MA40198 Coursework

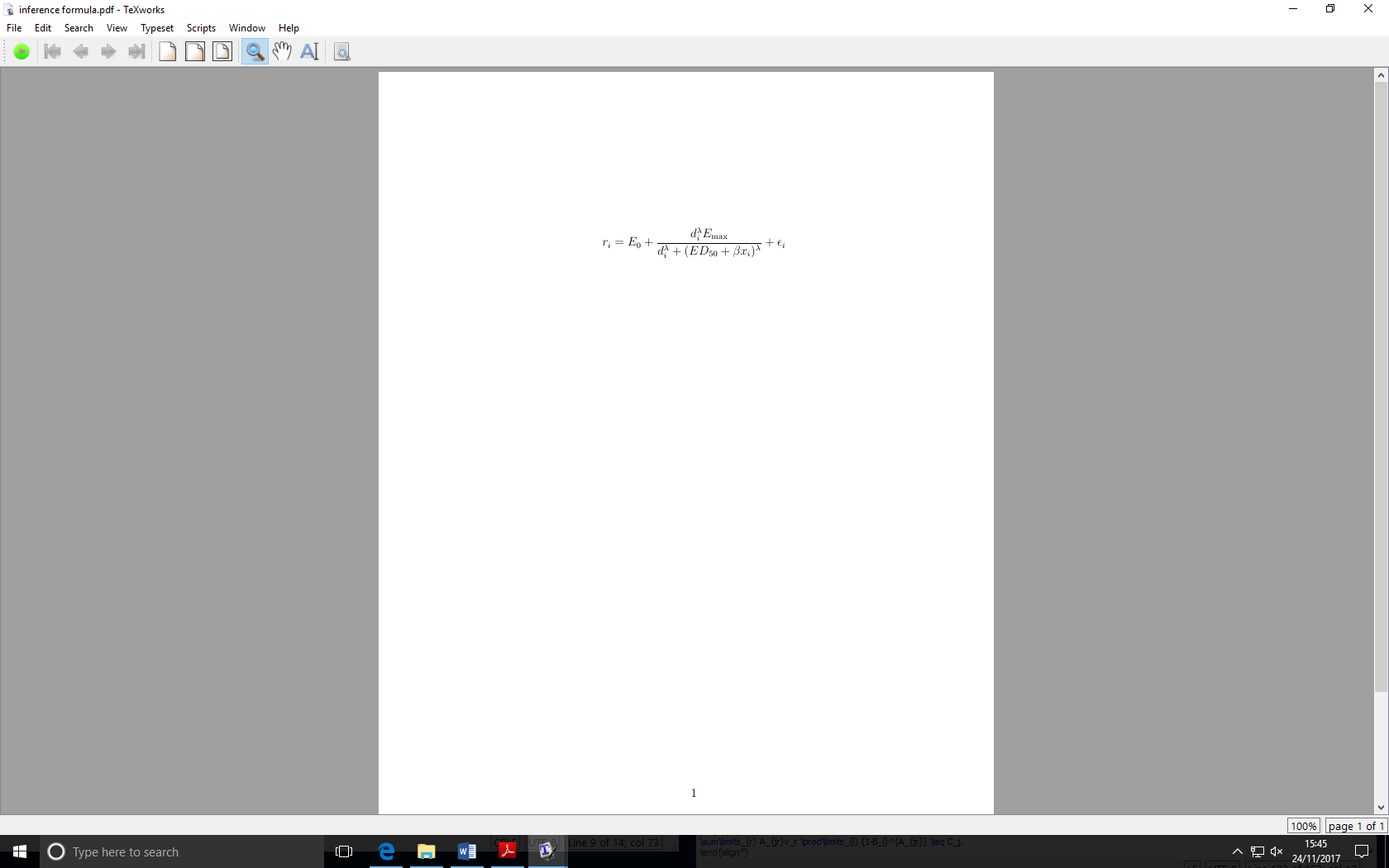
Introduction and Aim

This statistical report explores the capabilities of a new pharmaceutical treatment; primarily finding the maximum safe dosage of a treatment. The collated data is from a Phase one clinical trial where few patients (40 in total) are tested on and if deemed safe, the treatment will pass onto the next stage of the clinical trial. Three observations were measured in each of the patients: the dose received, the measured response of the dose and the presence of the biomarker.

The second part of this analysis is to study whether a certain biomarker, identified by clinicians, will raise the tolerance of the patient in response to the treatment. Therefore, the hypothesis test for this analysis is as follows: the null hypothesis is that the biomarker does not affect the tolerance of the patient to the treatment against the alternative hypothesis where the biomarker does affect the tolerance to the treatment.

The model considered

To model the response of the dose, we use the four parameter Emax model. This model is shown below:



Where the terms can be defined as follows:

ri := is the measure response for the dose for the ith patient

di := is the dose given to the ith patient

xi:= indicates whether the ith patient has the biomarker (given as 1) or not (given as 0)

E0:= this is the response when the drug is not given, sometimes given as the placebo effect the patient has when given the treatment in which the model adjusts for this.

λ:= is known as the slope factor defined as sensitivity measured to the dose of the treatment

ED50:= the dose of the treatment which is half of Emax

β:= measures the change in ED50  with the biomarker is present in the patient

εi:= is the error term for patient ith for εi~N(0,σ2)

It is worthy of note that the minimum expected value of our model is E0 which makes sense with our definition of E0, also the maximum value of our model is E0 + Emax and so we can find our Emax of our model.

Why is model suitable for what for this analysis? Firstly, this model adapts to the placebo effect, E0, therefore the model shifts around E0 meaning that this will not become a confounding factor. Secondly, the model accounts for the presence of the biomarker, denoted by xi, so it is possible to determine how and if the biomarker affects the patients’ tolerance to the treatment. Thirdly, the use of the slope factor coefficient, λ, accounts for the sensitivity to the dose of the treatment and is helpful to understand the relative differences between the levels of dosage given.

The function ll returns the log likelihood of the four parameter Emax model. An output is only calculated if ED50+beta1 is greater than zero else the output is -infinity. This makes sense as if this was not the case, ED50 is always positive (otherwise the patient would have a negative dose), meaning that if the beta1term was negative and the biomarker in the patient was present (x= 1), then if beta1\*x was greater than ED50 in absolute terms, then if lambda is 0.5 for instance then the model would have complex values which would not be useful! In physical terms, the patient would have an unlimited tolerance to the treatment which is not possible. Therefore the function would just return out which is defined as negative infinite.

The function pri returns the prior of our parameters where E0 has a normal distribution with mean 0 and standard deviation 10. Emax also has a normal distribution with mean 100 and standard deviation 10. ED50 has a beta distribution with shape parameters 2.5 and 5. Lambda has a uniform distribution between the interval 0.5 and 3. The standard deviation has a proposed truncated normal distribution with mean 3 and standard deviation 5. Finally beta has a normal distribution with mean 10 and standard deviation 4. Then we are returning the log likelihood of our proposed distribution making sure ED50+beta1 is greater than zero.

<http://www.math.chalmers.se/~rootzen/finrisk/reportwriting0315.pdf> : for how to write a report

<https://www.wikihow.com/Write-a-Statistical-Report>

<http://file.zums.ac.ir/ebook/75-Dose%20Finding%20in%20Drug%20Development%20(Statistics%20for%20Biology%20and%20Health)-Naitee%20Ting-0387290745-Sp.pdf>