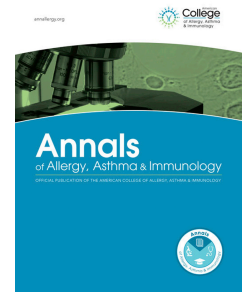


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Usability and Preference of Epinephrine Auto-Injectors: Auvi-Q and EpiPen Jr

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Conflict of Interest: CK and EE are employees of kaleo, Inc, which manufactures the Auvi-Q device; ED, SS, and TV are employees of Core Human Factors, Inc, which was contracted by kaleo to design and conduct the study; and EG is an employee of DP Clinical, Inc., which conducted the data analyses.

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Keywords

adrenaline, anaphylaxis, allergic emergency, allergy, simulated use, human factors, digital injection, successful use, correct use

Abbreviations

EAI = epinephrine auto-injector

SD = standard deviation

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INTRODUCTION

The onset of anaphylaxis—a serious and potentially life-threatening systemic allergic reaction—is typically rapid and can be induced by allergens such as food, medication, and venom or insect stings.^{1, 2} Current guidelines recommend epinephrine as first-line treatment of anaphylaxis,³⁻⁸ and in individuals who have experienced anaphylaxis or those at future risk, epinephrine should be carried at all times for prompt emergency use, preferably in the form of an epinephrine auto-injector (EAI).^{4, 5, 7-9} However, many patients do not use their EAI, even when readily available.¹⁰⁻¹³ Further, studies have shown patients and caregivers are sometimes unable to correctly use their EAI,¹⁴ and lacerations or accidental digit/palm injections have been reported.¹⁵⁻¹⁷

Despite the importance of prompt treatment of anaphylaxis, lack of patient knowledge regarding EAI administration and inadequate training may be potential reasons for failure to use EAIs.^{10, 18} EAI design may also be an important determinant of successful epinephrine administration.¹⁹ As such, simulated-use studies with EAIs have been conducted in non-medical professionals to determine usability and preference; however, participants in many of these studies are often educated on proper device use immediately prior to the study (e.g., given patient-information leaflets/instructions or training) and therefore may not be representative of individuals who receive training months or years prior to using the EAI or an untrained individual that may, in a worst-case scenario, have to administer epinephrine during a life-threatening allergic emergency.¹⁹⁻²⁷

The aim of this human factors study in untrained adults was to compare usability and participant preference of 0.15 mg Auvi-Q[®] (kaleo, Inc, Richmond, VA) and EpiPen Jr[®] (Mylan Specialty LP, Basking Ridge, NJ) in a simulated life-threatening allergic emergency-use scenario.

METHODS

Study overview

In this open-label, randomized, crossover, non-interventional human factors usability study, inexperienced adult caregivers were tasked to simulate injecting a child-sized manikin with epinephrine during a simulated life-threatening allergic emergency using Auvi-Q and EpiPen Jr EAIs. Both Auvi-Q and EpiPen Jr are single-use devices that require multiple steps to deliver 0.15 mg epinephrine via subcutaneous or intramuscular injection to children weighing 33 to 66 pounds (15 to 30 kg). Auvi-Q, approximately 3.5 inches long by 2 inches wide, has instructions printed on the device and audible voice instructions, with an administration hold time of 2 seconds. Auvi-Q has an outer case, a pull-off red safety guard on the needle end, and an automatic retractable needle system. EpiPen Jr, an elliptical cylinder approximately 6 inches long, has printed instructions on the side of the device and an administration hold time of 3 seconds. EpiPen Jr has a one-step flip-top carry case, blue safety release cap, and automatic needle cover.

This study utilized trainer devices that include the same use-steps as marketed EAIs but do not contain needles or epinephrine. The trainers were re-labeled with 0.15 mg EAI labels to match the external appearance of the marketed devices (**Figure 1**); the Auvi-Q trainer also had the voice script from the marketed 0.15 mg device.

