Big data and big pharma - mining the wealth of data held by GSK from respiratory clinical trials to uncover potential new uses for medicines

Introduction

To get any medicine to market, a pharmaceutical company must first test that medicine in the lab and then in humans, through clinical trials. Firstly to make sure it is safe and secondly to make sure it is efficacious.

GlaxoSmithKline (GSK) is one of the biggest pharmaceutical companies in the world and a leader in respiratory and infectious disease medications. They have carried out years of clinical trials and with clinical trials comes data collection.

The largest trials can include over 1000 patients who have many different measurements taken during the trial. The investigators are looking for a particular effect, for example a reduction in exacerbations of asthma attacks in a respiratory trial. The trial is split into different arms (typically 2-4) with each arm having a different dosing level (from placebo to a high concentration of the medicine being tested). But what if the medicine was affecting something else as well? What if there were another condition that the medicine was reducing or curing but that wasn't seen because it wasn't looked for?

This paper investigates the glucose measurements taken from patients in several GSK late stage or Phase 3 clinical trials. Glucose is of potential interest to GSK because if any trend of glucose reduction is seen it could indicate that the medicine may have potential as a cure for diabetes. It's expected that glucose will remain consistent for all patients on a trial regardless of whether they are given a placebo or the medicine. But there may be hidden trends in the glucose data that were not spotted because that's not what the investigators were looking for.

The most famous medicine that was discovered in this way is the blockbuster Viagra - it was on trial as a heart medication and what it's used for now was merely a side effect that was reported by the participants.

The dataset - creating a manageable dataframe for analysis

The GSK RDIP (research and development information platform)

In the last year, the Data Science Centre of Excellence at GSK has built a repository of many different data that exists across the company. This has been stored on a cloud platform called RDIP.

There are several databases housed on RDIP but the ones of interest for this project are the clinical trial test results (lb) and the demographic (dm) database. The former is the lab results collected from all trials conducted over the past 10 years and the latter is demographic data on each patient who has taken part in a GSK trial.

database	Table name
clntrl_e	t_anon_int_sdtm_dm_21jul2017
clntrl_e	t_anon_int_sdtm_ds_25sep2017
clntrl_e	t_anon_int_sdtm_dv_25sepl2017
clntrl_e	t_anon_int_sdtm_lb_25sep2017

The top of the list of the databases on the RDIP platform at GSK

Examining the data

As the data sits on RDIP, it's necessary to pull from the tables into R to conduct analysis. But it's important to make sure only the relevant data is pulled as the tables are huge and not all the data within them will be needed.

Size: A few SQL queries were run to get a feel for the size of these tables. There are 86,925 rows in the dm table, one for each patient. The lb table is huge, containing nearly 2.5million rows. Filtering on glucose shows just 92,585 rows which is easier to deal with so only glucose rows were pulled into R to create a dataframe to work with. A quick examination shows that glucose tests were conducted on both blood and urine samples. Urine should never contain glucose and it's only glucose tests on serum that are of interest so the dataset was refined further to filter out these results, leaving 71, 943 rows.

Variables of interest

A quick look at the lb table shows there are 97 variables. Of these, only 16 are actually required:

Studyid (the unique study identifier), usubjid (subject ID, unique patient identifier), lbdy (lab day in the trial that the test was conducted), lbdtc (lab day time code), visit (identifies which number visit this was), lbtest (what is being tested, in this case all Glucose), lbspec (how was the test done - in this case all Serum), lborres (result of the test), lborresu (units of the test), lbstresn (lab result in standard units), lbstresu (standard units for lab result), lbstnrlo (lower value of aveage glucose tests), lbstnrhi (higher value of glucose test), so_therapy_area (therapry area of the trial), so_indications (disease medicine is targeting), so_study_phase (stage of the study from Phase 1 to phase 3), so_abbreviated_title (study title).

The lbdy measures the day within the trial that the glucose test was conducted and the first day of dosing is lbdy = 1 (there is no day zero). Patients will routinely attend the clinic and have a glucose test before the trial begins (negative lbdy) and after they have finished taking the medicine (large lbdy). Therefore, to get a really accurate picture of whether the medicine is affecting glucose, it will be necessary to identify the date that the patient started the dosing and ended the dosing and pull the two glucose results for those days from the data set.

This is the information in the dm data table which is why it's needed - it contains the time code for the patient receiving their first dose of the medicine (rfxstdtc) and the last (rfxendtc) so can identify which lbdy was their first and last day.

The lbstrens is used for the glucose results as these are all in the same units.

A quick look at both lbdy and lbstrens shows that there are outliers and strangely large or small results that will need to be filtered out.

Summary of lbdy

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-3.403e+38	-6.000e+00	5.800e+01	-1.605e+37	1.650e+02	4.480e+02

Summary of lbstresn

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-3.403e+38	5.000e+00	5.000e+00	-7.095e+34	6.000e+00	2.160e+02

Initial data wrangling - identifying three trials to look at in detail

GSK is most interested in analysing Phase 3 trials - these later stage trials have a lot more patients so there's more chance of identifying any trend.

