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Design validation and labeling comprehension study for a new epinephrine autoinjector

Eric S. Edwards, PhD^{*}; Evan T. Edwards, MS^{*}; Ronald Gunn, MS, MBA^{*}; Patricia Patterson, BA[†]; and Robert North, PhD[‡]

^{*} Intelliject Inc, Richmond, Virginia

[†] Agilis Consulting Group, LLC, Cave Creek, Arizona

[‡] Human Centered Strategies, LLC, Colorado Springs, Colorado

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ABSTRACT

Background: To facilitate the correct use of epinephrine autoinjectors (EAI) by patients and caregivers, a novel EAI (Auvi-Q) was designed to help minimize use-related hazards.

Objective: To support validation of Auvi-Q final design and assess whether the instructions for use in the patient information leaflet (PIL) are effective in training participants on proper use of Auvi-Q.

Methods: Healthy participants, 20 adult and 20 pediatric, were assessed for their ability to complete a simulated injection by following the Auvi-Q instructions for use. Participants relied only on the contents of the PIL and other labeling features (device labeling and its instructions for use, electronic voice instructions and visual prompts).

Results: The mean $\pm$ SD age of the adult and pediatric participants was 39.4 ± 11.6 and 10.9 ± 2.3 years, respectively. In total, 80% of adult and 35% of pediatric participants had prior experience with EAI. All adults and 95% of pediatric participants completed a simulated injection on the first attempt; 1 pediatric participant required parental training and a second attempt. Three adult and 4 pediatric participants exhibited a noncritical issue while successfully completing the simulated injection. Most participants agreed that the injection steps were easy to follow and the PIL facilitated understanding on using Auvi-Q safely and effectively.

Conclusion: The PIL and other labeling features were effective in communicating instructions for successful use of Auvi-Q. This study provided validation support for the final design and anticipated instructions for use of Auvi-Q.

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Introduction

Epinephrine autoinjectors (EAI) are the first-line treatment of anaphylaxis in the community.^{1–4} However, currently marketed EAI may not be intuitive to use and can be associated with improper administration,⁵ have low use rates (approximately 30%),⁶ and be associated with unintentional injections by caregivers.^{7,8} In addition, currently marketed EAI are not easily portable, and patients do not always have them available at the time of an allergic reaction.⁹

Another barrier to proper use of EAI includes lack of proper training. Untrained patients (42%) have been reported to be unable

to successfully complete a simulated injection using printed instructions on the device or in a patient information leaflet (PIL).¹⁰ During an actual anaphylactic reaction, the challenge of administering epinephrine correctly is likely to be even more substantial because of the stress of the emergency situation and the possibility of death within minutes of exposure to an allergen. Continued education and training on the use of an EAI are important to enable patients and caregivers to correctly use their autoinjector during a life-threatening allergic emergency.⁹

With the aim of minimizing shortcomings associated with currently available EAI, Intelliject Inc (Richmond, Virginia) developed a compact, single-use, novel EAI (Auvi-Q) that can be administered by the patient or caregiver and delivers an injection of either 0.3 mg (0.3 mL) or 0.15 mg (0.15 mL) of epinephrine (adrenaline) for use in allergic emergencies. The product was designed to be portable (the length and width of a credit card and thickness of a small cell phone) and was designed specifically for the allergic patient population to reduce barriers to timely self-administration of epinephrine in an emergency. In addition, Auvi-Q includes several unique features to mitigate potential use-related hazards

Reprints: Eric S. Edwards, PhD, Intelliject Inc, 111 Virginia St, Ste 405, Richmond, VA 23219; E-mail: eric.edwards@intelliject.com.

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known to occur with other EAls.^{7,11} These hazards include a retractable needle system to reduce the potential for unintentional injections after use and minimize the time the needle remains in the tissue for drug delivery, a safety tab mechanism located on the same end as the needle to prevent user confusion on which end is the needle end, and an electronic prompt system that provides visual prompts and voice instructions for use through a speaker to assist the user through the injection process.