The study was conducted between June 18, 2018 and July 10, 2018 by Core Human Factors, Inc. (Core HF) at its usability laboratory in Bala Cynwyd, PA and was approved by the Allendale Institutional Review Board (Old Lyme, CT). Participants were recruited by Core HF's internal recruiting team via email, telephone, social media, flyers, and referrals. Prior to study initiation, all participants completed an informed consent form and confidentiality statement. All

participants were compensated for their participation in the testing session. Statistical analyses were conducted by DP Clinical, Inc. (Rockville, MD).

Participant selection and eligibility

Adult participants were selected to represent untrained bystanders during a real-world life-threatening allergic emergency (e.g., laypersons without previous EAI experience, severe allergies, or anaphylactic reactions). Participants were healthy English-speaking adults (18-65 years) with normal to corrected-to-normal vision and hearing who could manipulate a handheld object without significant difficulty. Individuals were excluded if they had: experience with or training to use an injection device; experience with severe or life-threatening allergies (themselves or close family members); participated in research evaluating products for the treatment of severe allergies or injection devices; worked in a profession that may introduce bias (e.g., human factors engineers, market researchers, medical device developers, healthcare professionals); or an affiliation with a pharmaceutical or medical device company.

Testing sessions

The study room was designed to represent a home setting (i.e., living room), with an injectable child-sized manikin lying supine on the sofa opposite the participant. To further mimic a typical-use environment, a movie played on a television as an element of distraction during simulated-use tasks. Testing sessions were approximately 60 minutes.

After a brief orientation and introduction, participants were presented an emergency-use scenario: *“Your friend’s child was prescribed an epinephrine auto-injector called [Auvi-Q or EpiPen Jr] a few months ago after he was diagnosed with a severe allergy to peanuts. [Auvi-Q or EpiPen Jr] is a device that allows you to deliver epinephrine to someone if they are having a life-threatening allergic emergency... Your friend told you about his son’s epinephrine auto-*

injector in case you were ever with him when he had a life-threatening allergic emergency and you needed to help him. Imagine that you have just entered a room and see that your friend's son is having a life-threatening allergic reaction. He is having trouble breathing and has lost consciousness. You need to deliver epinephrine using the [Auvi-Q or EpiPen Jr] device found in this bag to prevent the reaction from becoming fatal."

Participants had to independently determine how to use the EAI. Only written instructions on the device label and/or device voice instructions were available to participants as participants were not given any EAI training and did not have access to any product leaflets (i.e., prescribing information, patient information, instructions for use). Participants were then presented the same allergic emergency-use scenario a second time and asked to use the alternate EAI to treat the patient. The order in which participants interacted with the study devices was randomized to minimize bias and the effects of order on participants' preferences. The session concluded with an interview and questionnaire to capture participants' ratings of device characteristics for each EAI and overall impressions.

Study endpoints and data collection

The primary endpoint was the percentage of participants that correctly used Auvi-Q versus EpiPen Jr. Correct use was defined as completing all injection tasks (with or without issues) according to instructions on the devices (e.g., printed labels and/or voice instructions). For Auvi-Q, injection tasks were: a) Pull device up from outer case, b) Pull red safety guard down and off, c) Place black end against outer thigh, and d) Push firmly and hold for 2 seconds. For EpiPen Jr, injection tasks were: a) Remove the auto-injector from the carrier tube, b) Remove blue safety release by pulling straight up without bending or twisting it, c) Swing and push

92 firmly the orange tip against outer thigh so the auto-injector “clicks”, and d) Hold firmly in place
93 for 3 seconds.

94 Both devices also included a fifth use task to “seek medical attention” (Auvi-Q) or “get
95 emergency medical help” (EpiPen Jr). Successful completion was defined as a participant
96 indicating they would call 911 or emergency services during/immediately after the use scenario,
97 or when prompted “What would you do next?” after conclusion of the injection tasks.

