EVIDENCE DOSSIER EXERCISE 3 – Work Harder

1. Context

 "Work Harder" (WH) is a new drug with the promise of improving concentration. The pharmaceutical company that is developing it needs to run a clinical trial to demonstrate its efficacy and safety before it can be marketed.

To show the required improvement in concentration, the trial will test people's ability to type quickly and accurately. Half of the subjects in the trial will be given WH, while the other half will have caffeine.

The typing test will require subjects to type the phrase "big fjords vex quick waltz nymph" (6 words, 27 letters), and the trial will record the percentage of subjects in each treatment group who correctly type this phrase in 20 seconds. This is an example of a *pangram*, which is a phrase or sentence that contains all 26 letters of the alphabet, and so requires the subjects to use all the keys on the main area of the keyboard.

The subjects will be adolescents (aged 11-16 years), because this is where the company hopes to market WH profitably. Subjects in the caffeine group will each get a cola drink containing 1mg of caffeine per kg of their body weight. Subjects in the WH group will have a caffeine-free cola drink to which the appropriate dose of WH has been added. (Subjects will therefore not be able to tell which treatment group they have been randomly allocated to.)

2. The Parameter of Interest

The true treatment difference is defined as: the percentage of subjects correctly typing the pangram in 20 seconds in the WH group *minus* the corresponding percentage in the caffeine group.

Note that the parameter is the *true* treatment difference (i.e. the difference in percentages that would be found if we were able to test millions of subjects in each group), *not* the difference that will be observed in the trial (i.e. using just tens or hundreds of subjects in each group). The observed difference in the trial will be subject to random variability between subjects, and so will only be an approximation to the true treatment difference.

3. Data

<u>An earlier trial in adults</u>
The company has already conducted a small trial of WH, to decide whether it was worth proceeding with this drug. This trial differed from the currently trial proposed in the following respects.
- The subjects were aged 18-65 years, and so adults rather than adolescents.
- A different pangram was used: subjects were asked to correctly type "the quick brown fox jumps over the lazy dog" (9 words, 35 letters) within 20 seconds.
- As the subjects were adults, the caffeine was administered in coffee rather than cola, but the dose level, 1mg/kg, was the same.

Results: They observed a 73% (16 out of 22 subjects) response rate for WH vs 63% (14 out of 22) for caffeine. This is an observed treatment difference of 10%.

<u>A quick test</u>
The company has also run a quick test asking a sample of adolescents to type the 6 word pangram after drinking a regular can of Diet Coke (containing 42mg of caffeine). The 31 subjects were recruited by a letter to company employees, asking for them to volunteer their children for this exercise. (Despite the request for adolescents, defined as being in the age range 11 to 16, one subject was found to be 17. The youngest was 12.)
Result: 14 (about 45%) of the 31 subjects correctly typed the phrase in 20 seconds.

<u>Unpublished study of a competitor's drug</u>
The company is aware of a trial conducted by a competing pharmaceutical company, which differed from the proposed trial of WH in the following respects.
- The competitor's drug, Focus-X, also claimed to increase concentration, but through a different clinical mechanism than WH.
- Subjects were asked to type, but instead of recording the percentage of whole pangrams correctly typed this trial recorded the percentage of *words* correctly typed.

Results: The competitor's full results are not available, but it is known that the observed treatment difference (Focus-X versus comparator) in adolescents on typing accuracy (as measured by percentage of correct words typed) was numerically greater than that observed in adults.

<u>Published data</u>
The following guidelines are based on a variety of sources.
- The average person is 92% accurate when typing.
- The average typing speed is about 39 words per minute (wpm).
- Across the sources studied, average speed for a child varied from 21 to 30 wpm and for an adult from 36 to 45 wpm. (Definitions of 'child' and 'adult' were not always given, and were not consistent when given.)

4. Judgement

The size of the true treatment difference is an important parameter in designing a clinical trial, and in particular helps to determine how many subjects are needed in order to give the trial a good chance of success. Although we have some useful evidence in this example, expert judgement is still needed to pull it together and assess the likely value for the parameter of interest.

- How robust is the data from the study in adults? With just 22 subjects per group, how far might the true difference in adults be from the observed 10%?
- Will adolescents type faster or slower than adults? Will they be more or less accurate? How useful is the "quick test" in answering these questions?
- Will the new pangram be harder to type because it has more unusual words or easier to type as it's shorter? How will the change in pangram affect the response rate for WH?
- If the success rate using caffeine in the new study is around 45%, whereas in the adult study it was about 63%, can we assume the success rate with WH will also be lower? How will the true treatment *difference* be affected – does 45% give more potential for improvement?
- To what extent is the finding in the Focus-X study, that there was a larger observed treatment difference in adolescents than in adults, relevant for the proposed trial of WH?