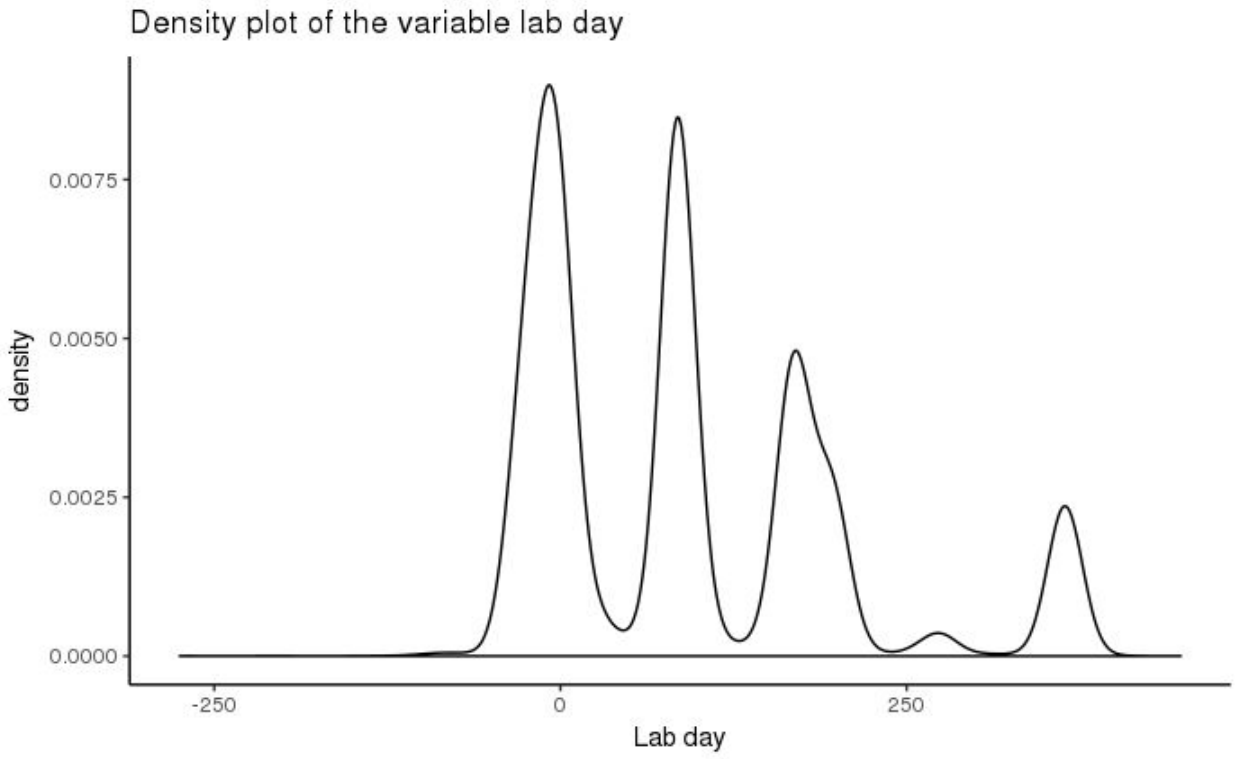
Therefore the first step was to take a look at the types of trials in the dataset:

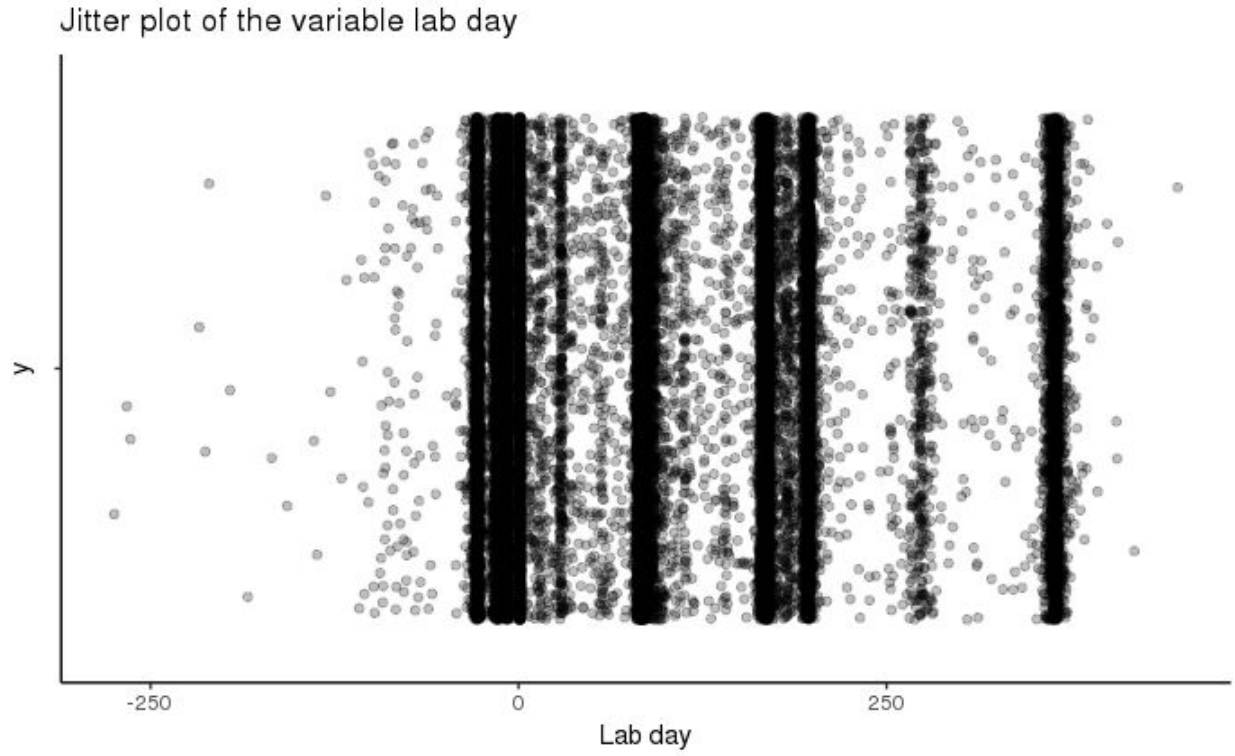
	so_therapy_area	so_indications	so_study_phase	n
1	Respiratory	Asthma	PHASE I	175
2	Respiratory	Asthma	PHASE IIA	157
3	Respiratory	Asthma	PHASE IIB	690
4	Respiratory	Asthma	PHASE IIIA	1663
5	Respiratory	Asthma	PHASE IIIB	792
6	Respiratory	Cystic Fibrosis	PHASE IIA	146
7	Respiratory	Dermatitis, Atopic	PHASE I	20
8	Respiratory	Dermatitis, Atopic	PHASE IIA	25
9	Respiratory	Lung Injury, Acute	PHASE I	3
10	Respiratory	Pulmonary Disease, Chronic Obstructive	PHASE I	416
11	Respiratory	Pulmonary Disease, Chronic Obstructive	PHASE IIA	265
12	Respiratory	Pulmonary Disease, Chronic Obstructive	PHASE IIIA	13029
13	Respiratory	Pulmonary Disease, Chronic Obstructive	PHASE IIIB	808