98 Secondary endpoints included: correctly completing key injection tasks, tabulation of task-use
99 errors, time to complete the injection process, and subjective ratings/preferences for each device.

100 Key injection tasks were defined as the minimum tasks required for a patient to receive an
101 epinephrine dose. To complete key injection tasks, it was permissible for a participant to inject
102 any muscle (e.g., abdomen, arm, thigh, buttock) with a hold time of ≥ 0.5 seconds; participants
103 were also not required to “swing” for EpiPen Jr (i.e., could activate the device by applying
104 pressure). A use error was defined as any user action or lack of action that led a participant to not
105 perform a task or perform a task incorrectly/unsuccessfully. Participants’ overall EAI preference
106 was assessed and participants rated 8 device characteristics for each EAI using a scale of 1 (very
107 poor) to 5 (very good): size, shape, portability (ease of carrying), ease of administration, clarity
108 of device instructions (verbal and/or written), perceived ruggedness/durability, confidence in
109 using during an emergency, and perceived safety. To limit bias, the order in which the device
110 characteristics were presented was counterbalanced for each participant.

111 To evaluate these endpoints, the number/type of use errors, task completion times, and
112 participants’ performance for each task were collected during test sessions. Participant feedback
113 was collected during the interview and questionnaire portion of the testing session.

Statistical analyses and Sample Size

Continuous data were summarized by number of observations, mean, standard deviation (SD), median, and interquartile range. Categorical data were tabulated using counts and percentages. Ordinal data for device characteristic ratings were summarized by number of observations, median, interquartile range, minimum, and maximum.

Correct completion of all injection tasks per instructions on the device (primary endpoint) and key injection tasks (secondary endpoint) were evaluated using a McNemar test for paired dichotomous data. The Exact McNemar test was used for cases where the discordant (i.e., number of participants completing the respective task on only 1 device) was <20; this included the seek emergency help task and digital/hand injection error. Time to completion was evaluated using Wilcoxon Signed-Rank t-test in participants that correctly completed both Auvi-Q and EpiPen Jr injection tasks. Overall EAI preference was evaluated using 2-sided sign test, where ties were excluded. A probability value of <.05 was considered the acceptable threshold for statistical significance. Statistical analysis excluded any missing participant data.

Using the McNemar test sample size calculation at .05 significance level and 90% power, 94 participants was chosen as the target population to detect 20% difference in subjects using both devices correctly, assuming 35% of subjects used one and only one device correctly (proportion discordant).

RESULTS

Participant disposition and characteristics

A total of 112 adults were screened; 97 completed the study session and 96 were included in study analyses (**Table 1**). Participants were an average age of 43.1 years and approximately half were female.

Task performance: completion of all injection tasks per instructions on device

A significantly higher percentage of participants were able to follow device injection instructions and complete all injection tasks with Auvi-Q (85.4%) versus EpiPen Jr (19.8%; $P<.001$; **Figure 2**).

With Auvi-Q, the most common use-errors were “did not place black end against outer thigh” (6.3% of participants) and “did not push firmly and hold for 2 seconds” (10.4%; **Figure 2**). The most common use-errors with EpiPen Jr were “did not hold firmly in place for 3 seconds” (36.5%) and “did not swing and push the orange tip firmly against outer thigh until the auto-injector clicks” (70.8%). When further evaluating this task, approximately two-thirds of individuals did not swing EpiPen Jr and one-fifth did not have the orange tip against the outer thigh (**Figure 2**).