Previous simulated usability studies comparing Auvi-Q to currently marketed EAls (EpiPen [Dey Pharma LP, Basking Ridge, New Jersey] and Twinject [Shionogi Inc, Florham Park, New Jersey]) demonstrated that Auvi-Q reduced the potential for sharps injury, improved the likelihood for correct use, and was preferred by both health care professionals and patients.^{12,13} This simulated use study was conducted as a part of an iterative, human factors engineering process aimed at reducing potential use-related risks and hazards before market introduction and to support validation of the final design of Auvi-Q and its proposed draft labeling, including the PIL.

Methods

Participants

In this single-site, open-label study, 20 healthy pediatric (aged 7–15 years) and 20 adult (aged 16–55 years) participants simulated Auvi-Q use, relying on only the contents of the PIL and other labeling features (such as the labeling found on the product itself, including its written instructions for use, electronic voice instructions, and visual prompts). A team of regulatory affairs professionals and human factors experts in patient labeling assisted in the development of the PIL. Participants were eligible for the study if they were 7 to 55 years of age, provided written informed consent to participate, had at least a second-grade reading level, were native English speakers, had normal or corrected-to-normal vision and hearing, and were able to manipulate a small device. This study was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments, and local regulations. This study evaluated the participants' behavior only in a deidentified manner, and informed consent was received from all participants; therefore, this study was not reviewed by an institutional review board.

Study Objectives

The primary objective was to validate that the patient labeling, specifically the instructions for use section in the PIL, is effective in training patients and caregivers on the proper use of Auvi-Q. Secondary objectives were to validate the changes in the design of Auvi-Q made as a result of a prior study (ie, redesign of the safety guard to make it easier to remove and minor changes to the electronic voice instruction system, including updates to the script for the electronic voice instructions)¹³ and to obtain feedback from patients and caregivers on the effectiveness of the PIL.

Study Design

When the participants arrived at the study site, the informed consent and nondisclosure forms were reviewed with the participant and signed. Participants were then asked for demographic information and received a briefing in which the specific procedures associated with product testing were reviewed. Participants were provided the PIL to review in its entirety and were then instructed to complete a simulated self-injection without any assistance, relying only on the instructions for use section of the PIL, written instructions for use on the EAI label, and electronic voice instructions and visual prompts (through the light-emitting diodes on the device) (eTable 1). If desired, pediatric participants had their parents instruct them on how to use Auvi-Q according to the PIL before the simulation.

The Auvi-Q used in the study had the labeling and functionality of the trade version, but the needle and drug (epinephrine) were removed (the Auvi-Qs used were not “trainer” devices but rather autoinjectors modified to not include epinephrine or a needle). The Auvi-Q outer case is rectangular in shape and is labeled on the front and back. Auvi-Q is removed from its outer case by sliding or pulling it upward out of the case. There are written instructions for use and visual diagrams on the Auvi-Q label to assist a user with completing an injection. Once the outer case is removed, the electronic prompt system provides voice instructions for use through a speaker on the front of the EAI and visual cues by light-emitting diodes located at the bottom of the device near the black base and red safety guard (eTable 1).

The test environment for this simulated use scenario included a typical allergist's office with fluorescent lighting and a single table for the participant to sit, review the PIL, and perform the simulated injection. The goal of this environment was to create a likely “first training” environment to determine whether participants, through the use of the PIL alone, could perform a successful injection without additional instruction and to uncover any areas on the wording or layout of the PIL that may need to be revisited or adjusted. Participants were not trained or introduced to Auvi-Q before the start of the simulation.

