs of 45% is assumed, which reflects a moderate within-subject correlation between the 2 treatments.

These numbers are based on the Yale 2017 study (Yale et al. 2017), where 15 out of 16 (93.8%) NG simulations were completely successful and 8/16 (50%) GEK administrations were partially successful in the "caregivers" group (the equivalent of the Trained Users group in this study). Note that for GEK, the "partial success" rate is used. In Yale 2017, only 2 out of 16 (12.5%) simulations were completely successful for the GEK treatment. Hence, we are using a best-case scenario approach for the successful administration rates of GEK in the current study. In conclusion, the 90% success rate for NG is based on the Yale 2017 NG success rate (15/16, 93.8%, rounded down) and the 50% success rate for GEK is based on the best-case scenario from the Yale 2017 study, i.e. partial administration of GEK in 8/16 (50%) simulations.

Based on these numbers, the sample size will provide 90% statistical power to detect a statistically significant difference between success rates of NG and GEK, using the test with a 2-sided alpha level of 0.05.

Enrollment will be continued per group until 26 Trained Users have been recruited (stratified into 13 who have an accompanying PWD with T1DM, and 13 who have a PWD with T2DM) and 26 Untrained Users have been recruited.

Participants who are randomized but do not participate in the study simulations may be replaced to ensure that enough participants may complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

An individual listing and summary of participant demographics will be provided at the end of the study.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

The McNemar test will be used to assess the primary objective of the study (Section 4). The exact-sign test will be used as a sensitivity analysis for the primary objective.

Successful administration will be assessed, for each cohort:

- NG (Trained User) versus GEK (Trained User)
- NG (Untrained User) versus GEK (Untrained User)

For Part A (Trained Users), assessment of successful administration will also be stratified between those users who have an accompanying PWD with T1DM, and those who have an accompanying PWD with T2DM.

For baseline data, continuous variables will be presented using simple descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be presented as n/N and percentage.

Time to administer a dose will be assessed, making the following comparisons:

- NG (Trained User) versus NG (Untrained User)
- GEK (Trained User) versus GEK (Untrained User)
- NG (Trained User) versus GEK (Trained User)
- NG (Untrained User) versus GEK (Untrained User)

This analysis, using descriptive statistics, will be assessed for successful and unsuccessful administration combined, as well as successful administration only. Time needed to complete glucagon administration will be shown categorically. A graphical presentation of the successful administration times may be provided.

To simultaneously model the training effect (Trained Users versus Untrained Users) and the treatment effect (NG versus GEK), a generalized estimating equations (GEEs) model will be performed, with treatment, training and the treatment-by-training interaction effect as independent variables, and the participant as participant identifier. As each Trained User and Untrained User will perform both the NG and the GEK administration, the data are paired for the device type but not paired for the level of training. Using a GEE model will enable estimation of both effects simultaneously, and also estimation of the interaction effect, which will test whether the difference between devices varies between Trained Users and Untrained Users. Furthermore, the randomization order (NG-GEK versus GEK-NG) can be tested within this model. Given the low sample size of this study and multitude of variables that can be entered, this GEE modeling can be exploratory in nature.

Primarily, a GEE model using the binary distribution (success versus no success) and the identity link will be produced: this will produce estimated rate differences with 95% confidence intervals. In case this model fails to converge, log or logit links can be attempted, to estimate relative risks or odds ratios, respectively.

All AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Data Review during the Study

No interim access to data is scheduled to occur.

10.3.2. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

11. References

American Diabetes Association. Glycemic targets: standards of medical care in diabetes - 2018. *Diabetes Care*. 2018;41(suppl 1):S55-S64.

Yale JF, Dulude H, Egeth M, Pichè CA, Lafontaine M, Carballo D, Margolies R, Dissinger E, Shames AR, Kaplowitz, N, Zhang MX, Zhang S, Guzman CB. Faster use and fewer failures with needle-free nasal glucagon versus injectable glucagon in severe hypoglycemia rescue: a simulation study. *Diabetes Technol Ther.* 2017;19(7):423-432.