Task performance: completion of key injection tasks

The completion rate was higher for both devices when analyzing key injection tasks; however, differences between the EAIIs remained significant, with a higher percentage of participants completing key injection tasks with Auvi-Q (94.8%) versus EpiPen Jr (72.9%; $P<.001$; **Figure 3**). The percentage of participants completing a successful injection increased 9.4% among Auvi-Q users and 53.1% among EpiPen Jr users when the analysis was limited to key injection tasks rather than all injection tasks (Auvi-Q users: all injection tasks=85.4%, key

injection tasks=94.8%; EpiPen Jr users: all injection tasks=19.8%, key injection tasks=72.9%]; comparison of **Figures 2 and 3**). For both Auvi-Q and EpiPen Jr, the shorter hold time defined as a key task contributed to the higher completion rate; for EpiPen Jr, eliminating the requirement to “swing” the device was the largest contributor to the higher completion rate. The most common key injection task error was “did not push firmly and hold for at least 0.5 seconds” for Auvi-Q (3.1%) and “did not push the orange tip firmly against muscle until the auto-injector clicks” for EpiPen Jr (22.9%; **Figure 3**).

Task performance: seeking emergency help and accidental injections

For both devices, a high percentage of participants reported they would seek emergency help after delivering or attempting to deliver a dose of epinephrine to the child-sized manikin (Auvi-Q, 85.4%; EpiPen Jr, 87.5%; $P=.75$).

There were no digital- or hand-injection errors with Auvi-Q, while 14 participants (14.6%) would have accidentally received an injection with EpiPen Jr ($P<.001$). Of these participants, 4 (4.2%) would have injected their finger/thumb (by manipulating the orange tip [needle end] when exploring EpiPen Jr, before attempting manikin injection) and 10 (10.4%) would have injected their digit/palm (while attempting to deliver epinephrine by incorrectly placing the white end of EpiPen Jr against the manikin and pushing on the orange tip). Some reasons participants gave for these errors were: thought needle would be under the blue safety release because the white end had a hole; orange tip looked similar to a plunger; bright orange color indicated it was the end that required interaction; thought to hold thumb on the orange tip because of the pen-like shape.

Task time

On average, participants took less than 1 minute to complete the simulated injection with either device, though average completion time was faster with Auvi-Q versus EpiPen Jr (**Figure 4**). In participants that successfully completed key injection tasks for both Auvi-Q and EpiPen Jr, the difference in time to complete key injection tasks was significant ($P<.001$). In participants that successfully completed all injection tasks per device instructions, time to complete was not significantly different between the EAIs ($P=.055$; **Figure 4**).

Overall device preference and rating of device characteristics

Auvi-Q was significantly preferred overall, with 91.7% of participants preferring Auvi-Q versus 6.3% preferring EpiPen Jr ($P<.001$; **Figure 5**). Median scores for each of the 8 EAI characteristics evaluated were also higher for Auvi-Q versus EpiPen Jr (**Figure 6**).

DISCUSSION

In this randomized, human factors usability study, inexperienced adults were tasked with using Auvi-Q and EpiPen Jr trainer EAs to simulate epinephrine administration to a child-sized manikin representing a child experiencing a life-threatening allergic emergency; the trainers used in the study had labeling (both devices) and audio instructions (Auvi-Q) that matched the marketed devices. Overall, a significantly higher percentage of participants were able to correctly complete injection tasks with Auvi-Q versus EpiPen Jr ($P<.001$). This included correct completion of *all* injection tasks per the instructions on the device (Auvi-Q, 84.5%; EpiPen Jr, 19.8%) and *key* injection tasks required to inject epinephrine (Auvi-Q, 94.8%; EpiPen Jr, 72.9%). Results from this usability study are consistent with data from a preference study where significantly more participants (including experienced and inexperienced adults, caregivers, and children) correctly completed injection steps with Auvi-Q versus EpiPen in a simulated-use test (all steps: 75% vs 35%, respectively; all steps excluding time step [5 seconds for Auvi-Q and 10 seconds for EpiPen]: 81% vs 61%).²⁰

Rates for correctly completing injection steps with EpiPen Jr in this study were lower than other simulated-use studies of EpiPen in untrained participants; differences may be due in part to the prompts participants received in the other studies. For example, in one study 89% and 94% of participants correctly demonstrated all and “critical” EpiPen steps, respectively, after being given “2 minutes to familiarize themselves with the trainer device”²⁵; participants in the current study were not provided with the device prior to starting the simulated allergic emergency-use scenario. A second study of naïve adolescents reported 88% correct completion rate with EpiPen, though “subjects were advised that the epinephrine devices had instructions on the outside and how and where to use them correctly.”²³ Finally, a study of caregivers of food-allergic children

reported a 28.6% correct completion rate with EpiPen after reading instructions,²⁴ which more closely aligns to the 19.8% rate for completing all injection tasks according to the instructions on the device for EpiPen Jr in this study.

