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Allergy Related Clinical Prescribing Alerts (ARCPA): Description and Impact

By

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31st August 2021

A Dissertation submitted in part fulfilment of the MSc Data Science for Research in Health and Biomedicine

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Abstract

Aim of study
The primary aim of the study is to explore and analyse a retrospective electronic healthcare records (EHR) dataset in order to quantify the impact of allergy and intolerance alerts (warning status).

Data sources
The data was provided following approval from University College London Hospitals NH Foundation Trust (UCLH) and was an extract of anonymised patient data from the Epic EHR platform taken from between June 2019 and March 2021. The dataset consisted of 35 variables pertaining to potential patient allergies and intolerance alert warnings, prescriber and patient characteristics, along-with details of importance, severity, warning types and drug-allergy interactions.

Methods
A descriptive analysis was carried out on the total dataset (n=53,057) for counts and percentages and then for a select data-frame (n=43,119) of variables focusing on overridden (n=32,520) and removed (n=10,599) entries. This data-frame included provider type, provider speciality, description, context, drug-allergy reactions, drug-allergy contraindication group, importance level, severity, along-with the patients' sex and age variables. This was followed by unadjusted and adjusted logistic regression analysis with results presented as odds ratios, 95% confidence intervals and p values.

Results
Prescriber overrides were significantly associated with provider type, provider speciality, description, context, drug-allergy reactions, drug-allergy contraindication group, importance level, severity, along-with the patients' sex and age. There were fewer overrides in males (adjOR1.07 [1.01-1.14], p=0.026) and allergies (adjOR 0.88 [0.82-0.94], p<0.001) were 12% less likely to be overridden than 'Adverse Reactions/Drug Intolerances', while, 'Drug Class Match' (adjOR 0.50 [0.35-0.72], p<0.001) and 'Ingredient Match' (adjOR 0.26 [0.18-0.37], p<0.001) were less likely to be associated with an override as compared to cross-sensitive matches. Registrars and pharmacists were the most likely to override, while steroids/corticosteroids, immunoglobulins and opioids were between ~3.5 and ~5 times more likely to be overridden than antibiotics prescriptions.

Conclusion
This study quantified the impact of overall allergy and intolerance alerts contained in an anonymised data extract obtained from the UCLH EHR system and presented and analysis of factors associated with warning overrides (alerts were not adhered to) versus warning removals (alerts were effective and adhered to) at point of prescribing. Overrides are more likely for registrars and pharmacists, while override reasons indicated that in >21% of overrides the prescribers considered the warning to be either inaccurate or did not apply to the patient. However, due to the complexity of prescriber and patient interaction, a definitive recommendation for alert optimisation is not possible with this study.

Keywords: prescribing, allergy, intolerance, adverse reactions, alert fatigue

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1.0 Introduction

1.1 Background and study rationale

Allergies can have a number of causes such as heredity factors, mineral deficiencies, food related allergies and in the case of this study those pertaining to drug prescribing ("Anaphylaxis Campaign," 2020). For instance, hospital admissions in the United Kingdom (UK) for allergies in patients of 19 years and older have been rising since at least 2013, with 12,834 admissions in 2013-2014 to 27,172 admissions in the 2019-2020 year ("Anaphylaxis Campaign," 2020). With potentially the most serious type of allergic response, anaphylaxis accounting for 3,092 reactions in 2013-2014 and 4,756 reactions in 2019-2020, equating to a 34.99% rise in cases in that period ("Anaphylaxis Campaign," 2020). Anaphylaxis is described as a 'severe and often sudden allergic reaction' that can be immediately apparent or be a reaction delayed by several hours ("Anaphylaxis Campaign," 2020)(Nasser, 2015).