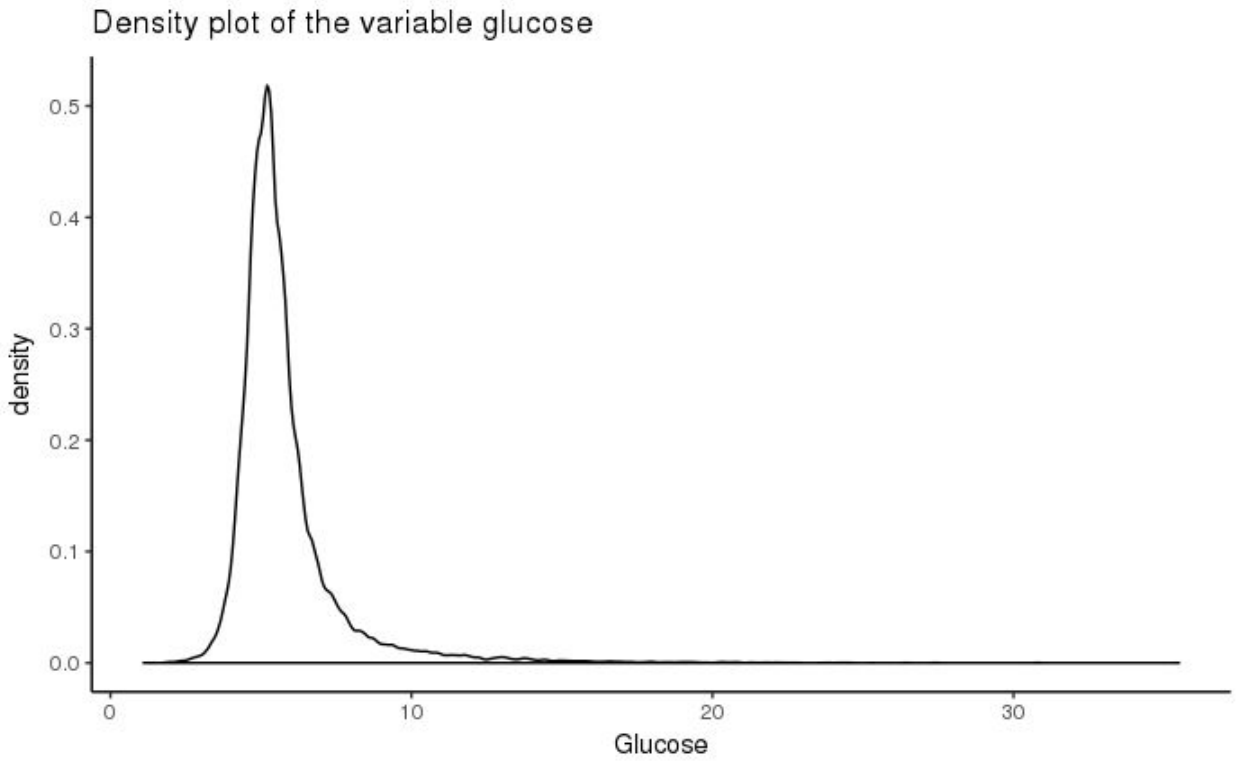
Next, all but the phase 3 trials (PHASE IIIA and PHASE IIIB) were filtered out. GSK is also not interested in analysis on mixed dosing trials in this project, where each patient is given three different medicines, just in a different order (so ABC or BCA or CAB etc). To figure out if a trial is

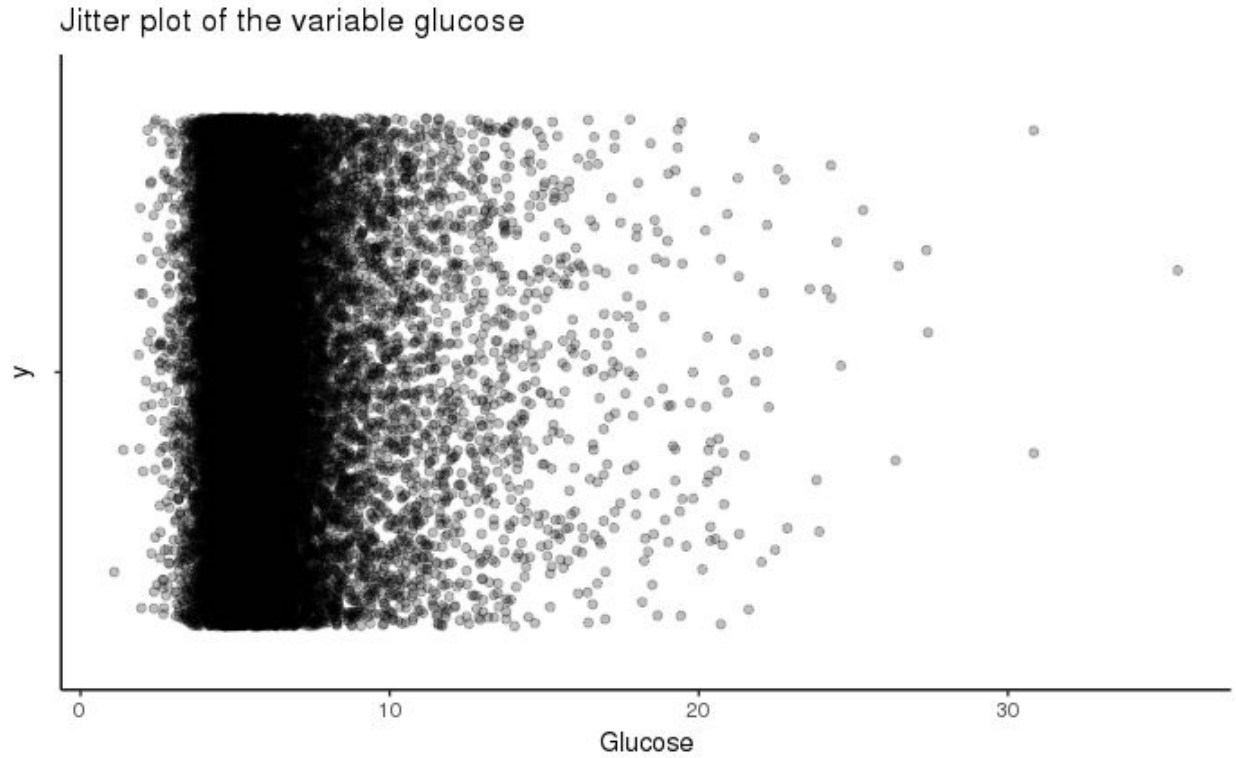
mixed dosing, the studyid had to be crossed checked against the full trial documentation on clinicaltrials.gov. Each study has a unique identifier and the website allows a user to search for the title and a few details on any study. Using the identifiers and the company name GSK, each trial was searched on the website. One of the pieces of information is whether the trial was mixed or parallel (where patients get just one medicine dosage in the trial) so the mixed ones can easily be identified and removed.