Accidental injections in this study were observed in 14.6% of EpiPen Jr participants versus none with Auvi-Q ($P<.001$). This included 4.2% digital injections while exploring EpiPen Jr and 10.4% digital/palm injections while incorrectly pushing the orange tip (needle end) during manikin injection. These data align with previous simulated-use studies in which 5.4%²⁴ and 8.8%²³ of untrained individuals pressed on the wrong end of EpiPen when simulating injection. In studies including trained individuals, accidental-injection rates of 5.4% (at 6 weeks after training),¹⁹ 3.6% (at 3 months),²⁴ and 13.6% (at 12 months)¹⁹ have been reported. The potential for needle injuries are not limited to simulated studies, as reports of unintentional injections, injuries, and lacerations have been reported in real-world scenarios.^{15-17, 28, 29} Direct effects of accidental EAI injections to a non-patient (i.e., the caregiver) are often not serious.^{16, 29-31} However, in the case of accidental injection, the potential loss of an epinephrine dose required to treat an anaphylactic emergency could prove fatal to the patient due to delayed or inadequate treatment.^{16, 29}

Average injection completion time was faster with Auvi-Q versus EpiPen Jr in this study; however, this difference may not be clinically meaningful, as participants took, on average, less than 1 minute to complete simulated injections with either device. Additionally, both Auvi-Q and EpiPen Jr users reported that they would seek emergency help.

In addition to EAI usability, participant preference was also assessed in this study. Auvi-Q was significantly preferred overall, with 91.7% of participants preferring Auvi-Q versus 6.3% preferring EpiPen ($P<.001$; 2.1% no preference). This preference may be due, in part, to the

design of Auvi-Q; when asked to rate 8 EAI characteristics for each of the devices, median scores were higher for Auvi-Q versus EpiPen Jr for each characteristic—size, shape, portability, ease of administration, clarity of device instructions (verbal and/or written), perceived ruggedness/durability, confidence in using during an emergency, and perceived safety. These results are consistent with a previous preference study in which Auvi-Q was significantly preferred over EpiPen for all study endpoints, including instruction method, preference and ease of carrying, device size and shape, ease of use and in following instructions, and overall preference to use ($P<.05$ for all).²⁰ Additional human factors engineering studies for Auvi-Q have demonstrated device labeling features and voice prompts were effective in communicating proper use, though training and/or patient information leaflets/instructions for use were also provided.^{21, 22}

Labeling information for US Food and Drug Administration-approved devices note that individuals should be trained on and familiar with EAI use.^{32, 33} Yet, proper EAI administration technique is often lacking in patients, caregivers, and healthcare practitioners.¹⁶ While this study represented a “worst-case scenario” (i.e., unexperienced, untrained individual tasked with administering epinephrine in an emergency situation), the preference for and higher rates of correct use with Auvi-Q versus EpiPen Jr suggest that there may be EAI features that are beneficial to both trained and untrained individuals administering epinephrine during an allergic emergency. This idea is supported by a randomized device-switch study in which participants using Auvi-Q had the highest rate of successful epinephrine administration (93%) versus other EAI devices (49% [Anapen[®]/EpiPen, new EpiPen, and JEXT[®]]; $P<.001$), regardless of the device on which they had been previously trained the year before (Anapen or EpiPen).¹⁹ Further, this 93% Auvi-Q success rate (1 year after training on a different EAI) was higher than

participants' 57% success rate in the preceding anaphylaxis scenario with the device they had been directly trained to use ($P=.006$). The authors concluded that in addition to training, EAI device design is critical for effective epinephrine delivery during emergency anaphylaxis.¹⁹

It is important to note that there are factors outside of device design and usability that may impact prescribing behaviors and patient access to EAI devices. Differences in insurance coverage, coupons, manufacturer discounts, access programs, and out-of-pocket costs may impact an individual's access to specific EAI devices.

