Prefilled syringes for intravitreal injection reduce preparation time

Yousif Subhi1, 2, Birgit Kjer3 & Inger Christine Munch1, 2

ABSTRACT
INTRODUCTION: The demand for intravitreal therapy has increased dramatically with the introduction of vascular endothelial growth factor inhibitors. Improved utilisation of existing resources is crucial to meeting the increased future demand. We investigated time spent preparing intravitreal injection treatment using either prefilled syringes or vials in routine clinical practice.

METHODS: We video-recorded preparations of intravitreal injections (n = 172) for each preparation type (ranibizumab prefilled syringe (n = 56), ranibizumab vial (n = 56) and aflibercept vial (n = 60)) in a multi-centre time and motion study. The preparation times for each step were extracted from videos and the three preparation types were compared.

RESULTS: Prefilled syringes eliminated several steps in the preparation process. Total preparation time was 40.3-45.1 sec. using vials, and the use of prefilled syringes saved 25.5 sec. (95% confidence interval (CI): 23.3-27.6 sec., p < 0.0001). The preparation time when aflibercept vials were used was 3.7 sec. (95% CI: 1.45-5.96 sec., p = 0.0014) longer than when ranibizumab vials were used.

CONCLUSIONS: Prefilled syringes for intravitreal injections reduce preparation time by eliminating preparation steps that both entail a risk of contamination and are subject to variation. The amount of time saved may enable increased utilisation of existing resources and outsourcing to non-ophtalmologists.

FUNDING: This study was supported by a grant from Novartis. The funders had no influence on the design of the study, analysis of the data, preparation of the manuscript or the decision to publish.

TRIAL REGISTRATION: not relevant.

Treatment with inhibitors of vascular endothelial growth factor (VEGF) given as intravitreal injections has changed the prognosis for a range of retinal conditions such as wet age-related macular degeneration [1-4]. Notably, the incidence of legal blindness from age-related macular degeneration has halved since the introduction of intravitreal therapy (0.16%) [8, 9]. However, the number of patients in treatment is high and still increasing [10, 11]. We therefore need to combine a safe treatment with optimal utilisation of staff and operating rooms in order to meet the demand.

Solutions for intravitreal injections are contained in vials and the medicine is transferred from the vial to an injection syringe with a special aspiration needle that is subsequently replaced by a thinner needle for injection in the eye bulb. Since 2014, the VEGF inhibitor ranibizumab (Lucentis, Novartis, Basel, Switzerland) has been available in prefilled syringes (PFS) that eliminate several steps in the preparation (Table 1) at the same price as ranibizumab in vials in Denmark. Fewer steps in the preparation may shorten preparation time, increase utilisation of operation rooms, and thus enable treatment of more patients. PFS has yielded such results in other fields of medicine [12].

This study aimed to compare the time spent preparing intravitreal injection treatment using either PFS or vials with ranibizumab or aflibercept in routine clinical practice.

METHODS
Study design
Two Danish public hospitals with ophthalmological departments, Roskilde Hospital and Sønderborg Hospital, participated in this study. Intravitreal administration of ranibizumab in vials or PFS and aflibercept (Eylea, Bayer, Leverkusen, Germany) in vials were video-recorded consecutively. A minimum of 28 injection procedures were video-recorded for each preparation type (ranibizumab PFS, ranibizumab vial, and aflibercept vial) at each site based on our power calculation (Δ = 15 sec., standard deviation (SD) = 15 sec., α = 0.05, β > 0.95, two-sided t-test comparing PFS with vials (ranibizumab or aflibercept)). All preparations were performed according to local routine clinical practice, and we did not include procedures deviating from routine clinical practice, e.g. treatments provided as part of clinical trials. Furthermore, we excluded recordings of procedures that involved training of new personnel (assisting or injecting).

This study protocol was submitted to the Regional
Committee on Health Research Ethics of Region Zealand and was exempted from board review as the study explored internal workflows and did not involve any randomisation of patients or any patient intervention. All involved patients gave verbal informed consent. All aspects of this study were conducted according to the principles of the Declaration of Helsinki.

Data collection
We used an iPad (Apple Inc., Cupertino, CA, USA) to video-record the involved physicians' and nurses' preparation of the procedure in the operating room. We then extracted exact time stamps from the videos for each step of the preparation (Table 1). We registered the age and gender of the patient, the identity of the injecting physician/nurse, and the VEGF inhibitor (ranibizumab PFS, ranibizumab vial, or aflibercept vial). We noted whether the injection was the patient's first, which we hypothesised might increase the time used due to more interaction with the patient. No patient-identifying data were collected. The injecting physicians and nurses were asked to complete a user survey regarding self-perceived benefits and drawbacks.

