EXPERT OPINION

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The recombinant human chorionic gonadotropin prefilled pen: results of patient and nurse human factors usability testing

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Objectives: The first prefilled pen for administration of recombinant human chorionic gonadotropin (r-hCG) has been developed. Usability testing was undertaken to evaluate the risk of dosing errors versus the existing r-hCG prefilled syringe, and assess function and handling of the pen.

Methods: Infertile women who were trying to conceive, and specialist nurses, were recruited in Germany. Usability goals were defined and categorized as critical or functional operational goals. Individual, non-interventional, standardized, usability tests (including ease-of-use assessment) were performed with patients and nurses. Cumulative test scores for critical operations were compared. Non-standardized qualitative analyses of nurse–patient training sessions were performed.

Results: The cumulative test score for the r-hCG prefilled pen was better than that of the existing prefilled syringe, so it was concluded that the overall risk of dosing errors was not higher with the pen. The ease of use of the pen was rated favorably by patients and nurses. Both user groups were confident that they could inject the correct dose using the pen.

Conclusions: The overall risk of dosing errors was not higher with the r-hCG prefilled pen than the existing prefilled syringe. The ease-of-use of the r-hCG prefilled pen was rated favorably by patients and nurses.

Keywords: human factors, *in vitro* fertilization, infertility, injection device, pen injector, recombinant human chorionic gonadotropin, usability testing

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1. Introduction

Infertility treatment protocols are complex [1]. Gonadotropins such as follicle-stimulating hormone (FSH) are administered daily to stimulate the development of ovarian follicles. A single dose of human chorionic gonadotropin (hCG) is then used to trigger final follicular maturation and luteinization in cycles of assisted reproductive technology (ART), or follicular rupture in ovulation induction (OI). The efficacy and safety of a single dose of recombinant hCG (r-hCG; 250 mcg administered subcutaneously) is well established in both ART and OI [2,3].

Administration of hCG signifies the culmination of the ovarian stimulation cycle. However, errors in reconstitution, self-injection technique or timing of hCG administration occur frequently in clinical practice [4]. Injection of the correct dose of hCG and the timing of delivery is critical as errors may result in cancellation

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Article highlights.

- Infertility treatment protocols are complex.
- A family of pens with a common design concept and similar operating system has been developed to simplify the self-administration of gonadotropins, and includes the first and only pen device available for injection of hCG.
- The ready-to-use hCG prefilled pen incorporates various patient-friendly design features and is designed for single-use only.
- Usability testing was undertaken to assess the function, handling, and risk of dosing errors of the r-hCG prefilled pen when used by patients and nurses.
- The overall risk of dosing errors was not higher with the r-hCG prefilled pen than an existing prefilled syringe, and the ease-of-use of the pen was rated favourably.

This box summarizes key points contained in the article.

of the treatment cycle [5,6]. Failure to retrieve oocytes during ART cycles causes substantial psychological and financial stress for patients and their partners [7].

r-hCG is currently available for administration as a premixed solution in a ready-to-use, prefilled syringe. Urine-derived hCG is also commercially available but only as lyophilized powder for reconstitution with the accompanying diluents for administration using a needle and syringe.

Fertility treatment cycles may involve the use of a variety of therapies and complicated dosing schedules [1,8]. Various devices have been developed to simplify the injection process and allow well-motivated patients to self-administer gonadotropins [9]. Patients undergoing fertility treatment regularly report pen injectors to be simpler and easier to use than other administration methods [9-11].

Self-injection of gonadotropins may cause anxiety among patients about whether each dose has been administered correctly [9,12]. Accordingly, a substantial proportion of consultation time is spent listening and responding to patients' queries about injection technique [3]. Thus, it is important that gonadotropin administration devices are convenient and easy to use, and deliver the correct dose.

Moreover, different training by specialist nurses is required for administration of each product and the use of each device [13]. In a recent study, most nurses considered that the use of a common device would facilitate self-injection technique training (26/28; 93%), reduce the teaching time required (24/28; 86%) and minimize self-injection errors (25/28; 89%) [14]. Thus, a single platform for delivery of the full spectrum of fertility medications would confer advantages [14].