Participants were assessed on their ability to complete a simulated injection in accordance with Auvi-Q instructions for use and were scored by 2 independent evaluators as follows: completed without issues, completed with issues, or did not complete for any of the following 6 predefined steps: step 1, remove outer case; step 2, pull off red safety guard; step 3, press black end against the middle of outer thigh; step 4, push Auvi-Q firmly against outer thigh to activate; step 5, hold Auvi-Q in place for 5 seconds; and step 6, remove Auvi-Q from outer thigh. Because it was anticipated that some younger pediatric participants might require additional training, children who did not complete any of the 6 steps during their first attempt were given a second opportunity after being retrained by their parent. Success was defined as completing each step without making a use error that would have led to a patient not receiving the epinephrine dose during an actual allergic emergency. Participants were under the direct supervision of the investigational site staff during the study to ensure adherence to the protocol and safety guidelines. A digital video recorder and digital audio recorder taped all participants. To ensure consistency of the results, all participants' simulations were reviewed by 2 independent evaluators, and any scoring discrepancies were reviewed and resolved by consensus.

After the simulated testing, participants were probed as to how easy each task was to complete (via a questionnaire) and provided subjective preferences regarding the effectiveness of the electronic voice instruction feature. Participants were also asked via a questionnaire if they thought the PIL was effective in training them to use Auvi-Q correctly.

Statistical Analysis

Descriptive statistics were calculated to summarize continuous measures, and frequency count and percentages were used for summarizing categorical measures regarding participant demographics and baseline characteristics. The sample size used for this study was consistent with human factors industry standards (minimum of 15 participants for each distinct user population) because it was designed to validate specific changes made to the user interface from the previously conducted summative design validation study.¹²

In addition, a posttest analysis was conducted on the steps for successful injection and the understandability of the PIL, product labeling, and electronic voice instructions. The proportion of adult

and pediatric participants who (1) successfully completed the steps with no issues and met the criteria, (2) completed the steps with issues, and (3) did not complete each of the 6 instruction steps for all allowable attempts were reported as counts and percentages. Furthermore, responses regarding the ease of following the instructions for use, effectiveness, and audibility of the voice instructions in helping the participant use Auvi-Q and the effectiveness of the PIL for training the participant on how to use Auvi-Q were described with frequency counts and percentages by age group.

Results

Participants

The demographics and baseline characteristics of the 40 participants are listed in Table 1. The mean $\pm$ SD age was 39.4 ± 11.6 years for the adult participants and 10.9 ± 2.3 years for the pediatric participants. Most adult participants (80%) had previous personal experience with EAI, compared with 35% of pediatric participants. Previous personal experience with EAI was defined as whether participants ever used or had any previous experience with an EAI system.

Completion of Simulated Injection

All participants successfully completed a simulated injection. All of the adult participants and 95% of the pediatric participants completed the simulated injection on the first attempt (Table 2). One 8-year-old pediatric participant did not complete a step correctly at the first attempt but did so correctly at the second attempt after parental training (as per protocol).

Three adults (15%) and 4 pediatric participants (20%) experienced a noncritical issue while successfully completing the simulated injection. The 3 adults experienced noncritical issues during completion of step 4 (ie, they did not press Auvi-Q firmly enough against their outer thigh to activate the injection); however, they were able to complete the task successfully after the electronic voice instruction was repeated. The 4 pediatric participants experienced noncritical issues during completion of steps 1, 2, 4, and 5. During step 1, 1 child took longer than 5 seconds to remove the red safety guard. During step 2, 1 child took approximately 10 seconds to remove the outer case and had to refer to the PIL to correctly complete the step. During step 4, 1 child did not press Auvi-Q firmly enough against the thigh but was able to complete the step correctly after the electronic voice instruction was repeated. During