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	American Diabetes Association
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Complaint	A complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
Enroll	The act of assigning a participant to a randomization schedule.
Enter	Subjects entered into a study are those who sign the informed consent form.
ERB	ethical review board
GCP	good clinical practice
GEE	generalized estimating equation
GEK	glucagon emergency kit
ICF	informed consent form
ICH	International Council for Harmonisation
IFU	Instructions for Use
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
NG	nasal glucagon
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PWD	person with diabetes
Randomize	The process of assigning subjects/patients to an experimental group on a random basis.
SAE	serious adverse event
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

Appendix 2. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment materials should be approved by Lilly.

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site. Lilly or its representatives must approve the ICF before it is used at the investigative site. All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current Investigator's Brochure and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with the protocol and with

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include medical records and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject/patient personal information collected will be provided in a written document to the subject/patient by the sponsor.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and GCP.

Appendix 3. Protocol Amendment I8R-MC-IGBM(a) Summary
A Simulation Study Comparing Successful Administration, Time to Administer, and User Experience of Ready-to-Use Nasal Glucagon with Reconstitutable Injectable Glucagon

Overview

Protocol I8R-MC-IGBM, A Simulation Study Comparing Successful Administration, Time to Administer, and User Experience of Ready-to-Use Nasal Glucagon with Reconstitutable Injectable Glucagon, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Section 5.1.3.1 (Detailed Description of Study Procedures, for Part A) now states that the PWD will not observe the simulations in real time. This is to minimize the risk of their intervening or otherwise influencing the Trained User.
- Section 5.1.3 (Detailed Description of Study Procedures, for both parts A and B) and Section 9.10 (Questionnaires) now clarify that the individual device-specific questionnaires will only be given if the Trained or Untrained User attempted to administer the device in question. Likewise, the comparative questionnaire will only be given if the user attempted to administer both devices during the respective simulations. This is to allow for the possibility that a user may wrongly administer insulin instead of a glucagon device, or not attempt to administer any device, rendering the questionnaire void.
- Section 6.4 (Screen Failures) now states that subjects may be rescreened once.
- Section 5.1.3.4 (Assessment of Successful Administration) now specifies that, in order to achieve a successful administration, users must shake or swirl the GEK vial to ensure the drug powder is dissolved.
- In Section 2 (Schedule of Activities) and Section 5.1.3.2 (Detailed Description of Study Procedures for Part B), the delay between Untrained Users watching the video and filling in the questionnaires has been changed to “55 to 60 minutes”, instead of “at least an hour”. This is to match Part A and ensure each participant’s experience is comparable.
- Section 2 (Schedule of Activities) now clarifies that the safety follow-up may also address significant errors made during simulations, such as insulin being administered instead of glucagon. This is to allow site staff to educate participants in the best way to respond to severe hypoglycemia events in the real world.
- Other minor editorial changes.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

2. Schedule of Activities

Study Schedule Protocol I8R-MC-IGBM: Part A (Trained Users)

Procedure	Study Visits			Comments
	Visit 1	Visit 2	Visit 3	
	Day 1	Days 8-9	Days 15-17	There must be a gap of at least 7 days between visits.

[…]

Safety Assessment/ Follow-up/Early Discontinuation	X	X	X	The safety assessment covers any accidents during training or simulations (see Section 9.4), or significant errors (e.g. insulin was administered during the simulation instead of glucagon). For follow-up of discontinued participants see Section 8.

Study Schedule Protocol I8R-MC-IGBM: Part B (Untrained Users)

Procedure	Visit 1	Visit 2	Comments
	Day 1	Days 8-9	

[…]

Questionnaires		X	After the simulation at Visit 2, each Untrained User will watch a video showing both simulations. Then, after a delay of 55 to 60 minutes, ~~at least an hour,~~ each Untrained User will answer the comparative and individual-device questionnaires (Section 9.10)

[…]

Safety Assessment/ Follow-up/Early Discontinuation	X	X	The safety assessment covers any accidents during simulations (see Section 9.4), or significant errors (e.g. insulin was administered during the simulation instead of glucagon). For follow-up of discontinued participants, see Section 8.

5.1.3.1. Part A (Trained Users)

At **Visit 2**, approximately 7 days after Visit 1, each Trained User will take part in a simulation of a severe hypoglycemia emergency with a manikin (see Section 5.1.3.3). The gender of the manikin will match the gender of the PWD. The PWD will not be in the room and will not observe the simulation~~from a separate room~~.

