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Analysis of the report *GEDSA Low Dose Syringe Accuracy Test*, dated 31 January 2016, by SMTL

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Executive Summary

There is little evidence of a difference between the mean absolute dosing errors of device LDT1 and any of the following devices: the standard ENFit device (A) and the reverse orientation devices (E and F). There is strong evidence that the standard orientation devices (B, C and D) each have smaller mean absolute dosing errors than LDT1.

Introduction

Select Statistical Services is a full-service statistical consultancy company offering a range of statistical research, analysis and training services. All our consultants are Chartered Statisticians and hold a Master's degree in statistics and most also have a PhD. We have extensive experience in analysing data arising from studies and experiments from across a wide range of industries.

We were asked by Vygon to provide an independent analysis of data arising from this syringe dosing accuracy study. This report summarises the most pertinent results. The full results of our analysis are provided in our report VYG001 dated 3 March 2016.

In the study, seven devices were tested in a variety of scenarios on their performance in delivering a target dose of 0.2 ml. The devices being tested were:

- Device LDT1
- A standard ENFit device, labelled A.
- Three currently marketed standard orientation devices, labelled B, C and D.
- Two currently marketed reverse orientation syringes, labelled E and F.

In the study measurements of the actual dose delivered were recorded. We subtracted the target dose of 0.2 ml from the actual dose delivered and took the absolute value (i.e. converting negative numbers to positive numbers of the same size) to obtain the *absolute dosing errors*.

Several factors were varied during the study.

- filling method: the syringe filling method. This is either "cup", "straw-up" (meaning straw with the syringe orientated up) and "straw-down" (meaning straw with the syringe orientated down).
- t.orient: the orientation of the tube on connection to the syringe, either "up" or "down".
- flick: an indication of whether the tip of the syringe has been flicked by the technician, either "flick" or "no flick".

The design is not a full factorial design, meaning that not every combination of device and factor level has observations. The design is also imbalanced, meaning that the number of replications varies between different combinations of device and factor levels. Missing combinations of device and factor levels and imbalance have implications for the statistical analysis, which are discussed in the next section.

Table 1 gives the number of replications for each device at each combination of levels of the factors.

f.method	t.orient	flick	A	B	C	D	E	F	LDT1
cup	down	flick	0	0	0	0	0	0	49
straw-down	down	flick	0	0	0	0	0	0	0
straw-up	down	flick	0	0	0	0	0	0	0
cup	up	flick	0	0	0	0	0	0	49
straw-down	up	flick	0	0	0	0	0	0	0
straw-up	up	flick	0	0	0	0	0	0	36
cup	down	no-flick	16	16	16	16	16	16	49
straw-down	down	no-flick	16	16	16	16	16	16	0
straw-up	down	no-flick	16	16	16	16	16	16	0
cup	up	no-flick	16	16	16	16	16	16	49
straw-down	up	no-flick	16	16	16	16	16	16	0
straw-up	up	no-flick	16	16	16	16	16	16	36

Table 1: The number of replications at each combination of factor levels and device. The rows highlighted pink indicate those combinations of factor levels that are included in the analysis.

Statistical considerations

In the analysis we compare the dosing errors of the devices averaged across various combinations of factor levels. In order to make a fair comparison between the devices we only include the three combinations of factors that have measurements for every device, as indicated in Table 1 by the pink highlighting. Note in particular that we only use the no-flick trials of device LDT1 because the other devices only have no-flick trials.

Another consideration to ensure a fair comparison is the numbers of trials at each combination of factor levels. While devices A-F have balanced trial designs, meaning they have the same number of trials (16) at each combination of factor levels, device LDT1 has an imbalanced design: two of the included groups have 49 trials while the third has 36. To avoid bias in the device comparisons, in our analysis we make an adjustment that reweighs the LDT1 trials in a way that mimics the situation where LDT1 has the same number of trials for each of the three combinations of factors.

The absolute dosing errors have a distribution that is very unlike the bell-shaped Gaussian distribution that standard parametric statistical tests, such as t-tests, tend to assume. We therefore adopted a widely used non-parametric method known as *bootstrapping* for our analysis. More details of the bootstrapping procedure can be found in the report VYG001 dated 3 March 2016.

To test the differences between LDT1 and the other devices we take each device A-F in turn and calculate the difference between its mean absolute dosing error and that of LDT1. We also calculate a 95% confidence interval for this difference. A confidence interval indicates a range of values in which we expect the difference in the population mean absolute dosing errors to lie. (By *population mean* we mean the average across a hypothetical very large set of trials.) If the confidence interval does not cross zero then we interpret this as strong evidence that there is a real difference in the mean absolute dosing errors between the devices in question.