Once this is done, there are 14 trials left. The demographic data is joined on to those trials for statistical analysis later. The large and small values for lbdy and lbstren are filtered out and the data is visualised to check it looks reasonable (jitter and density plots).
For the lab days, it's expected to see several peaks as a patient will attend a trial 4-5 times. There will be a peak around zero for the first day they went and then several others that are regularly spaced out. A trial can last more than a year so it's possible to see peaks up to day 365.
For glucose, most of the data should be concentrated between zero and ten, the standard normal range. There may be some larger figures for patients who have high glucose due to other factors but not too many.


Density plot of the variable lab day
density
0.0075
0.0050
0.0025
0.0000
-250
0
250
Lab day


Jitter plot of the variable lab day
y
-250
0
250
Lab day





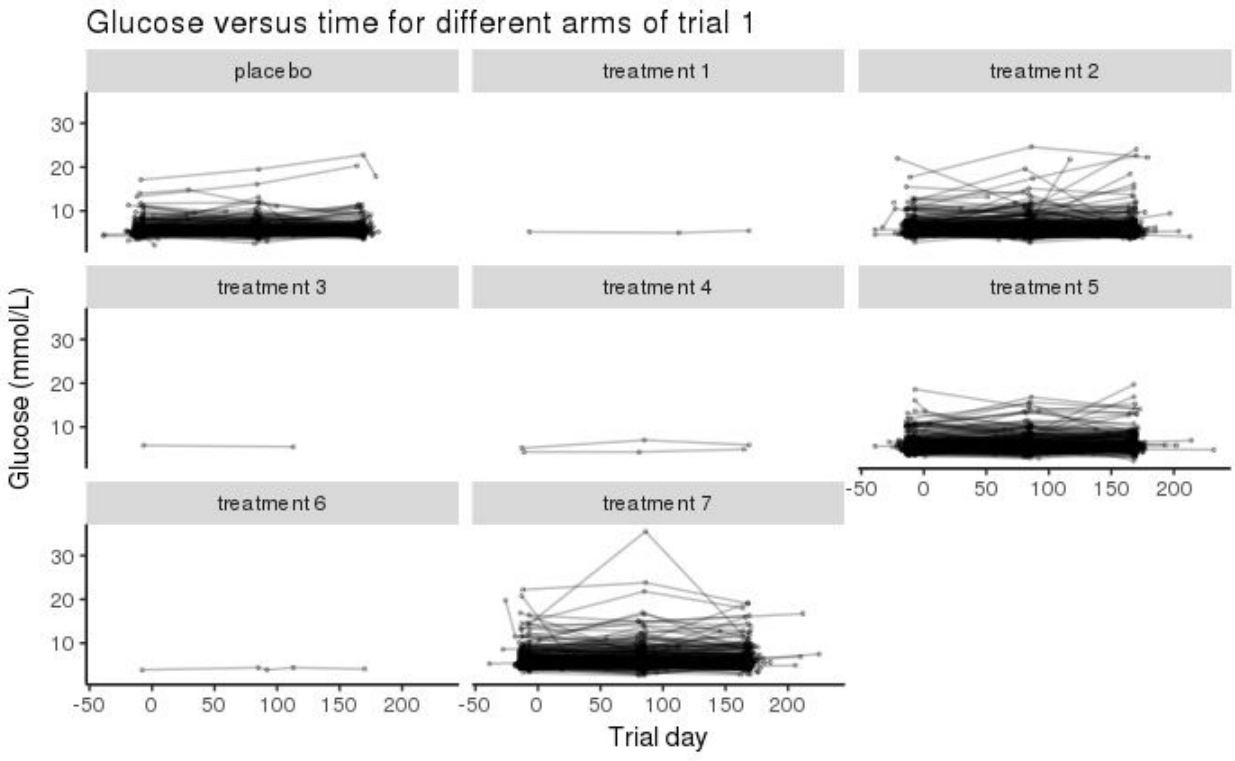
Analysis of glucose levels in the trials

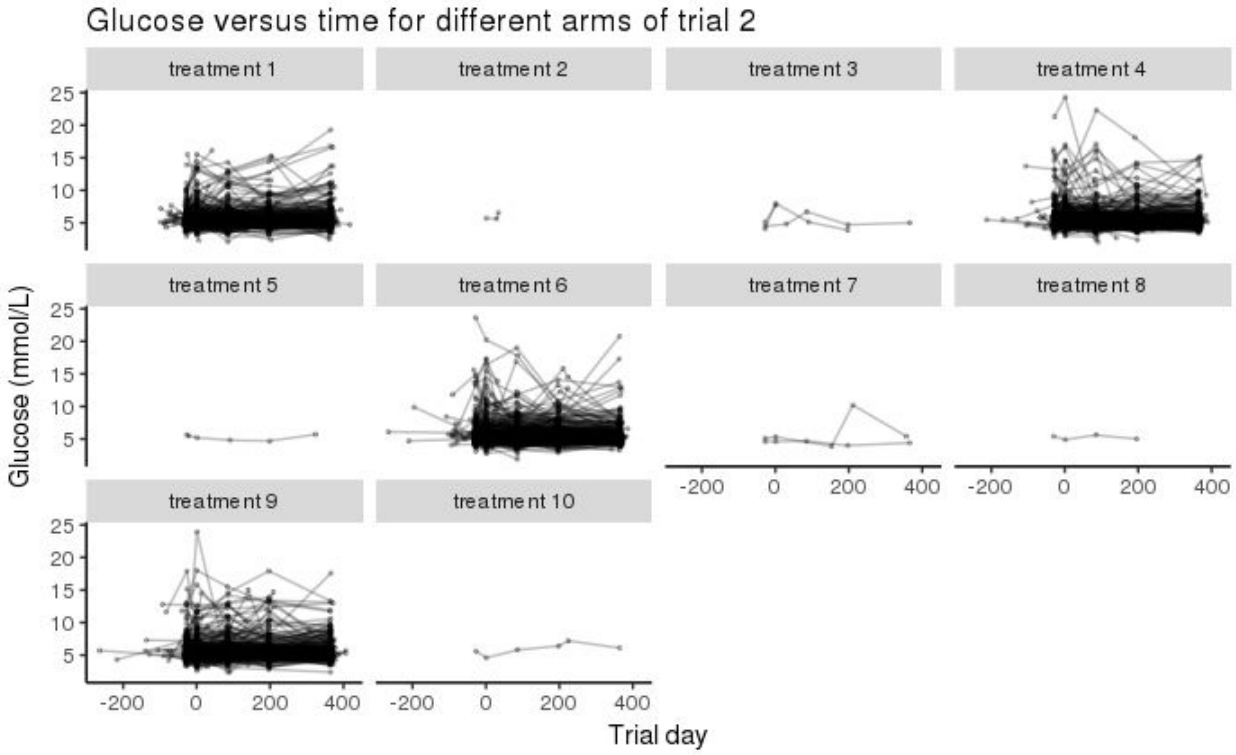
The three trials with the most patients were selected for further examination of glucose levels:

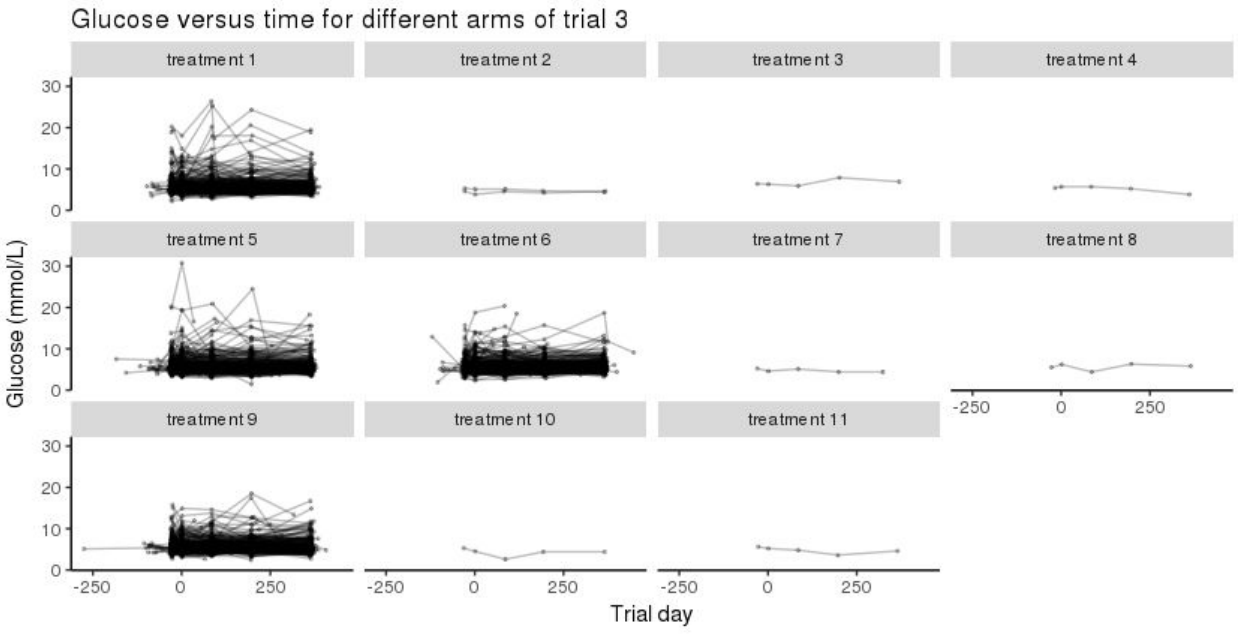
Therapy Area	Indication	Phase	No of patients
Respiratory	Chronic Obstrucitve Pulmonary Disease	Phase IIIA	1532
Respiratory	Chronic Obstrucitve Pulmonary Disease	Phase IIIA	1633
Respiratory	Chronic Obstrucitve Pulmonary Disease	Phase IIIA	1622

These trials are all in the same disease area and indication but are testing different medicines (these cannot be identified in this project). They were carried out in different geographies and with different patients.

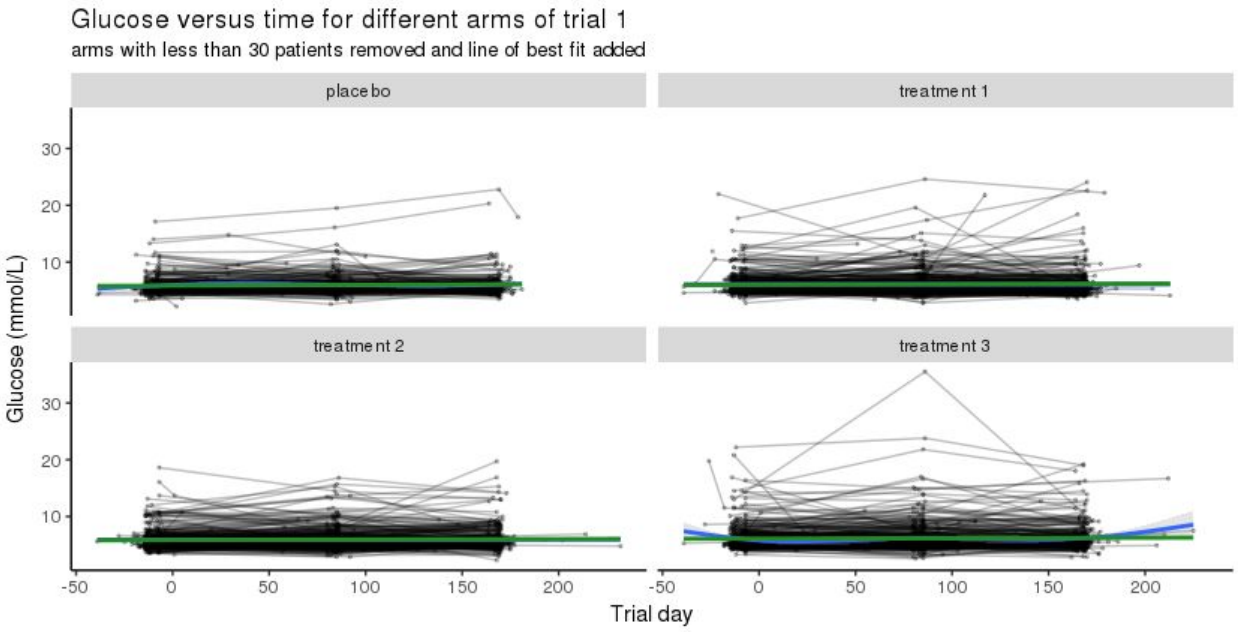
Initial plots were made of these three trials. The variable actarm was used to split the data into separate plots. Actarm is the arm of the trial the patient was assigned to. In one arm, a patient receives a certain dosage of the medicine on trial or the placebo. Pharma companies do this so they can test different concentrations to see if an increased dose has a better effect. There should be no change in glucose in patients who are on the placebo. The data is split this way so it will be clear if there's one particular dose that is affecting glucose. The actarm labels have been replaced with blind treatment labels.