Table 1
Participant demographics and baseline characteristics

Variable	Age group, No. (%) ^a	
	Pediatric (n = 20)	Adult (n = 20)
Age, mean $\pm$ SD, y	10.9 $\pm$ 2.3	39.4 $\pm$ 11.6
Female sex	12 (60)	16 (80)
Right-handed	20 (100)	17 (85)
Highest level of education completed		
Elementary (1st–5th grades)	15 (75)	
Middle school (6th–8th grades)	3 (15)	2 (10)
Some high school (9th–11th grades)	2 (10)	5 (25)
Completed high school (12th grade)		7 (35)
Associate or bachelor's degree		6 (30)
Master's or doctoral degree		
Required reading glasses	5 (25)	13 (65)
Required hearing aid	0	0
Colorblind	2 (10)	0
Previous experience (personal) ^b	7 (35)	16 (80)
Previous experience (observing others) ^c	0	1 (5)

Abbreviation: SD, standard deviation.

^aData are presented as number (percentage) of patients unless otherwise indicated.

^bEver used or had any previous experience with an epinephrine autoinjector system.

^cEver seen anyone use an epinephrine autoinjector system.

step 5, 1 child did not use sufficient force to activate Auvi-Q at first; however, realizing this, the child then tried again and was successful.

Participant Evaluations

Most participants agreed that the injection steps were easy to complete (Fig 1), the PIL facilitated understanding of how to use Auvi-Q (Table 3), the PIL provided all the information required to use Auvi-Q safely and effectively (Table 3), and the audible voice instructions were effective in helping participants use Auvi-Q (Table 4). Most adults (95%) reported that the electronic voice instructions were “very effective” or “effective” in helping them use Auvi-Q. All pediatric participants (100%) reported that the voice instructions “helped” them use Auvi-Q.

Safety

No adverse events were reported.

Discussion

Without receiving any training from a health care practitioner, all participants were able to complete a simulated injection with Auvi-Q without committing a critical use error; however, 1 pediatric participant required parental training to do so successfully. It was expected that some pediatric participants would require parental training; therefore, the protocol allowed the parent to demonstrate correct injection technique after an unsuccessful first attempt. In this study, the PIL and product label were effective in helping participants understand how to use Auvi-Q correctly.

The most common noncritical issue experienced by the participants was not pressing Auvi-Q firmly enough against the outer thigh (step 4). Overall, 3 adults and 1 child had difficulty with this step. In each case, however, the participants responded to the electronic voice instruction and correctly completed the step, highlighting the benefits of this system. In addition, participants

Table 2
Percentage of participants correctly completing each of the steps leading to a successful simulated injection

Step	Age group, No. (%)	
	Pediatric (n = 20)	Adult (n = 20)
1. Remove outer case		
Completed on first attempt	20 (100)	20 (100)
Completed on second attempt	0	0
Did not complete	0	0
2. Pull off red safety guard		
Completed on first attempt	20 (100)	20 (100)
Completed on second attempt	0	0
Did not complete	0	0
3. Press black end against the middle of outer thigh		
Completed on first attempt	20 (100)	20 (100)
Completed on second attempt	0	0
Did not complete	0	0
4. Push Auvi-Q firmly against outer thigh to activate		
Completed on first attempt	19 (95)	20 (100)
Completed on second attempt	1 (5) ^a	0
Did not complete	0	0
5. Hold Auvi-Q in place for 5 seconds		
Completed on first attempt	20 (100)	20 (100)
Completed on second attempt	0	0
Did not complete	0	0
6. Remove Auvi-Q from outer thigh		
Completed on first attempt	20 (100)	20 (100)
Completed on second attempt	0	0
Did not complete	0	0

^aAfter the child's father demonstrated proper injection technique (as per protocol for pediatric participants after an unsuccessful first attempt), the child was able to complete all steps correctly on the second attempt without issues.