A family of pens with a common design concept and similar operating system has been developed to simplify the ease of use and ease of teaching of gonadotropin self-administration. The first available member of the family of pens was the redesigned recombinant human FSH (follitropin alfa) pen injector (GONAL-f®/GONAL-f® RFF (Revised Formulation Female) (Prefilled Pen, Merck Serono S.A. – Geneva, Switzerland‡) [8,13,14]. The redesigned follitropin alfa pen injector has a number of new features to improve the ease of teaching and ease of learning, and accuracy of small dosing increments [8,13,14].

A similar ready-to-use, prefilled pen for administration of r-hCG (Ovitrelle®/Ovidrel® Prefilled Pen [Merck Serono S.A. – Geneva, Switzerland‡]) has also been developed (**Figure 1**). The r-hCG prefilled pen contains 250 mcg of the same premixed solution as the existing prefilled syringe, and is the first pen device available for administration of hCG.

The r-hCG prefilled pen benefits from a number of patient-friendly design features, including: a fully transparent cartridge reservoir with a magnifying window that enlarges the 250 mcg graded marking; a dose display that shows only the approved dose; return of the dose reading to zero after injection of the full prescribed dose. The r-hCG prefilled pen is designed for single-use only. The pre-installed cartridge cannot be removed and is intended to be discarded safely (in designated safety containers) after use.

Usability testing aims to ensure that medical devices reflect good human factor engineering practices and thus reduce any potential use-related risks to operators [15]. Regulatory agencies require manufacturers to validate the suitability of new devices for their intended use [15]. Design validation is accomplished when the development process is nearing completion to confirm whether a manufacturer has effectively addressed users' needs [15]. Summative usability testing was undertaken as part of the human factors evaluation to assess the function, handling and risk of dosing errors of the r-hCG prefilled pen when used by patients and nurses.

2. Methods

The methods employed in this usability study are similar to a recently reported human factors evaluation of the redesigned follitropin alfa pen injector [13]. Please refer to the previous publication for a detailed account of the methodology used [13]. Of note, pre-summative testing was not performed in the current study.

2.1 Objectives

The primary objective of this study was to show that the risk of dosing errors in the primary user group (patients) was not higher with the r-hCG prefilled pen (Ovitrelle®/Ovidrel® Prefilled Pen) than with the existing prefilled syringe (**Figure 2**). The overall objectives of the study included evaluation of the impact of human factors on the use of the r-hCG prefilled pen under simulated use conditions, with particular focus on the risks for misuse and dosing errors by infertile women and specialist fertility nurses.

2.2 Participants

Two discrete groups of intended users of the r-hCG prefilled pen were identified: infertile patients who were considered by healthcare professionals to be capable of safely and effectively self-injecting; and specialist nurses who would train and

Figure 1. The recombinant human chorionic gonadotropin prefilled pen.
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Figure 2. The existing recombinant human chorionic gonadotropin prefilled syringe (needle cap not pictured).
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supervise patients on proper use of the pen. Representatives of both of these user groups were included in the usability testing.

Infertile women who were currently undergoing, or about to undergo, fertility treatment, and specialist fertility nurses were recruited via infertility clinics in Germany and independent databases. Patients aged 18–45 years who were willing to receive hormonal treatment to become pregnant were recruited. To simulate a realistic user population, screeners were instructed to include patients from a wide range of educational backgrounds, and include a balanced mix of gonadotropin injection-naïve versus experienced participants.

Specialist fertility nurses aged up to 55 years with varying levels of clinical experience were recruited. The nurses also participated in usability testing of two other pen injectors in development. The sequence of testing was rotated so one-third of nurses evaluated the r-hCG prefilled pen before the other devices.

All participants provided written, informed consent. No actual patient injections were performed as only simulated use of the pen and interviews were conducted. Ethical approval to perform the usability testing was not required in Germany.

2.3 Usability risk assessment

Appropriate use of the prescribed device is described in the instructions for use (IFU) included in the packaging of the r-hCG prefilled pen. During the development of the r-hCG prefilled pen, Merck Serono S.A. – Geneva, Switzerland[‡] used the step-by-step directions in the IFU to identify and analyze potential causes of failure associated with use of the device by patients. This risk assessment was undertaken in compliance with ISO 14971 Standard, *Medical devices – application of risk management to medical devices* [16]. Identified risks were related to erroneous dose presetting and mishandling of air bubble removal (**Figure 3**).