Globally, allergic responses to medications is a growing concern (Légat et al., 2018), which can result in adverse outcomes of differing levels of severity for patients and if undetected at point of prescription, increase patient risk and potentially increase hospital work-loads (Goss et al., 2013). According to the National Institute for Health and Care Excellence (NICE), drug-allergy reactions for hospital inpatients between 1998 and 2005 led to longer hospital stays for up to 15% of patients (NICE, 2014a), with a reported incidence of 3.2% in 2007 (NICE, 2014b). For comparison, total hospitalisations in a Singapore based hospital due to drug-allergy response, were reported to be as high as 4.2 per 1000 (Thong et al., 2003).

With clinical decision support systems becoming more common in clinical settings as hospitals modernise data management structures to improve overall efficiency and safety, there is an increased ability to carry out drug-allergy interaction monitoring (Jani et al., 2011). When prescribing medications, these clinical decision support systems are designed to raise alert warnings for patients with pre-existing allergies or intolerances at the point of prescribing in order to improve patient care and reduce the need for prescribers to assess paper notes (Nanji et al., 2018). These automated alerts are raised in all cases where drug-allergy interactions might occur (Nanji et al., 2018). In most cases, when risk factors are explored, a patient's negative reaction to a prescription is not allergic, but rather an intolerance where a patient has difficultly digesting or metabolising a drug (Blumenthal et al., 2019). A drug intolerance refers to a 'pseudo-allergic' reaction which can lead to a confusion between intolerance and an actual allergic reaction resulting in the possibility of misclassification of a drug intolerance as an allergic reaction to a drug (NICE, 2014c).

The alert warnings generated by such clinical decision support systems are based on standard protocols which may not be applicable to all patients (Jani and Franklin, 2021). Thus, these systems allow for prescribers to exercise their clinical judgment when assessing relative risk-benefit for individual patients, to override inappropriate alert warnings. A number of factors may influence override decisions by prescribers. In addition to drug allergies, alert warnings also flag potential patient intolerance to medications that may result in nausea, vomiting, gastrointestinal distress; overrides have been reported to be more likely in these circumstances, possibly because the expected benefits of the medication are considered to outweigh such intolerance symptoms (Topaz et al., 2016).

Contextual factors may also be associated with override decisions and it has been reported that overrides differ between hospital inpatients (50% to >90%) and outpatients (33% to >90%) with more overrides occurring for the former (Nanji et al., 2018). Prescribers may also take in to account factors like cross-sensitivity when reviewing alert warnings. Cross-sensitivity between the drug and allergen class is based on either a specific prescribed medication or with the chemical composition common across a number of medications (Topaz et al., 2016). Cross-sensitive class matches are those which relate to patients with allergies or intolerance to drugs with similar chemical structures; drug class matches relating to allergy warnings are raised for drugs in the same drug class as the drug a patient has an allergic or intolerance reaction to; and ingredient matches relate to patients with allergic reactions or intolerance to a drug that is prescribed the same drug but in an alternate format (for *e.g.*, tablet form instead of solution). In a study by (Topaz et al., 2016) on outpatient data, 'Immune mediated and life threatening reactions' were found to be overridden in > 70% of instances. The quality of inputted data by prescribers determines the accuracy of the information held on the EHR database, which in turn can influence the classification of an adverse drug event as being a drug-allergy or drug-intolerance (Isaac et al., 2009).

According to (Nanji et al., 2018), the use of thresholds provide a level of alert appropriateness at the point of prescribing which are based on clinically defined criteria to promote meaningful alerts. Alert overrides can be used by prescribers in order to select an appropriate medication and represent normal operating practice (Nanji et al., 2018)(Wong et al., 2018). Thus, alerts should be carefully considered by prescribers before they are overridden, as the main function of alerts is to eliminate adverse drug events (ADEs) (Lee et al., 2010). However, alert fatigue could be caused by low alert thresholds which potentially lead to a high incidence of prescriber overrides (Jani et al., 2011). Some of these may include overrides of relevant alerts and thus result in unintended and potentially avoidable, adverse drug events (ADE) (Nanji et al., 2018) (Isaac et al., 2009). It is therefore important to continually monitor alert warning systems including the frequency of alerts, actions taken by prescribers in response to these alerts and reasons for any override decisions. Such an analysis could provide insights into potential alert fatigue and appropriateness of alerts, that could inform system optimisations.