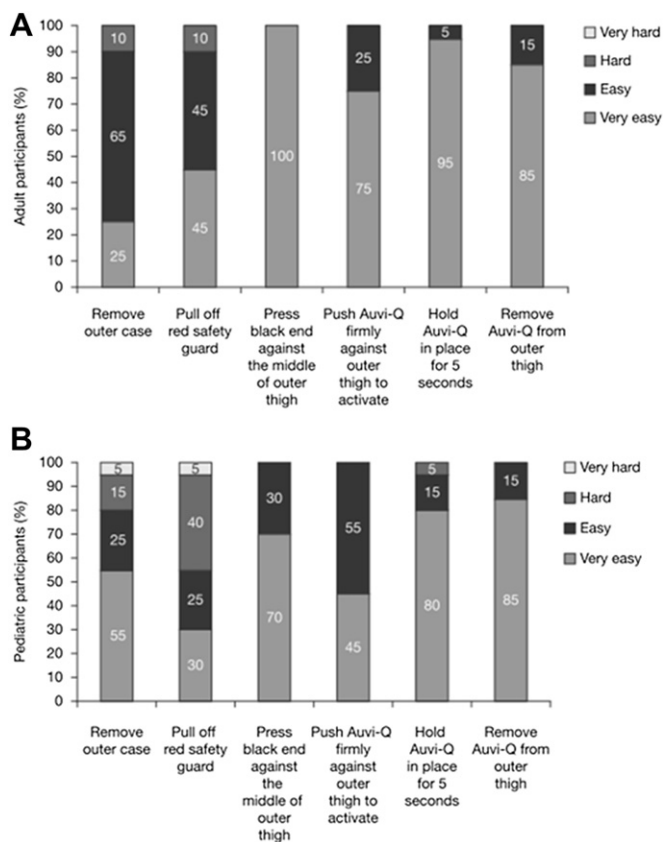


Figure 1. Ease of following each of the instructions for use steps for adult (A) and pediatric (B) participants.

may have been more likely to complete this step without issues during a real-life situation using Auvi-Q because the needle would provide tactile feedback of an injection occurring when being introduced beneath the skin. In this simulated study, the tactile feedback could not be sensed because the study devices had the needle and epinephrine removed with no injection administered.

Table 3
Effectiveness of the PIL in training the participants to use Auvi-Q correctly

Statement	No. (%) of participants
Adult Participants	
"The PIL was effective in training me to use Auvi-Q"	
Strongly disagree	0
Disagree	0
Agree	4 (20)
Strongly agree	16 (80)
"The PIL provides all the information I need to use Auvi-Q safely and effectively"	
Strongly disagree	0
Disagree	1 (5)
Agree	6 (30)
Strongly agree	13 (65)
Pediatric Participants	
"Having my parent read the instruction sheet made it easy for me to understand how to use Auvi-Q"	
No	1 (5)
Yes	19 (95)
"The instruction sheet gives my parent all the information they need to teach me to use Auvi-Q"	
No	0
Yes	20 (100)

Abbreviation: PIL, patient information leaflet.

Table 4
Effectiveness of voice instructions in helping participants use Auvi-Q

Question	No. (%) of participants
Adult Participants	
"How effective were the audible voice instructions in helping you use Auvi-Q?"	
Very ineffective	0
Ineffective	1 (5)
Effective	3 (15)
Very effective	16 (80)
Pediatric Participants	
"How effective were the audible voice instructions in helping you use Auvi-Q?"	
Did not help at all	0
Helped a little bit	3 (15)
Helped a lot	17 (85)

The child who had difficulty with step 4, not applying sufficient force to cause Auvi-Q to activate, was successful on the second attempt after being trained again. Two children took longer than anticipated (>5 seconds) to remove the red safety guard (step 1) and the outer case (step 2), indicating that these safety features can be challenging for some children to remove. Although these noncritical issues would have caused a slight delay in injection, the residual risk associated with these issues was determined to be low. Each participant was able to complete the task, which would have resulted in a successful dose of epinephrine being administered within seconds of commencing the injection steps.