Results

The box plots in Figure 1, below, show the distributions of the absolute dosing errors of the devices across the three factor combinations that are included in the analysis. From this diagram we can see that the device LDT1, the standard ENFit device (A) and the reverse orientation devices (E and F) have broadly similar absolute dosing errors, and that the standard orientation devices (B, C and D) tend to have smaller dosing errors than the other devices.

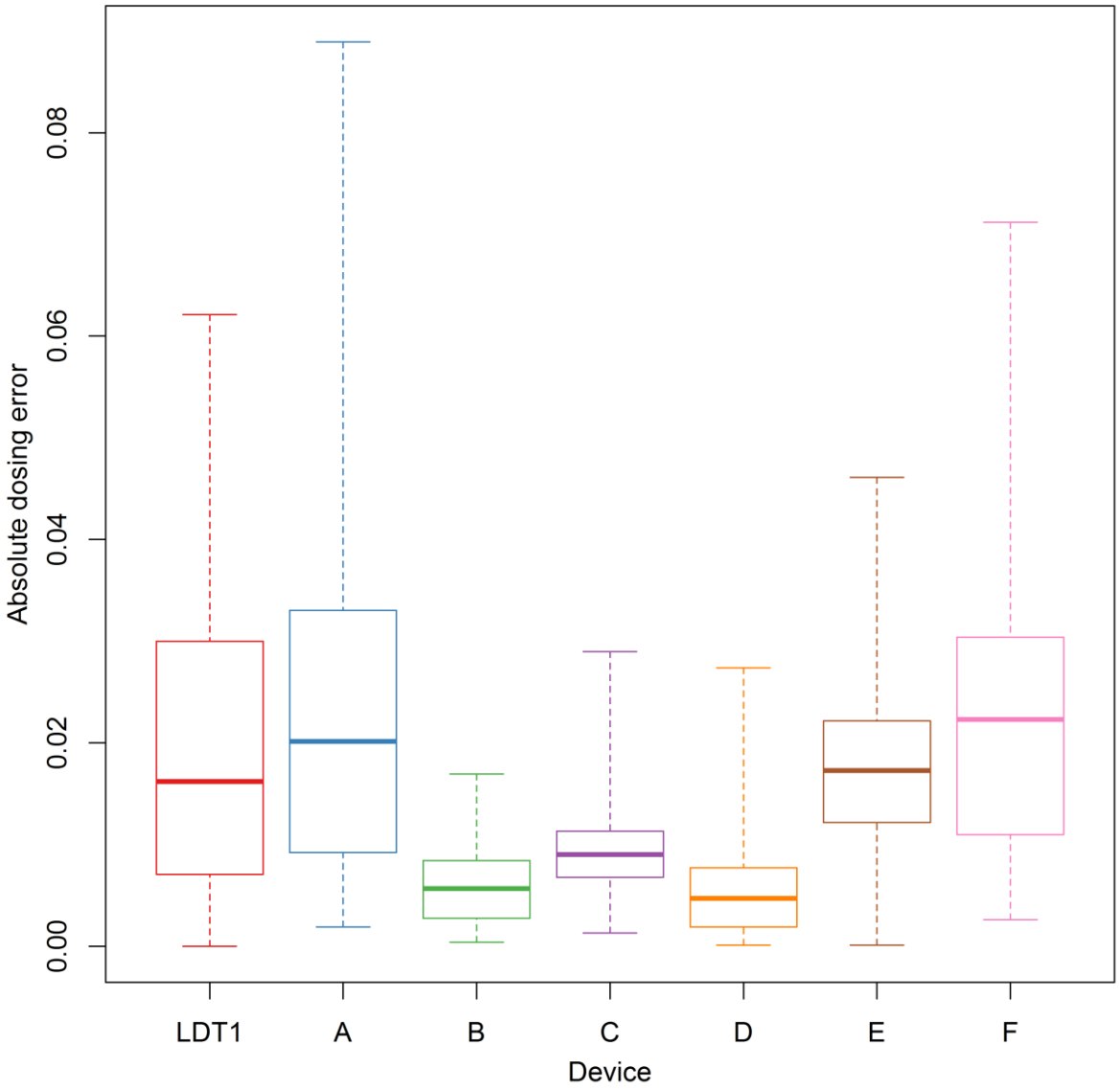

Figure 1: Box plots showing the distributions of absolute dosing errors. In each box the central line shows the median, the ends of the box show the first and third quartiles, and the whiskers show the minimum and maximum.

Figure 2, below, shows the difference between the mean absolute dosing error of LDT1 and that of each of the other devices, together with 95% confidence intervals. Points above the horizontal dashed line through zero indicate that LDT1 has a smaller mean absolute dosing error; points below the line indicate the opposite. For the standard ENFit device (A) and the reverse orientation devices (E and F) the confidence intervals cross zero, indicating that there is little evidence of a difference between these devices and LDT1 in terms of mean absolute dosing errors. For the standard orientation devices (B, C and D) the confidence is fully below zero, indicating strong evidence that these devices have smaller mean absolute dosing errors than LDT1.