1.2 Study-specific context: UCLH Epic EHR system

In March 2019, University College London Hospitals NHS Foundation Trust (UCLH) launched an electronic health record (EHR) system on the Epic platform (Postelnicu, 2019). The Epic EHR system is populated with existing UCLH patients' records transferred to the system and will continue to serve as a central database for medical and non-medical professionals to dynamically add and update patient records, such as for the prescribing of medications (Postelnicu, 2019). Medical and non-medical prescribers can use the Epic EHR system to assess patient records for potential allergies or intolerances in order to inform clinical decision making in an efficient manner without the need to reference paper notes (Postelnicu, 2019). This study aims to quantify the impact of overall allergy and intolerance alerts contained in an anonymised data extract obtained from the UCLH EHR system and more specifically, undertake an analysis of factors associated with warning overrides (alerts were not adhered to) versus warning removals (alerts were effective and adhered to) at point of prescribing. An exploratory analysis of alert appropriateness will also be carried out.

2.0 Methodology

The analysis was based on a retrospective dataset of 5,628 unique individuals with 53,057 prescription records sampled from the UCLH Epic electronic health record (EHR) database and are coded using the Drug, Medicines and Devices (DM+D) coding system. The dataset consisted of 11 months of data taken from a specific time period (June 2019 to March 2021) and included data on prescriber actions, prescription description and frequency of allergic response and patient intolerance (*i.e.*, adverse reactions/drug intolerances) to various prescriptions (Topaz et al., 2016). The raw dataset consists of thirty-five variables that were updated by prescribing clinicians in a clinical setting (*i.e.*, UCLH) and includes anonymised patient characteristics, prescribing information, if an alert warning was raised due to allergic response or patient intolerance and the subsequent prescribers' actions. The dataset does not provide information on patient outcomes and each prescription was treated as an independent patient record for the purposes of the alert warning analysis. The anonymised dataset reflects a dynamic data entry environment using both drop-down options and free text; therefore, data entry errors and missing data were expected in the dataset.

Using the raw dataset, a new data-frame of twelve variables was generated consisting of warning status, provider type, provider speciality, description, context, drug-allergy reactions, drug-allergy contraindication group, importance level, severity, along with patient sex and age.

Table 1. List of data-frame variables, what they consist of and meaning.

Variable	Consists of:	Meaning
Warning Status	Overridden, Removed, Cancelled, Viewed, Held	Alert warning type
Provider Type	Prescriber	Medical (for e.g., Consultant) or non-medical prescriber (for e.g., Registered Nurse, Technician)
Provider Speciality	Specialty in which prescriber is based	For e.g., Anaesthesiology & Emergency Medicine
Description	Prescription	Prescribed medication
Context	Inpatient, Outpatient or Both inpatient and outpatient	Patient hospital admissions status Both Inpatient and Outpatient' = patients initial treated as outpatient before admission as inpatient
Drug-Allergy Reactions	Patient-prescription allergic reaction list	Recorded patient reaction to prescription
Drug-Allergy Contraindication Group	Allergy or Adverse Reactions/Drug Intolerances	Allergy or intolerance response to prescription
Importance Level	High, Very High	Alert importance based on possible patient reaction to medication
Severity	Cross-sensitive class match, drug class match or ingredient match	Drug-allergy interaction leading to possible patient reaction
Sex	Male, Female	Patient sex
Age	Age in years and months	Patient age ranging from <1 to >80 years year(s) old.

The variable indicating the warning status presented four options to the prescribers: overridden (override the alert and continue with the prescription), removed (remove the alert and change to an alternate prescription), cancelled (cancels all alerts), viewed (used to viewed alerts

without further action) and held (hold the prescribing action on the system until a later time). The cancelled option may follow any alert warning that arises and was therefore difficult to analyse. The viewed and held options are where prescribers did not continue with prescribing at the time of the alert warning. For this project overridden and removed was explored as these represent the primary decision-making actions of the prescriber: to either continue with the prescription or not, depending on available information and prescriber experience.