2.4 Usability goals

Usability goals for the prefilled pen and syringe devices were established based on data from the risk assessment. Detailed operations and sub-operations of the usability goals were then described. For example, putting on a needle was an operation comprising the following sub-operations: controlling the closure integrity of the outer needle cap; removing the peel tab; attaching the needle; and removing the outer needle cap.

Each goal was designated as 'critical operational' or 'primary functional'. Two critical operational goals that could potentially lead to patient-related dosing errors with the prefilled pen were identified: removing a large air bubble and presetting the prescribed dose. Seven primary functional goals that could affect the correct functioning of the prefilled pen were identified: attaching a needle; managing a large air bubble; presetting the prescribed dose; completing the required steps before injecting; completing the required steps for injection; checking the dose delivered; and removing the needle from the pen.

Critical operational goals were evaluated for patients to assess the primary objective; these operations were also evaluated for nurses as primary functional goals.

2.5 Summative usability testing

The summative usability testing was performed by Point-Blank International (Berlin, Germany) on behalf of Merck Serono S.A. – Geneva, Switzerland[‡].

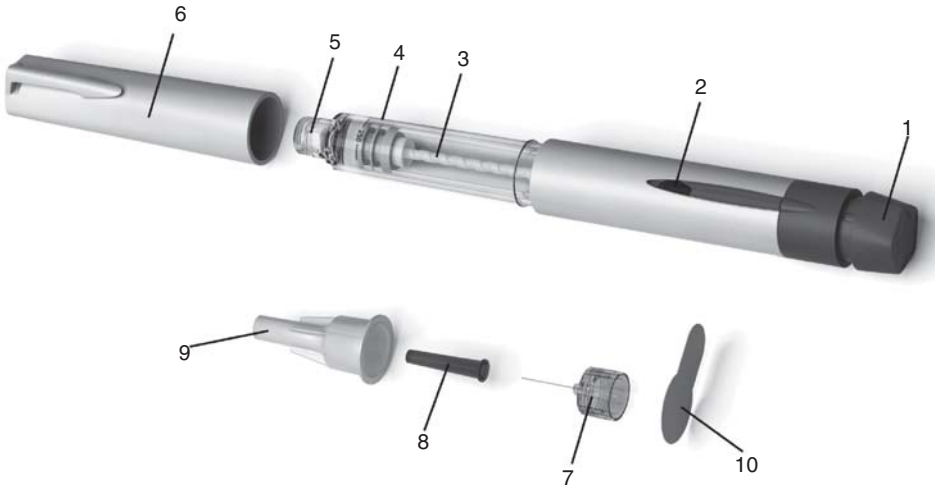

Figure 3. The components of the recombinant human chorionic gonadotropin prefilled pen. 1. Dose setting knob. 2. Dose display. 3. Plunger piston. 4. Reservoir holder. 5. Threaded needle connector. 6. Pen cap. 7. Removable needle. 8. Inner needle shield. 9. Outer needle cap. 10. Peel-off seal tab.

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Based on the critical operational and primary function goals, standardized patient and nurse questionnaires were developed with the aim of documenting all possible risks for mishandling of the r-hCG prefilled pen and existing prefilled syringe.

The following items were used in the test: the r-hCG prefilled pen and existing prefilled syringe containing placebo solution with needles for injection (pre-packaged in unlabelled cardboard boxes); an injection sponge; IFU as appropriate for each device; and a sharps container.

All training, questionnaires, ease-of-use assessments and interviews were performed in German.

2.5.1 *Handling tests*

Individual, non-interventional, standardized, usability tests were performed to observe how the patient or nurse used the r-hCG prefilled pen and where major or minor risks may have occurred. Four experienced and appropriately trained research professionals conducted the sessions.

Participants received an individual demonstration on use of the r-hCG prefilled pen or syringe using a placebo solution injected into a sponge. Patients and nurses were then asked to mimic use of the injection device and verbalize their actions. There was particular focus on use of the injection device and identification of any problems of misuse or dosing errors. The research professional provided the minimum amount of assistance considered necessary to allow task progression.

Patients and nurses were then asked a series of questions to assess the ease of use of the r-hCG prefilled pen (with reference to a printed rating scale from 1 [lowest] to 5 [highest]). Participants were asked to rate the ease of removing an air bubble, injecting the dose, and the overall handling of the pen. Participants were also asked how certain they were that the correct dose had been injected using the pen.