Limitations of this study are inherent to simulated use studies. Participants simulated injections on a child-sized manikin using EAI trainer devices that contained no drug or needles (but included labeling and audio instructions to match marketed devices) to minimize the risks to participants. Additionally, the orange tip of the EpiPen Jr trainer had grooves not present on the real EAI, and the "drug-viewing windows" on both study devices were not windows through which epinephrine was visible, but were filled with plastic casing of the trainer; however, no participant who experienced use errors or difficulties attributed their use-related issue to lack of a functional viewing window. Finally, participants did not administer epinephrine using Auvi-Q and EpiPen Jr during an actual life-threatening allergic emergency. As such, many participants were not under the same amount of stress and pressure to complete tasks correctly that they might experience during an actual emergency.

Conclusions

Results from this study demonstrate untrained adults preferred and were more likely to use Auvi-Q correctly versus EpiPen Jr, highlighting the importance of device design on successful epinephrine administration during a life-threatening allergic emergency.

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Figure 1. Epinephrine Auto-Injector Devices

Auvi-Q (left) and EpiPen Jr (right) trainer devices used in this study. The trainer devices, which do not contain needles or epinephrine, were re-labeled with the 0.15 mg EAI labels to match marketed devices. The Auvi-Q device also had the voice script from the marketed 0.15 mg device. Abbreviation: EAI, epinephrine auto-injector.

Figure 2. All Injection Tasks Per Instructions on Device: Completion and Use Errors (N=96)

Use errors shown for participants unable to complete a task. The percentage of overall completion and use errors do not add up to 100% as some participants encountered more than 1 use error.

Figure 3. Key Injection Tasks: Completion and Use Errors (N=96)

Use errors shown for participants unable to complete a task. The percentage of overall completion and use errors do not add up to 100% as some participants encountered more than 1 use error.

^aKey injection tasks defined as minimum tasks required for a patient to receive an epinephrine dose (e.g., permissible for injection in any muscle with a hold time of at least 0.5 seconds; no requirement to “swing” for EpiPen Jr).

Figure 4. Time to Completion of All and Key Injection Tasks

Horizontal lines indicate median values; boxes indicate interquartile range; dots indicate mean values.

^aKey injection tasks defined as minimum tasks required for a patient to receive an epinephrine dose.

^bParticipants that correctly completed tasks for either Auvi-Q or EpiPen Jr (no statistical comparisons).

^cParticipants that correctly completed tasks for both Auvi-Q and EpiPen Jr; statistical comparisons (i.e., intraindividual analysis) are shown.

Figure 5. Overall EAI Preference (N=96)

Percentages do not total 100% due to rounding.

Abbreviation: EAI, epinephrine auto-injector.

Figure 6. Participant Rating of EAI Characteristics (N=96)

Participants used a 5-point scale to rate characteristics for each device (1=very poor; 5=very good).

Horizontal lines indicate median values; boxes indicate interquartile range; whiskers indicate minimum/maximum. Statistical comparisons were not conducted for this assessment.

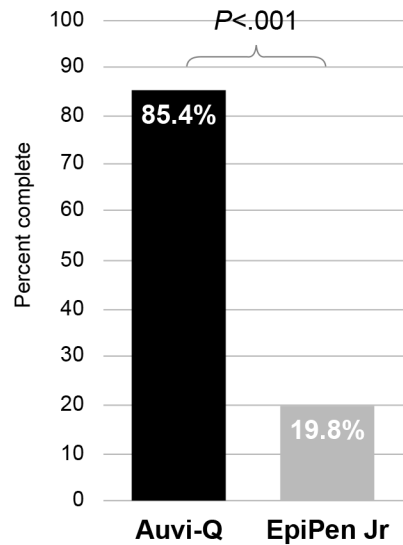
Abbreviation: EAI, epinephrine auto-injector.