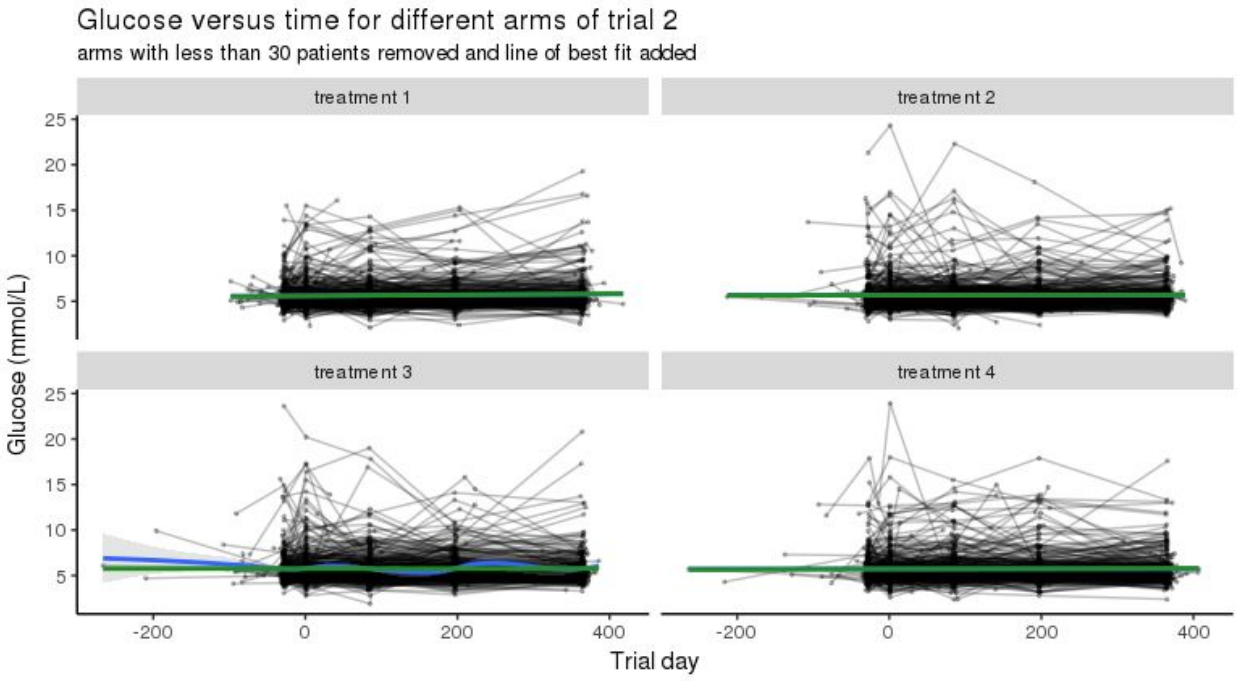


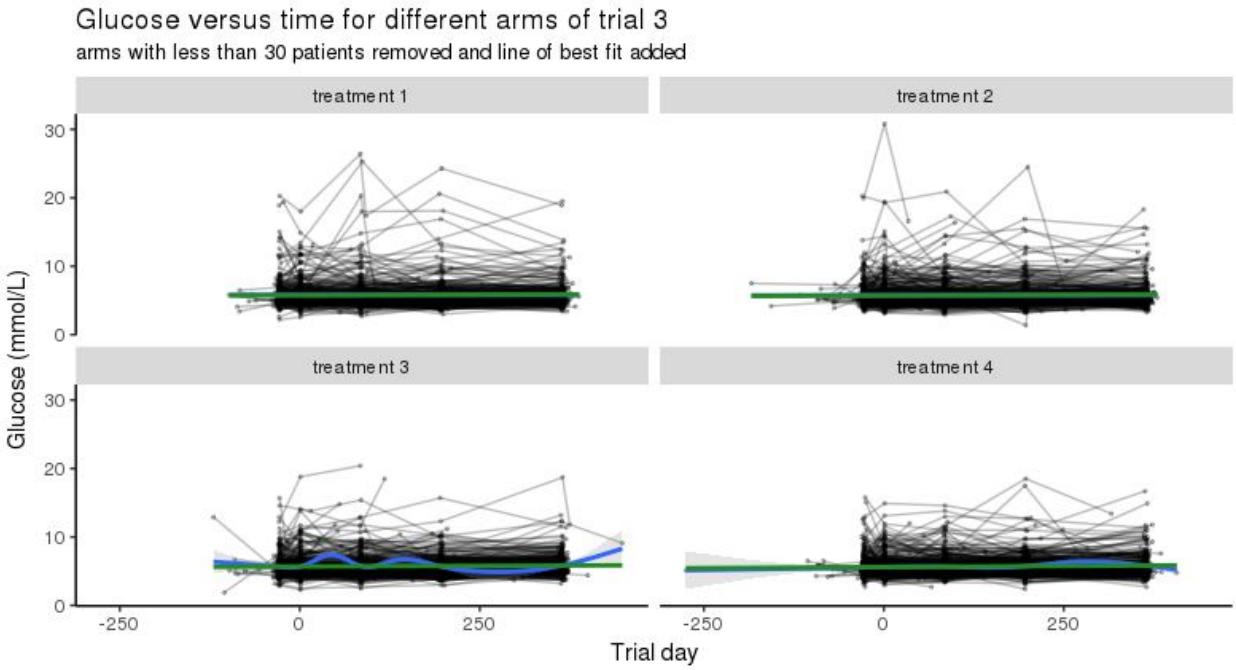




From the initial plots it's clear there are some arms of the trials that only have one patient. These will not be useful for modelling so are removed. A crude linear model is also added to the remaining plots to see if it looks like there are any trends in the glucose levels.