2.5.2 *Nurse–patient training observations*

Non-standardized qualitative analyses were also conducted to understand in detail the reasons for any perceived benefits, or weaknesses, of use of the r-hCG prefilled pen. First, the use of the r-hCG prefilled pen and existing prefilled syringe was explained to nurses. 'Real-life' nurse–patient training sessions were performed in the presence of a research professional who then discussed with the patient and nurse reasons for possible risks and misunderstandings when handling each device. All participants were encouraged to comment openly and honestly. The discussions were then transcribed and reviewed.

2.6 Data analysis

The sample size for the summative usability testing was based on Health Authority requirements, which demand a minimum of 15 participants from each user group (patients and nurses) [17,18].

For each operation and sub-operation, possible user scores were: 0 – operation missed; 1 – operation performed with help; or 2 – operation performed without help. As the prefilled pen should only be used under medical supervision and after adequate training [19], user scores of '2' and '1' were considered as a handling success whereas a user score of '0' was considered a failure. For some operations, such as checking the preset dose, not remembering to complete a particular step was considered a failure.

To address the primary objective, direct comparison of the two devices was planned for critical operations performed by patients. However, as the r-hCG prefilled pen and existing

Table 1. Numbers of patients and nurses recruited from each city.

	Patients	Nurses	Nurse–patient training sessions
Berlin	5	10	2
Cologne	5	1	1
Frankfurt	6	3	0
Hamburg	5	4	2
Total	21	18	5

Table 2. Demographic characteristics of patients (n = 21) who participated in the individual handling test.

Parameter	Descriptive statistics
Age, (years)	
Mean (SD)	38.0 (5.66)
Median (range)	37.4 (28–45)
Education, n (%)	
GCSE*	7 (33.3)
High school‡ or higher education	14 (66.7)
Treated, n (%)	
Yes	12 (57.1)
No	9 (42.9)

*GCSE (General Certificate of Secondary Education) level indicates schooling up to 16 years of age.
‡High school level indicates schooling up to 18 years of age.
SD: Standard deviation.

Table 3. Demographic characteristics of nurses (n = 18) who participated in the individual handling test.

Parameter	Descriptive statistics
Age, (years)	
Mean (SD)	36.8 (10.66)
Median (range)	31.5 (24–61)
Experience (years)	
Mean (SD)	13.4 (8.43)
Median (range)	11.0 (4–33)
Education, n (%)	
GCSE*	16 (88.9)
High school‡ or higher education	2 (11.1)

*GCSE (General Certificate of Secondary Education) level indicates schooling up to 16 years of age.
‡High school level indicates schooling up to 18 years of age.
SD: Standard deviation.

prefilled syringe use different injection systems, direct comparison of operating steps could not be made. Therefore, cumulative data were evaluated. The test score was calculated as the total number of patients who missed an operation divided by the total number of patients who performed the operation. Thus, a lower test score indicated a better outcome than a higher test score.

Ease-of-use assessments from patients and nurses were rated on a scale of 1–5 where: 1 indicated 'it was very difficult' and 5 indicated 'it was very easy'. The ease-of-use rating to each of four questions was calculated as the sum of the ratings divided by the total number of participants. Thus, a higher ease-of-use score indicated a better outcome than a lower ease-of-use score.

The usability assessment was not designed to allow formal statistical comparisons between groups. Descriptive statistics are presented, including number (n), mean, standard deviation (SD), median, minimum and maximum.

3. Results

3.1 Handling tests

Twenty-one patients and 18 nurses participated in the handling tests. The number of patients and nurses recruited from each city is shown in **Table 1**.

3.1.1 *Demographic characteristics*

Patient demographic characteristics are presented in **Table 2**. Mean (SD) patient age was 38.0 (5.66) years. Twelve patients were gonadotropin injection-experienced and nine were gonadotropin injection-naïve.

Nurse demographic characteristics are presented in **Table 3**. Mean (SD) nurse age was 36.8 (10.66) years and they had a mean (SD) number of years of nursing experience of 13.4 (8.43). One nurse (aged 61 years) exceeded the stated age limit, but this was not considered to be a major protocol deviation.

3.1.2 *Operational and functional goal testing*

In accordance with the primary objective, cumulative test scores for critical operations from patients (n = 21; the primary population) were compared for each device. The cumulative test score for critical operations from patients was lower for the r-hCG prefilled pen than the existing prefilled syringe (0.016 vs 0.060). This shows that the overall risk of dosing errors with the r-hCG prefilled pen was not higher than with the existing device.