2.1 Data exploration

Using Excel, the raw dataset in csv format was explored for missing values in the data and informed future covariate recoding decisions which affect the subsequent analysis and interpretation. Provider type, provider speciality, context, drug-allergy reactions and importance level variables were found to have missing data values. The csv file was uploaded to Python v3.5 using jupyter notebooks in order to perform descriptive analysis, using python libraries such as numpy, pandas, scikit-learn and matplotlib for data cleaning, visualisation (where needed), data-frame formulation and file type formatting (*i.e.,* csv) for use in further analysis. The full Python scripting is presented via a Github link in Appendix 7.

2.1.1 Variables

The categorical variables relating to provider type, provider speciality and description were recoded into profession, specialisation and prescription categories to aid interpretation. The continuous variable age (another potential factor influencing prescribe decisions) was categorised into meaningful age ranges.

The 77 Provider types were recoded to twelve medical and non-medical levels: registrar, pharmacist, consultant, registered nurse, junior doctor, technician, allied health professional, other doctor, pre-registration pharmacist, pre-registration nurse, consultant dental surgeon, other.

The 92 provider specialities were categorised into nine levels: anaesthesiology & emergency medicine, general medicine & other medicine specialty, pharmacy, general surgery & other surgical specialty, oncology & palliative care, obstetrics gynaecology, general practice, neonatology paediatrics and other non-medical specialty. Appendix 6 presents how the provider types and specialities contained in the dataset were recoded for the purposes of statistical analysis.

There were 503 unique prescriptions in the raw dataset that were recoded into nine drug categories following guidance from the NICE BNF website (“BNF,” 2021). The initial descriptions were categorised as follows: opioid, antibiotic, NSAID (non-steroidal anti-inflammatory drugs), immunoglobulin, anti-emetic, steroid, corticosteroid, antihistamine and other.

Drug-allergy reactions were recoded from the initial 77 levels to eight levels: rash, itching or hives & other, anaphylaxis, anaphylaxis & other, shortness of breath, swelling & other, GI intolerance & other, shortness of breath & other and other. The initial patient age variable was first converted to months before calculating years by dividing by 12 months.

Age ranges were categorised into nine levels in years: 0-5, 6-15, 16-25, 26-35, 36-45, 46-55, 56-65, 66-80, >80. Appendix 6 presents how the age, D-A reactions and prescription variables were recoded for the purposes of statistical analysis.

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Using Python (Pandas), counts and percentages were determined for the data-frame variables. For instance, overridden and removed counts and percentages were determined for each variable and further tests of significance performed using the R statistical package. The relevant results of this analysis have been presented in the Results section.

2.2 Further analysis

Further analysis and visualisation were carried out using R Studio v1.4 statistical analysis software on the pre-cleaned and recoded data-frame. The full R Studio scripting is presented via a Github link in Appendix 8.

2.2.1 Unadjusted logistic regression analysis

As with (Isaac et al., 2009), a univariate logistic regression analysis was carried out to investigate the relationship between the warning status and each of the individual variables: provider type, provider speciality, description, context, drug-allergy reactions, drug-allergy contraindication group, importance level, severity, along-with the patients' sex and age. Results of the unadjusted analysis are presented as crude odds ratios, confidence intervals and p values (tests of significance). The relevant results of this analysis have been presented in the Results section.

2.2.2 Adjusted logistic regression analysis

An adjusted multi-variate logistic regression was performed on the data-frame in order to investigate the association between alert warnings and various factors including provider type, provider speciality, description, context, drug-allergy reactions, drug-allergy contraindication group, importance level, severity, along-with the patients' sex and age as covariates in the multivariate model. Results of the adjusted analysis are presented as adjusted odds ratios, confidence intervals and p values (tests of significance). The relevant results of this analysis have been presented in the Results section.