Glucose versus time for different arms of trial 1
arms with less than 30 patients removed and line of best fit added
placebo
treatment 1
treatment 2
treatment 3
Glucose (mmol/L)
Trial day


Glucose versus time for different arms of trial 2
arms with less than 30 patients removed and line of best fit added
treatment 1
treatment 2
treatment 3
treatment 4
Glucose (mmol/L)
Trial day



These crude models seem to show there is nothing strange happening with the glucose but models are created for these trials to check.

Mixed effects linear modelling

This type of modelling was recommended by the director of data science at GSK. A mixed effect linear model allows for random as well as fixed effects on the variable of interest whereas a standard linear model only allows for fixed effects.

In this data set, each arm of the trial is a subset of patients. Not every patient has been in each arm of the trial which means the way the patients have been split up is a random effect. Patients also didn't have their glucose taken on exactly the same day, also a random effect.

The model allows for these random effects and the variance that may be happening because of them (for example, there may be an unusual amount of people with naturally high glucose in one arm of the trial) to be taken into account.

The summaries of the three models are shown below:

```
Linear mixed-effects model fit by REML
 Data: Trial1A
       AIC      BIC    logLik
  16868.24 16931.89 -8424.119

Random effects:
 Formula: ~1 | usubjid
        (Intercept) Residual
StdDev:    1.679846  1.23485

Fixed effects: lbstresn ~ lbdy + actarm + lbdy:actarm
                               Value  Std.Error   DF  t-value p-value
(Intercept)                 5.860045 0.11867186 2772 49.38024  0.0000
lbdy                        0.000797 0.00064896 2772  1.22782  0.2196
actarmUMEC 62.5             0.157112 0.15345081 1523  1.02386  0.3061
actarmUMEC/VI 62.5/25      -0.000034 0.15368099 1523 -0.00022  0.9998
actarmVI 25                 0.244164 0.15299698 1523  1.59588  0.1107
lbdy:actarmUMEC 62.5        0.000109 0.00083203 2772  0.13149  0.8954
lbdy:actarmUMEC/VI 62.5/25 -0.000019 0.00082600 2772 -0.02277  0.9818
lbdy:actarmVI 25           -0.000209 0.00082991 2772 -0.25189  0.8011
 Correlation:
                           (Intr) lbdy   aUMEC62 aUMEC/6 acVI25 l:UMEC62 l:UMEC/6
lbdy                       -0.369
actarmUMEC 62.5            -0.773  0.285
actarmUMEC/VI 62.5/25      -0.772  0.285  0.597
actarmVI 25                -0.776  0.286  0.600   0.599
lbdy:actarmUMEC 62.5        0.288 -0.780 -0.369  -0.222  -0.223
lbdy:actarmUMEC/VI 62.5/25  0.290 -0.786 -0.224  -0.371  -0.225  0.613
lbdy:actarmVI 25            0.289 -0.782 -0.223  -0.223  -0.370  0.610    0.614

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-6.26040330 -0.35648115 -0.07097604  0.22262025 14.67328191

Number of Observations: 4303
Number of Groups: 1527
```

```
Linear mixed-effects model fit by REML
 Data: Trial2A
       AIC      BIC    logLik
  26380.86 26450.18 -13180.43

Random effects:
 Formula: ~1 | usubjid
        (Intercept) Residual
StdDev:    1.359359 1.098172

Fixed effects: lbstresn ~ lbdy + actarm + lbdy:actarm
                            Value  Std.Error   DF  t-value p-value
(Intercept)              5.594588 0.07534142 5948 74.25647  0.0000
lbdy                     0.000622 0.00019083 5948  3.25802  0.0011
actarmFF/VI 200/25       0.060449 0.10596900 1620  0.57044  0.5685
actarmFF/VI 50/25        0.156012 0.10581065 1620  1.47444  0.1406
actarmVI 25              0.096673 0.10597413 1620  0.91223  0.3618
lbdy:actarmFF/VI 200/25 -0.000627 0.00026713 5948 -2.34896  0.0189
lbdy:actarmFF/VI 50/25  -0.000626 0.00026730 5948 -2.34044  0.0193
lbdy:actarmVI 25        -0.000412 0.00027036 5948 -1.52550  0.1272
 Correlation:
                        (Intr) lbdy   aFF/V2 aFF/V5 acVI25 l:FF/2 l:FF/5
lbdy                    -0.254
actarmFF/VI 200/25      -0.711  0.180
actarmFF/VI 50/25       -0.712  0.181  0.506
actarmVI 25             -0.711  0.180  0.505  0.506
lbdy:actarmFF/VI 200/25  0.181 -0.714 -0.255 -0.129 -0.129
lbdy:actarmFF/VI 50/25   0.181 -0.714 -0.129 -0.251 -0.129  0.510
lbdy:actarmVI 25         0.179 -0.706 -0.127 -0.127 -0.252  0.504  0.504

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-8.0654330 -0.3787987 -0.0735543  0.2569946 11.5295104

Number of Observations: 7576
Number of Groups: 1624
```

```
Linear mixed-effects model fit by REML
 Data: Trial3A
       AIC      BIC   logLik
  26602.79 26672.13 -13291.4

Random effects:
 Formula: ~1 | usubjid
        (Intercept) Residual
StdDev:    1.459194 1.096653

Fixed effects: lbstresn ~ lbdy + actarm + lbdy:actarm
                            Value  Std.Error   DF  t-value p-value
(Intercept)              5.767015 0.07991961 5973 72.16020  0.0000
lbdy                     0.000274 0.00018703 5973  1.46597  0.1427
actarmFF/VI 200/25      -0.049152 0.11277208 1610 -0.43585  0.6630
actarmFF/VI 50/25       -0.083182 0.11253593 1610 -0.73916  0.4599
actarmVI 25             -0.159183 0.11244271 1610 -1.41568  0.1571
lbdy:actarmFF/VI 200/25  0.000170 0.00026478 5973  0.64021  0.5221
lbdy:actarmFF/VI 50/25   0.000233 0.00026365 5973  0.88413  0.3767
lbdy:actarmVI 25         0.000253 0.00026560 5973  0.95245  0.3409
 Correlation:
                        (Intr) lbdy   aFF/V2 aFF/V5 acVI25 l:FF/2 l:FF/5
lbdy                    -0.244
actarmFF/VI 200/25      -0.709  0.173
actarmFF/VI 50/25       -0.710  0.173  0.503
actarmVI 25             -0.711  0.173  0.504  0.505
lbdy:actarmFF/VI 200/25  0.172 -0.706 -0.242 -0.122 -0.122
lbdy:actarmFF/VI 50/25   0.173 -0.709 -0.123 -0.244 -0.123  0.501
lbdy:actarmVI 25         0.172 -0.704 -0.122 -0.122 -0.241  0.497  0.500

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-7.01435721 -0.37454169 -0.06663456  0.25715937 11.90392058

Number of Observations: 7591
Number of Groups: 1614
```