The two critical operations were: removing a large air bubble and presetting the prescribed dose. The operation 'presetting the prescribed dose' was applicable only to the r-hCG prefilled pen, as the entire volume of solution is administered when using the prefilled syringe. Only 1 of 21 (5%) patients failed this operation. No patients (0%) using the prefilled pen failed to complete the operation 'removing a large air bubble' versus 4/21 (19%) patients using the prefilled syringe.

Both patients and nurses achieved most of the primary functional goals of the r-hCG prefilled pen (**Table 4**). The operations with the highest failure rates were controlling the closure integrity of the outer needle cap and checking the preset dose before injecting. In addition, three patients and three nurses failed to remember to read the number

Table 4. Results of the critical operation* and primary functional goal testing of the recombinant human chorionic gonadotropin prefilled pen in patients (n = 21) and nurses (n = 18).

Critical operation* or primary functional goal	Number of failures (score '0')	
	Patients	Nurses
Put on needle		
Control closure integrity outer needle cap	6	2
Remove peel-off tab	0	0
Attach needle	0	0
Remove outer needle cap	1	0
Manage large air bubble		
Check presence of large air bubble	0	0
Remove large air bubble	0*	0
Preset prescribed dose		
Turn dose setting knob	0*	1
Read prescribed dose figure	1*	1
Before injecting		
Check again preset dose	7	6
Correct preset dose (if incorrect)	0	0
Remove inner needle	0	0
Injecting		
Inject	0	0
Insert needle into skin‡	0	0
Press dose-setting knob as far as it goes	0	0
Keep pressing with the needle in the skin‡	2	0
Remove needle from skin‡	1	0
Check the dose delivered		
Read number in dose display	3	3
Remove the needle		
Wind in the outer needle cap	3	0
Unwind the outer needle cap and with needle	1	0
Dispose of safely	0	0
Put on pen cap	0	0

*Critical operational data were collected only from patients. Nurses also completed these functions as primary functional goals.
‡The term 'skin' is used to indicate the sponge provided for simulation testing.

in the dose display to check that the complete dose had been delivered.

3.1.3 *Ease-of-use ratings*

The ease of use of the r-hCG prefilled pen was rated favorably by patients and nurses (**Table 5**). The mean scores for the four ease-of-use questions ranged from 3.9 to 4.9 for patients and from 4.3 to 4.9 for nurses (maximum possible score = 5). The mean overall handling scores from patients and nurses were 4.0 and 4.3, respectively. Both patients and nurses were confident that they would be able to inject the correct dose using the r-hCG prefilled pen (mean scores 4.9 and 4.6, respectively).

3.2 Nurse–patient training observations

Five patients and five nurses participated in the qualitative nurse–patient training sessions for the r-hCG prefilled pen (**Table 1**). The information below is based predominantly on the transcripts of these nurse–patient training sessions.

The most important advantage of the r-hCG prefilled pen was its perceived reliability in delivering the correct (complete) dose. Patients and nurses commented that the 'zero' displayed after injection was a useful indicator that the full dose had been delivered. Furthermore, both patients and nurses reported that they felt confident that the correct dose had been delivered by the prefilled pen.

4. Discussion

In this summative usability testing, the cumulative test score for critical operational goals for the r-hCG prefilled pen was better than the score for the existing prefilled syringe. Thus, the r-hCG prefilled pen was not associated with an overall increase in the risk of dosing errors by patients compared with the existing syringe.

This study was also designed to evaluate the impact of human factors on the use of the r-hCG prefilled pen with particular focus on the risks for misuse and dosing errors. Most of the primary functional goals of the r-hCG prefilled pen were achieved by both patients and nurses. Failure rates were highest for controlling the closure integrity of the outer needle cap, checking the preset dose before injecting, and reading the dose display to check the dose delivered. It should be noted that one-third of patients (7/21) and nurses (6/18) failed to remember to recheck the preset dose immediately prior to injection. We believe that this omission occurred because participants were confident of the originally dialled dose, and so they considered further confirmation to be unnecessary.

During the qualitative training sessions, patients and nurses commented that the 'zero' displayed after injection was a useful indicator that the full dose had been delivered. Moreover, both user groups reported a high level of confidence regarding administration of the correct (complete) dose using the r-hCG prefilled pen.