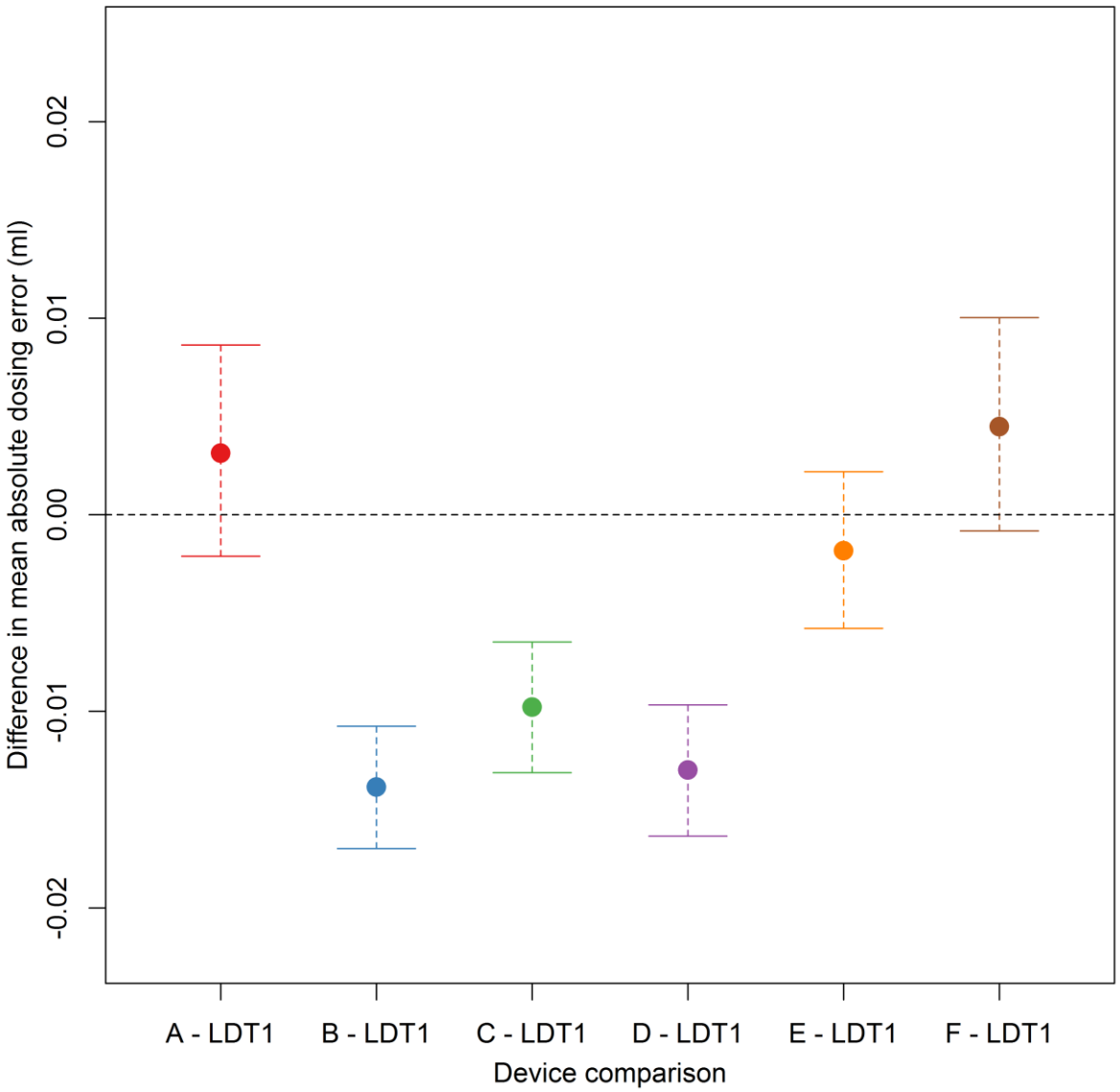

Figure 2: A comparison of the mean absolute dosing error in LDT1 versus the other devices. The dots give the differences in the mean absolute dosing errors and the bars give the 95% CIs.

Conclusion

In terms of the mean absolute dosing errors of the devices, we have found little evidence of a difference between LDT1 and any of the following devices: the standard ENFit device (A) and the reverse orientation devices (E and F). On the other hand, we have found strong evidence that the standard orientation devices (B, C and D) have smaller mean absolute dosing errors than LDT1.

In this analysis we have averaged the results across the three combinations of factors which have observations for every device. In our full report (VYG001, dated 3 March 2016) we also describe an analysis at a subgroup levels for each of factor combinations. In each subgroup analysis the results are consistent with the overall level results presented here.