Table 1. Participant Disposition and Characteristics

DISPOSITION	Participants, n
Screened	112
Included in study analyses ^a	96
CHARACTERISTICS	N=96
Age, y	
Mean (SD)	43.1 (13.6)
Range	19-65
Age group, n (%)	
18 to 34 y	34 (35.4)
35 to 49 y	25 (26.0)
50 to 65 y	37 (38.5)
Female sex, n (%)	54 (56)
Education level, n (%)	
High school degree or less	42 (44)
Associate's degree	10 (10)
Bachelor's degree	29 (30)
Advanced degree (Master/Doctorate)	15 (16)
^a Of the 97 individuals who completed the study session, 1 participant was not included in analyses per pre-defined exclusion criteria; following study completion, the investigator learned that participant had misrepresented previous participation in studies evaluating injection devices. A second participant—who reported injecting her cat many years ago—was included in the study as the one-time injection experience was not expected to bias study results. Abbreviation: SD, standard deviation.	

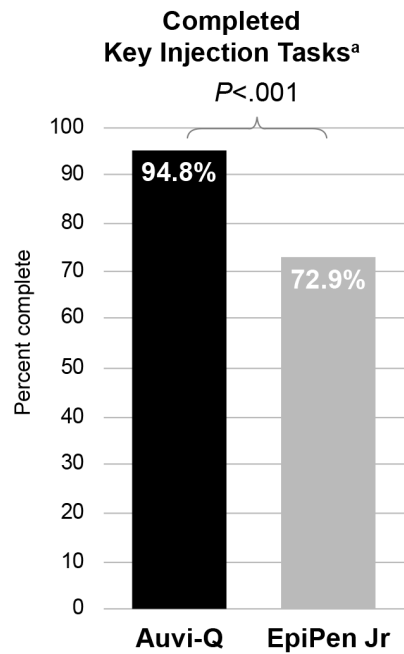


Completed All Injection Tasks, Per Instructions on Device



Use Errors When Following All Injection Tasks, Per Instructions on Device

n (%)	Participants N=96
Auvi-Q Tasks	
Did not pull device up from outer case	1 (1.0)
Did not pull red safety guard down and off	1 (1.0)
Did not place black end against outer thigh	6 (6.3)
Did not push firmly and hold for 2 seconds	10 (10.4)
EpiPen Jr Tasks	
Did not remove auto-injector from carrier tube	2 (2.1)
Did not remove blue safety release by pulling straight up without bending	6 (6.3)
Did not swing and push the orange tip firmly against outer thigh until the auto-injector clicks	68 (70.8)
<i>a: Did not swing</i>	65 (67.7)
<i>b: Did not have orange tip against outer thigh</i>	20 (20.8)
<i>c: Did not push firmly</i>	8 (8.3)
Did not hold firmly in place for 3 seconds	35 (36.5)



Use Errors When Completing Key Injection Tasks^a

n (%)	Participants N=96
Auvi-Q Tasks	
Did not pull device up from outer case	1 (1.0)
Did not pull red safety guard down and off	1 (1.0)
Did not place black end against muscle	2 (2.1)
Did not push firmly and hold for ≥ 0.5 seconds	3 (3.1)
EpiPen Jr Tasks	
Did not remove auto-injector from carrier tube	2 (2.1)
Did not remove blue safety release by pulling straight up without bending	6 (6.3)
Did not push the orange tip firmly against muscle until the auto-injector clicks	22 (22.9)
Did not hold firmly in place for ≥ 0.5 seconds	6 (6.3)