It's clear from the intercepts and also the p values that there is no difference in glucose through the trials.

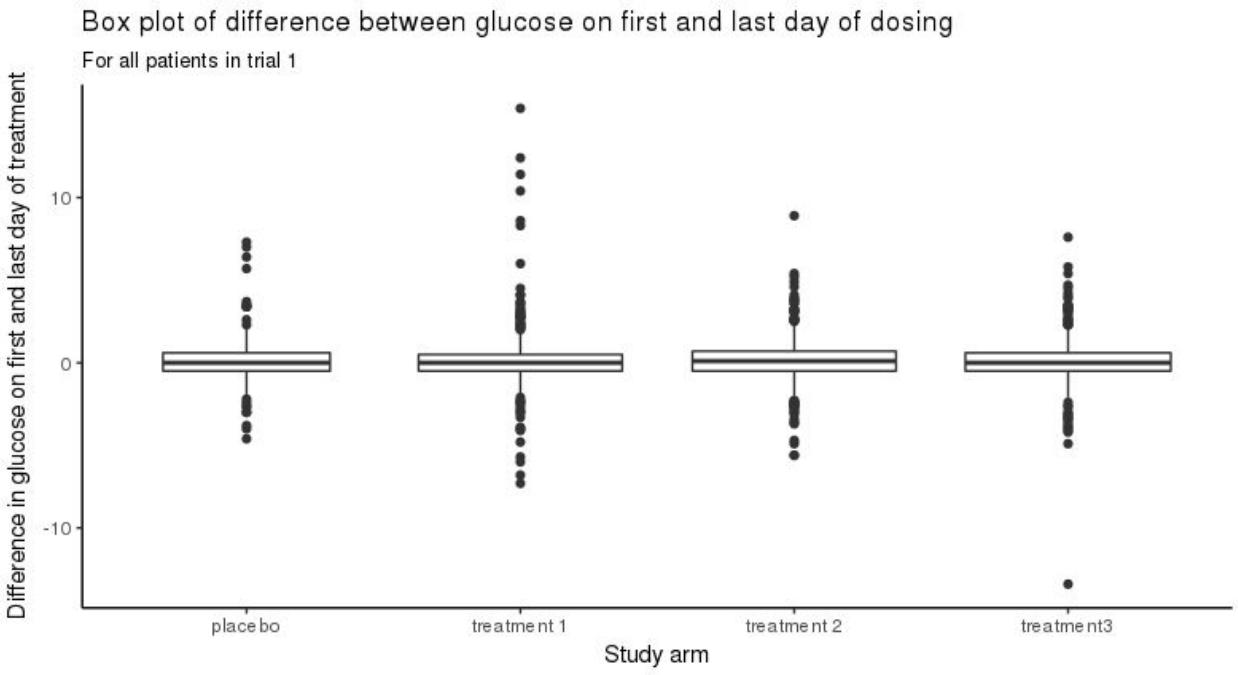
Detailed statistical examination of one trial

As well as using the model above, GSK asked for one trial to be examined statistically, looking at the absolute differences in glucose values for patients on the first and last days of dosing. This was why the dm data was added to the dataset. The first trial was chosen.

The first dose was identified by pulling the glucose result for the lbdy that was closest to zero. The mean glucose was assigned to any patients where there were two tests done on the same lbdy.

The last dose was identified by subtracting the first dose date (rfxendtc) from the last dose date (rfxstdtc) to calculate which lbdy the last dose was given. Then the glucose result for that lbdy was pulled out.

The differences between these first and last glucose measures were taken for all patients and examined:



This box plot shows that the majority of the differences were near zero.

A further numerical analysis of the differences in glucose on first and last day of dosing for all arms of the trial was performed as well:

actarm	No of patients	Mean of differences	SD of differences	Median of differences
PLACEBO	279	0.08956833	1.347520	0.0000000
UMEC 62.5	416	0.17142856	1.947642	0.0000000
UMEC/VI 62.5/25	413	0.15496368	1.448704	0.0999999
VI 25	421	0.06380953	1.530213	0.0000000

This statistical analysis also shows that the differences were mostly near to zero, showing that nothing interesting is happening to glucose in any arm of the trial.

Conclusions and further work

It's clear that there was no hidden trend in the glucose levels of the patients in these three trials.

However there are 61 other trials in the dataset that could be examined through applying the code developed for this report.

There are also other tests, not just glucose, that could be examined.

It may also be interesting to split the data using demographics - age, sex, race - and see if there are changes to glucose in those smaller subsets that are masked in these larger cuts of the data.

This work would not have been possible without the constant support of Tilo Blenk, director of data science at GSK who was always ready to go through lines of code to help refine it and to explain new concepts like SQL and mixed effects linear models.