2.3.3 Missing data

Instances of missing data in the data-frame was explored using the tabulation in both Python and R Studio. As mentioned previously, provider type, provider speciality, context, drug-allergy reactions and importance level had missing values. Missing value counts and percentages are presented in the Results section. Missing data was included as a dummy variable category in the unadjusted and adjusted logistic regression analysis.

3.0 Results

3.1 Descriptive analysis

Using the total dataset (n=53,057), females represented 68.53% (n=36,361) and males represented 31.4% (n=16,696) of the cohort.

Overrides made up 61.29% (n=32,520) and removed made up 19.98% (n=10,599) of the total warning status entries. Viewed, cancelled and held entries when combined, accounted for 18.73% (n=9,938) of the warning status entries.

There were 63.74% (n=33,818) inpatients and 30.32% (n=16,089) outpatients. Patients classified as both inpatient and outpatient, made up 0.28% (n=151) of the dataset.

Registrars (doctors undergoing specialty training) were most represented prescribers (designated by the variable provider type) in the dataset (n=18,766; 35.37%), followed by pharmacists (n=11,341; 21.38%), consultants (n=8,858; 16.7%) and registered nurses (n=5,427; 10.23%). Each of the remaining prescriber types were <6% of the overall dataset.

The majority of the prescribers in the dataset were based in three specialties; anaesthesiology & emergency medicine specialty departments (n=14,387; 27.12%), followed closely by those based in general medicine & other medicine specialties (n=14,372; 27.09%) and pharmacy departments (n= 13,878; 26.16%). The remainder of the records related to other provider specialties (n=9,996; 18.85%).

Allergies accounted for 80.88% (n=42,912) of the drug-allergy contraindication groups, while adverse reactions/drug intolerances accounted for the remaining 19.12% (n=10,145).

Alert warning importance levels were categorised as ‘very high’ in 54.61% (n=28976) of cases and ‘high’ in 36.42% (n=19,325) cases, with missing values in 8.96% (n=4,756) of the cases.

42.4% (n=22,494) of the warnings were categorised as ‘cross-sensitive class matches’ in terms of severity, while 39.68% (n=21,053) were classified as ‘drug class matches’ and 17.92% (n=9,510) were classified as an ‘ingredient match’.

Opioids represented the largest category of prescribed drugs at 47.45% (n=25,177), antibiotics were the next largest category at 15.01% (n=7,963) while remaining prescribed drugs made up 21.56% (n=11,446) of the dataset entries. The ‘other’ category made up 15.97% (n= 8,471) of the dataset.

Missing data accounted for 59.42% (n=31,524) of the drug-allergy reactions with the ‘other’ category accounting for 19.95% (n=10,584). Of the remaining 20.63% of the dataset, ‘Rash, Itching or Hives & Other’ amounted to 13.89% (n=7369) and anaphylaxis amounted to 1.39% (n=1,025) of cases. Detailed results are presented in Table 2. A further sub-category breakdown of drug-allergy reactions is presented in Appendix A1. The sub-category analysis in Appendix A1 includes overall counts and percentages for the dataset (n=53,057), along-with override and removed counts and percentages in relation to the full dataset and by each D-A reaction.

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Table 2. Total dataset counts and percentages for provider type, provider specialty, description (prescription), warning status, context and D-A reaction. (n=53,057).