[…]

At **Visit 3**, approximately 7 days after Visit 2, each Trained User will take part in a second simulation, similar to the first. They will be asked to treat the manikin with Device 2, again observed by site staff only~~and the PWD~~.

[…]

Details of the questionnaires are in Section 9.10. Participants will be given a device-specific questionnaire only if the Trained User attempted to administer that device. For example, there will be no questionnaire for a simulation if insulin was wrongly administered instead of the glucagon device, or if no attempt was made to administer a device. Similarly, participants will be given the comparative questionnaire only if the Trained User attempted to administer both NG and GEK during the respective simulations.

5.1.3.2. Part B (Untrained Users)

At **Visit 2**, approximately 7 days after Visit 1, each Untrained User will be shown an example of Device 2. As at Visit 1, no instruction will be given on how to use the device. The Untrained User will take part in a simulation using Device 2, and then complete the NASA TLX. Site staff will assemble a video of both simulations, and the Untrained User will watch it. After a delay of 55 to 60 minutes ~~at least an hour~~, the Untrained User will fill in a questionnaire comparing both devices, and then individual-device questionnaires in randomized order (Table IGBM.2). Details of the questionnaires are in Section 9.10. The Untrained User will be given a device-specific questionnaire only if they attempted to administer that device. For example, there will be no questionnaire for a simulation if insulin was wrongly administered instead of the glucagon device, or if no attempt was made to administer a device. Similarly, Untrained Users will be given the comparative questionnaire only if they attempted to administer both NG and GEK devices during the respective simulations.

5.1.3.3. Example Simulation

The participant in the simulation (Trained User or Untrained User) will be taken into a room where a fully clothed adult manikin is present (e.g. lying face-up on the ground, on a bed, or in a chair).

5.1.3.4. Assessment of Successful Administration

1. Complete All Critical Steps

GEK	• Remove device from packaging • Inject the diluent from the syringe into the vial containing the drug powder • Ensure drug powder is dissolved (by shaking/swirling) • Draw the dissolved drug into the syringe • Inject the drug into the manikin at an appropriate site for intramuscular administration (e.g. thigh/buttock/upper arm)

5.4. Scientific Rationale for Study Design

A manikin will represent a person experiencing severe hypoglycemia; this allows for better control of the variables of each simulation, and avoids ethical issues related to the induction of severe hypoglycemia in people.

The PWD will not observe simulations in real time, so as to minimize the risk of their intervening or otherwise influencing the Trained User. This is intended to ensure simulations are like-for-like between participants and between devices, which will aid comparison.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) ~~will not~~ may be rescreened once, after consultation with the Sponsor.

7.2. Method of Treatment Assignment

Table IGBM.2. Example Randomization Schedule - Study IGBM

	Device for Simulation 1 ("Device 1"); and~~or~~ Device Specified in Questionnaire 1	Device for Simulation 2 ("Device 2"); and~~or~~ Device Specified in Questionnaire 2

9.10. ~~Example Qualitative~~Questionnaires

As detailed in Section 5.1.3, Trained Users and Untrained Users will complete NASA TLX questionnaires soon after each simulation, and all participants (Trained Users, Untrained Users and PWDs) will complete further questionnaires at the end of the study.

As detailed in Section 5.1.3.1 and 5.1.3.2, the individual (device-specific) and comparative questionnaires will be given only for devices that participants actually attempted to administer during the simulations. The NASA TLX will be administered for all participants, whether they attempted to administer a glucagon device or not.

Assuming the comparative questionnaire is given, it ~~For the end-of-study questionnaires, the questionnaire directly comparing both devices~~ will always be given before the device-specific questionnaires~~first~~. The order of the NG- and GEK-specific questionnaires will be randomized (Table IGBM.2).

9.10.3. Device-Specific Questionnaires (NG and GEK)

All participants (Trained Users, Untrained Users and PWDs) will be given a~~answer 2~~ device-specific questionnaire~~s~~ for each device (NG and/or GEK) that the participant attempted to

administer~~, regarding NG and GEK individually~~. The~~se~~ questionnaires will include questions related to ease of use and confidence in using each device, without comparing to the other device.