The r-hCG prefilled pen has a similar operating system to the redesigned follitropin alfa pen injector. The redesigned follitropin alfa pen injector was developed following a comprehensive market research exercise involving more than 100 healthcare providers from six European countries [8]. It is intended for subcutaneous self-injection and is available in three dosing presentations (300 IU, 450 IU and 900 IU).

The usability of the redesigned follitropin alfa pen injector was confirmed in a recent study of patients (n = 18) and specialist fertility nurses (n = 18) [13]. No unexpected operational risks or major concerns regarding the risks of misuse or dosing errors were identified, and the overall ease of use of the pen was rated favorably by both patients and nurses. The ease of teaching and learning of the redesigned follitropin alfa pen

Table 5. Ease-of-use ratings for the recombinant human chorionic gonadotropin prefilled pen by patients and nurses.

Question, mean (SD)	Ease-of-use rating	
	Patients (n = 21)	Nurses (n = 18)
How do you rate the overall handling of the pen?	4.0 (1.10)	4.3 (0.91)
How easy or difficult was it to remove an air bubble?*	4.4 (0.76)	4.3 (1.23)
How easy or difficult was it to inject the dose?	3.9 (1.41)	4.9 (0.32)
How certain are you that you will be able to inject the correct dose?	4.9 (0.22)	4.6 (0.70)

Ratings were on a scale of 1–5 (1 = 'it was very difficult', 5 = 'it was very easy').
*Two patients and three nurses did not rate the ease of removal of an air bubble as they did not have to remove any air during the handling test.
SD: Standard deviation.

injector was further assessed in infertile women (n = 73) and specialist nurses (n = 28) [14]. Most (88%) patients found it easy to learn how to use the pen. All nurses considered that the redesigned pen was easy to learn how to use and believed it would be easy to teach patients to do so [14].

The r-hCG prefilled pen is another member of this family of pens. The r-hCG prefilled pen is the first and only pen device available for administration of hCG. In the current study, the ease of use of the r-hCG prefilled pen was rated favorably by patients and nurses. The mean overall handling scores (on a scale of 1–5) were 4.0 from patients and 4.3 from nurses, indicating that the r-hCG prefilled pen was very easy to use. Moreover, both patients and nurses were confident that they would be able to inject the correct dose using the r-hCG prefilled pen (mean scores 4.9 and 4.6, respectively).

The age of women presenting for fertility treatment in Europe has increased in recent years. Indeed, the mean age of women commencing ART in Germany has gradually risen since 1997 to reach almost 35 years in 2010 [20]. Registry data suggest that 86% of oocyte retrievals in Germany in 2010 were performed on women aged ≥ 30 years [20]. Patients aged 18–45 years were eligible for inclusion in this usability assessment but, in reality, women aged 28–45 years volunteered to participate and were thus enrolled. We believe that this outcome simply reflects the population attending for treatment. Theoretically, the omission of younger patients (aged 18–27 years) could have particularly excluded gonadotropin injection-naïve patients. However, we actively recruited a balanced combination of injection-naïve and -experienced women to participate in this study. Therefore, we do not believe that the age range of enrolled patients affects the interpretation of our data.

We acknowledge the following minor limitations of the current usability testing. This was designed as a simple simulation test to evaluate the functioning of the pen and, therefore, any comparisons with the existing prefilled syringe have limited statistical power. Only qualitative information was available from the nurse–patient training observations. Therefore, data on use of the r-hCG prefilled pen in clinical practice will be valuable.

5. Conclusions

The r-hCG prefilled pen is the first and only pen device available for administration of hCG. The cumulative test score for critical operations for the r-hCG prefilled pen was better than the score for the existing prefilled syringe. This usability study met its primary objective, which was to show that the risk of dosing errors by patients was not higher with the r-hCG prefilled pen than with the existing prefilled syringe.

In addition to meeting the primary objective, the ease of use of the r-hCG prefilled pen was rated favorably by patients and nurses in this study. The mean overall handling scores indicated that both patients and nurses found the r-hCG prefilled pen very easy to use. Moreover, both user groups were confident that they would be able to inject the correct dose using the r-hCG prefilled pen. Lastly, it is expected that the single platform for delivery of fertility therapies provided by the family of pens may offer advantages for teaching and learning to self-inject.

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Declaration of interest

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