Data analysis
Statistical analyses were made using SAS 9.2 (SAS Institute, Cary, NC, USA). The primary outcome was the total preparation time. Descriptive statistics were calculated for all variables and compared between centres with Student’s t-test and the chi-squared test, as appropriate. The mean time spent on each step of preparation was compared between groups with two-sided one-way analysis of variance. Total preparation time was analysed in a general linear model adjusting for age, gender, patient's first injection (y/n) and identity of injecting staff. The assumptions of linearity, variance homogeneity, and normality of the distribution of residuals underlying the statistical model were assessed by display of relevant plots. The level of statistical significance was set to a p-value below 0.05, and estimates were calculated with 95% confidence intervals (CI).

Trial registration: not relevant.

RESULTS
We included a total of 172 video-recordings of syringe preparation with VEGF inhibitors for intravitreal injections from the two centres. In Roskilde, three physicians performed the injections, and in Sønderborg six nurses performed the injections (Table 2). The proportion of patients receiving their first injection was higher in Sønderborg (19.5%) than in Roskilde (4.71%, p = 0.0030) as was the proportion of male patients (57.7% compared with 42.3%, p = 0.047). The mean age of the patients receiving the injection was comparable between the centres (Table 2).

The total syringe preparation time including data from both centres was 16.9 ± 3.6 sec. (mean ± SD) for ranibizumab PFS, which was shorter than the 40.3 ± 6.7 sec. preparation time recorded for ranibizumab vials and the 45.1 ± 6.9 sec. recorded for preparation with aflibercept vials (Table 3). The difference in total preparation
time between ranibizumab PFS and ranibizumab vial was 24.1 sec. (95% CI: –27.3 to –20.9 sec., p < 0.001) in Roskilde and 26.2 sec. (95% CI: –29.2 to –23.2 sec., p < 0.0001) in Sønderborg, after adjusting for the patient’s age and gender, first-time injection and for the identity of the injecting staff (Table 3). Based on data from both centres, the total syringe preparation time with ranibizumab PFS was 25.5 sec. (95% CI: 23.3 to 27.6 sec., p < 0.0001) shorter than the preparation time with ranibizumab vials.

Overall, preparation time was not influenced by whether or not the injection was the patient’s first (p = 0.91).

Comparing aflibercept vials with ranibizumab vials, we found that the total preparation time with aflibercept was 5.80 sec. (95% CI: 2.29 to 9.30 sec., p = 0.0015) longer in Sønderborg and 2.54 sec. (95% CI: –0.41 to 5.49 sec., p = 0.090) longer in Roskilde after adjusting for age and gender of the patient, first-time injection and for the identity of the injecting staff. The difference was significant when including data from both centres at 3.71 sec. (95% CI: 1.45 to 5.96 sec., p = 0.0014, Table 4).

We analysed the time spent on each step of the preparation (Table 4). With PFS, the total preparation time was broken into two steps: attaching the injection needle which took 9.43 ± 2.7 sec. in Roskilde and 9.54 ± 3.1 sec. in Sønderborg, and ensuring that there were no bubbles and adjusting the dose which took 7.39 ± 2.2 sec. and 7.31 ± 5.8 sec., respectively (Table 4).

With vials, the sequence of the procedures and the differences in time consumption with ranibizumab and aflibercept varied between the sites. Especially, the two steps disinfection of vial lid and attaching aspiration/injection needle are difficult to compare. In Roskilde, the vial lid was disinfected before the attaching the aspiration/injection needle step, while in Sønderborg the vial lid was disinfected by the assistant while the injecting personnel was attaching the aspiration needle. This meant that when the assistant was occupied disinfecting the vial lid, the injection staff had to wait for the assistant’s unpacking of the syringe or the aspiration needle and hence the attaching aspiration/injection needle was more time-consuming with vials than with PFS in Sønderborg (p < 0.0001, Table 4). In Roskilde, however, this step was not affected by the time spent with disinfection of the vial lid, and hence attaching aspiration/injection needle was more time-consuming with PFS than with vials (p = 0.0017, Table 4). From the videos, we learned that this difference was due to the injecting personnel struggling slightly to get the PFS out of its box.

In Sønderborg, the step disinfection of vial lid was less time-consuming with ranibizumab than with aflibercept, although the difference was clinically irrelevant (0.78 sec., p = 0.0014, Table 4).

The step drawing medicine from vial was less time-consuming with ranibizumab than with aflibercept in Roskilde (5.29 ± 1.1 sec. versus 7.1 ± 3.0 sec., p = 0.0042), whereas there was no difference in Sønderborg.