The Auvi-Q evaluated in this study was designed to address some of the limitations of currently marketed EAI. It is portable and incorporates unique features to reduce the potential risk of unintentional needlestick injuries and facilitate correct use. These features are important because there are numerous reports of unintentional needlestick injuries with currently marketed EAI,^{7,8} and even health care professionals can have difficulty using them correctly.¹⁴ In studies that compared Auvi-Q with marketed EAI (at the time the studies were performed), Auvi-Q reduced potential sharps injury, improved correct use (46% with Auvi-Q vs 12% with EpiPen and 0% with Twinject), and was preferred over the marketed EAI by health care professionals (100%) and patients (73%).^{12,13}

As a part of the human factors engineering process, some autoinjector design-related changes were made to address issues with the red safety guard and the electronic prompt system, which were identified in the summative design validation study.¹² This study validated these changes, which included redesign of the red safety guard to increase tactile features, clarification on the red safety guard use instruction on the autoinjector and PIL labeling, redesign of the script for the electronic voice instructions to ensure the safety guard removal instruction is repeated at appropriate timing, update of the electronic voice instruction system to eliminate the potential for malfunction during use, and revised labeling to more clearly emphasize correct injection location. In this study, all participants successfully completed a simulated injection, and most participants agreed that the PIL was effective in helping them use Auvi-Q, made it easy for them to understand how to use Auvi-Q, and provided them with all the information they needed to use Auvi-Q safely and effectively. These data demonstrate that the design changes were effective in resolving issues with the red safety guard and electronic system.

There are some potential limitations related to the design of the study. Although the data presented demonstrate that the PIL, Auvi-Q labeling, and device features are effective in helping users complete a successful injection in a simulated stressful environment, generalizability of these results to a real-life anaphylactic event should be carefully evaluated. We acknowledge that the

environment in our simulated study reflects only one potential environment in which a patient may experience anaphylaxis, a physician office setting. This setting may not be the environment that individuals face during a real-life anaphylactic event because many cases of anaphylaxis occur in an out-of-hospital setting; however, we believe this scenario was sufficient for answering the primary research question, which ultimately was to validate that the patient labeling was effective in training patients and caregivers on proper use of Auvi-Q. In addition, to avoid introducing potential additional confounding variables, the use of Auvi-Q in a more heterogeneous population (such as low-literacy groups and disabled populations) was not evaluated in this study.

In conclusion, the PIL, written instructions on the autoinjector labeling, electronic voice instructions, and visual prompts are all effective in communicating the instructions for successful use of Auvi-Q. This study provides validation support for the final design and anticipated instructions for use of Auvi-Q.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2012.12.008>

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eTable 1

Electronic voice instructions and visual prompts of Auvi-Q

Timing	Electronic voice instructions and visual prompts ^a	Additional information
When outer case is removed	BEEP, BEEP, BEEP 1) "If you are ready to use, pull off red safety guard." <i>LED Blinks Green</i> 2) "If not ready to use, replace the outer case."	Auvi-Q beeps 3 times followed by voice instruction number 1 followed by a green blinking LED. Voice instruction number 1 is repeated once if the safety guard is not removed and then, if still not removed after having been played a second time, voice instruction number 2 is played. Voice instruction number 2 is played twice if the safety guard is not removed.
When safety guard is removed	3) "To inject, press black end firmly against outer thigh and hold in place for 5 seconds." <i>LED Blinks Green</i>	Voice instruction number 3 is played and the LED blinks green. Voice instruction number 3 is repeated 3 times if the base is not depressed sufficiently to initiate an injection.
When base is pushed	4) "Five...four...three...two ...one." BEEP, BEEP, BEEP 5) "Injection complete. Call 911." <i>LED Turns Red</i> 6) "This device has been used and should be taken to your physician for proper disposal and a prescription refill."	Following voice instruction number 4, audible beeps occur. Once Auvi-Q has been used, voice instruction number 6 is repeated every time Auvi-Q is pulled out of its outer case.

^aNote: electronic voice instructions are numbered and in quotes, non-voice instructions are in all capital letters, and LED prompts are in italic font.