### Table 3

Differences in total preparation time of syringes with vascular endothelial growth factor inhibitor in pre-filled syringes or vials for intravitreal injections*

<table>
<thead>
<tr>
<th>Centre</th>
<th>Ranibizumab prefilled syringe</th>
<th>Ranibizumab vial</th>
<th>Aflibercept vial</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roskilde</td>
<td>16.8 ± 3.2</td>
<td>37.1 ± 3.8</td>
<td>42.1 ± 7.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sønderborg</td>
<td>16.9 ± 4.0</td>
<td>43.5 ± 7.4</td>
<td>47.8 ± 5.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Both centres</td>
<td>16.9 ± 3.6</td>
<td>40.3 ± 6.7</td>
<td>45.1 ± 6.9</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

SD = standard deviation.

### Table 4

Steps of preparation and time consumption using pre-filled syringes and vials with vascular endothelial growth factor inhibitors for intravitreal injections.

<table>
<thead>
<tr>
<th>Attaching aspiration/injection needle, mean ± SD, sec.</th>
<th>Ranibizumab prefilled syringe</th>
<th>Ranibizumab vial</th>
<th>Aflibercept vial</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roskilde</td>
<td>9.43 ± 2.7</td>
<td>7.36 ± 0.78</td>
<td>7.76 ± 2.6</td>
<td>0.0017</td>
</tr>
<tr>
<td>Sønderborg</td>
<td>9.54 ± 3.1</td>
<td>12.0 ± 5.2</td>
<td>16.1 ± 4.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Disinfecting vial lid, mean ± SD, sec.</td>
<td>-</td>
<td>1.79 ± 0.74</td>
<td>1.66 ± 1.2</td>
<td>0.62</td>
</tr>
<tr>
<td>Roskilde</td>
<td>-</td>
<td>1.96 ± 0.74</td>
<td>2.74 ± 1.0</td>
<td>0.0014</td>
</tr>
<tr>
<td>Sønderborg</td>
<td>-</td>
<td>8.5 ± 5.0</td>
<td>7.77 ± 1.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Drawing medicine from vial, mean ± SD, sec.</td>
<td>-</td>
<td>5.29 ± 1.1</td>
<td>7.1 ± 3.0</td>
<td>0.0042</td>
</tr>
<tr>
<td>Roskilde</td>
<td>-</td>
<td>8.5 ± 5.0</td>
<td>7.77 ± 1.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Sønderborg</td>
<td>-</td>
<td>4.11 ± 0.69</td>
<td>4.55 ± 1.8</td>
<td>0.22</td>
</tr>
<tr>
<td>Removing aspiration needle and attaching injection needle, mean ± SD, sec.</td>
<td>-</td>
<td>4.21 ± 3.0</td>
<td>8.0 ± 5.2</td>
<td>0.0012</td>
</tr>
<tr>
<td>Roskilde</td>
<td>-</td>
<td>11.9 ± 2.4</td>
<td>13.5 ± 2.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sønderborg</td>
<td>7.32 ± 5.8</td>
<td>10.3 ± 5.2</td>
<td>7.84 ± 5.8</td>
<td>0.058</td>
</tr>
<tr>
<td>Ensuring there are no bubbles and adjusting dose to 0.05 ml, mean ± SD, sec.</td>
<td>-</td>
<td>7.39 ± 2.2</td>
<td>11.9 ± 2.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Roskilde</td>
<td>7.32 ± 5.8</td>
<td>10.3 ± 5.2</td>
<td>7.84 ± 5.8</td>
<td>0.058</td>
</tr>
<tr>
<td>Sønderborg</td>
<td>16.8 ± 3.2</td>
<td>37.1 ± 3.8</td>
<td>42.1 ± 7.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Overall preparation time, mean ± SD, sec.</td>
<td>16.9 ± 4.0</td>
<td>43.5 ± 7.4</td>
<td>47.8 ± 5.0</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

SD = standard deviation.

a) For vials, this meant attachment of aspiration needle. For pre-filled syringes, this meant attachment of injection needle.

b) 1-way analysis of variance.
On the other hand, the step removal of aspiration needle and the attachment of injection needle was less time-consuming with ranibizumab than with aflibercept in Sønderborg (4.21 ± 3.0 sec. versus 8.0 ± 5.2 sec., p = 0.0012), but not in Roskilde. From the videos, we learned that the reason for this difference was that in Sønderborg the step removal of aspiration needle and the attachment of injection needle included efforts to eliminate bubbles, whereas in Roskilde bubbles were handled at the final step ensuring that there were no bubbles and adjusting the dose to 0.05 ml. This step was less time-consuming with PFS than with vials in Roskilde (7.39 ± 2.2 sec., 11.9 ± 2.4 sec., 13.5 ± 2.9 sec., p < 0.0001, PFS, ranibizumab vial, and aflibercept vials, respectively), but not in Sønderborg (Table 4).

The user surveys were filled in by two out of three injecting physicians from the Roskilde centre and by four out of six injecting nurses from the Sønderborg centre. All wrote that their self-perceived experience was that PFS was faster and offered a higher safety owing to a reduced number of preparation steps, and three out of six expressed that PFS provided less risk of needle-related injuries. Out of six, three noted that the plunge in the PFS felt looser than that of usual syringes.

**DISCUSSION**

Ranibizumab in PFS saved 25.5 sec. of preparation time compared with ranibizumab in vials by reducing the number of preparation steps and the need for elimination of bubbles. Ranibizumab in vials saved 3.7 sec. of preparation time compared with aflibercept. The injecting staff were satisfied with the PFS and considered them an improvement.

The use of vials requires time spent disinfecting the vial lid, attaching the aspiration needle, aspirating medicine from the vial and removal of the aspiration needle—all these steps are eliminated when PFS are used as only the injecting needle needs to be attached and the dose adjusted. Drawing medicine from vials may lead to turbulence and bubble formation, which explains why we found that less time was spent on ensuring that there were no bubbles and on adjusting the dose when ranibizumab PFS was compared with ranibizumab vials. Our findings suggest that the difference in preparation time between PFS and vials is due to fewer steps and fewer bubbles.

A recent study compared the preparation time of 97 intravitreal injections of ranibizumab PFS with ranibizumab vials in a private and in a public clinic. The study data were recorded by external observers using directly entered time stamps [13]. The study found that PFS saved 17-29 sec. of preparation time [13], which is similar to our findings. Attaching the aspiration needle, disinfecting the vial lid and drawing ranibizumab from the vial took 20.2 sec. in one centre, and 12.2 sec. in another centre that did not disinfect the vial lid [13]; times that are similar to ours (22.5 sec. in Sønderborg and 14.4 sec. in Roskilde). The authors also described that the staff reported that they felt like they spent less time on bubbles when using PFS [13], a notion that is confirmed by our results. Our study also noted whether the injection was the patient’s first, as we hypothesised that more interaction with the patient would lead to increased time-consumption, but our data did not support this hypothesis. Studies on the use of PFS and time savings in other settings, such as heparin and adrenaline syringes [14, 15], also find that less time is used when using PFS in clinical practice.

A solution of aflibercept has higher viscosity than a solution of ranibizumab, and the higher viscosity causes bubbles to form more easily, and the bubbles are also more difficult to eliminate [16]. Bubbles are a problem because when they are injected into the vitreous, they cause visual disturbances leading to discomfort, fear of falling, and lower dose of drug being administered [17]. We confirm that more time is spent on preparing the syringe for injection when using aflibercept, and we believe that is due to bubbles. Avoiding and eliminating bubbles were handled differently at the two sites. At Roskilde, the aspiration was performed more slowly with aflibercept to avoid bubble formation, and more time was spent on eliminating bubbles when adjusting the dose. At Sønderborg, on the other hand, aflibercept was aspirated at the same speed as ranibizumab, but more time was used changing from the aspiration needle to the injection needle because the bubbles were handled just before attaching the injection needle.

The number of patients in intravitreal injection therapy is increasing [10, 11]. The growing demand for...
intravitreal injections makes it necessary for non-ophthalmologists to perform the procedure [18-20]. Outsourcing this procedure should not compromise patient safety, which is why efforts are made to ensure adequate education of the injecting staff and streamlining of the injection process [18-20]. Our study demonstrates that the use of PFS speeds up the procedure by eliminating steps whereby fewer bubbles are formed. The fewer and simpler steps streamline the process and thus facilitate outsourcing of the procedure to non-ophthalmologists.

The strengths of the study include that we used video-recording for precise and reproducible recording of the time. The number of recorded procedures was considerable, and data from two independent high-volume centres were included. Furthermore, we allowed for differences in preparation procedure between the centres to reflect actual clinical practice. This, however, made data from the two centres on the time-consumption of the individual steps of the procedure difficult to integrate. Another important limitation is that the study was not powered to study safety measures such as the rate of endophthalmitis, which would require thousands of participants.

CONCLUSIONS
The use of prefilled syringes for intravitreal injections reduced preparation time by eliminating steps that pose a potential risk of contamination and are subject to variation by the injecting staff, notably the elimination of air bubbles in the solution for injection. A fast, safe, and streamlined injection procedure is mandatory as intravitreal treatments are increasing in number and as these treatments are more and more frequently performed by non-ophthalmologists.