Variable	Count n=53057	%	Variable	Count n=53057	%
Provider Type			**Provider Specialty**		
Registrar	18766	35.37	Anaesthesiology & Emergency Medicine	14387	27.12
Pharmacist	11341	21.38	General Medicine & Other Medicine Specialty	14372	27.09
Consultant	8858	16.7	Pharmacy	13878	26.16
Registered_Nurse	5427	10.23	Missing data	3243	6.11
Junior_Doctor	3176	5.99	General Surgery & Other Surgical Specialty	3038	5.73
Technician	2545	4.8	Oncology & Palliative Care	2168	4.09
Missing data	1247	2.35	Obstetrics Gynaecology	986	1.86
Allied_Health_Professional	1091	2.06	General Practice	561	1.06
Other_Doctor	445	0.84	Neonatology Paediatrics	360	0.68
Pre-Registration Pharmacist	119	0.22	Other Non-Medical Specialty	64	0.12
Pre_Registration_Nurse	29	0.05			
Consultant Dental Surgeon	10	0.02			
Other	3	0.01			
Warning Status			**Context**		
Overridden	32520	61.29	Inpatient	33818	63.74
Removed	10599	19.98	Outpatient	16089	30.32
Viewed	7033	13.26	Missing data	2999	5.65
Cancelled	2861	5.39	Both Inpatient and Outpatient	151	0.28
Held	44	0.08			
Description			**Drug Allergy Reactions**		
opioid	25177	47.45	Missing data	31524	59.42
other	8471	15.97	Other	10584	19.95
antibiotic	7963	15.01	Rash, Itching or Hives & Other	7369	13.89
NSAID	5228	9.85	Anaphylaxis	1025	1.93
immunoglobulin	2130	4.01	Shortness Of Breath	832	1.57
anti-emetic	1762	3.32	Swelling & Other	793	1.49
steroid	882	1.66	Gi Intolerance & Other	696	1.31
corticosteroid	880	1.66	Shortness Of Breath & Other	181	0.34
antihistamine	564	1.06	Anaphylaxis & Other	53	0.1
Importance Level			**Severity**		
Very High	28976	54.61	Cross-sensitive Class Match	22494	42.4
High	19325	36.42	Drug Class Match	21053	39.68
Missing data	4756	8.96	Ingredient Match	9510	17.92
Drug Allergy Contraindication Group			**Sex**		
Allergies	42912	80.88	Female	36361	68.53
Adverse Reactions/Drug Intolerances	10145	19.12	Male	16696	31.47

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As seen in Table 3, missing data represents 38.71% of the override reasons, with the most frequently recorded reason for overrides being 'Benefit outweighs risk' (n=12,331; 23.24%.) Other reasons recorded as justification for overriding a warning were 'Does not apply to patient' (16.64%) and 'inaccurate warning' (4.57%), making up >20% of the reasons when combined. A further sub-category breakdown of the provider types and provider specialities in terms of description and context in relation to overrides and removals in counts and percentages for the full dataset (n=53,057) is presented in Appendices A2 to A5 (inclusive).

Table 3. Presents counts and percentages for the override reason selection.

Override reason	Count n=53057	%
Missing data	20537	38.71
Benefit outweighs risk	12331	23.24
Does not apply to patient	8829	16.64
Per protocol	6517	12.28
Inaccurate warning	2426	4.57
See comments	2417	4.56

3.2 Logistic regression analysis

The data-frame filtered to show overridden and removed warning status used for this analysis included 43,119 records consisting of 32,520 overrides and 10,599 removals (relating to 5,628 individual patients). It was found that 13,579 records were male, and 29,540 records are female. Males represented 77.57% (n=1,0533) overrides and 22.43% (n=3,046) removals, while females represented 74.43% (n=21,987) overrides and 25.57% (n=7,553) removals. Overall counts and percentages for each of the variables included in the logistic regression are presented in Table 4.

3.2.1 Unadjusted analysis

In the unadjusted analysis (Table 4), prescription warnings for males (OR 1.19 [1.13-1.25], p<0.001) were 19% more likely to be overridden than for females.

Patient age was not strongly associated with overrides in the unadjusted model, with the 6-15 year cohort being the only age group (OR 1.42 [0.74-2.58], p=0.316) that was 42% more likely than the 0-5 year cohort to have prescriptions overridden.

Most provider types were significantly less likely to override prescription warnings as compared to pharmacists. Technicians however, were the only group more likely to override prescription warnings as compared to pharmacists (OR 83.50 [18.88-1466.32], p<0.001).

There were significantly fewer prescription overrides (p<0.001) in all specialty departments as compared to pharmacy departments.

Prescription for steroids (OR 3.71 [2.93-4.77], p<0.001) were nearly 4 times and corticosteroids (OR 2.83 [2.30-3.51], p<0.001) were nearly 3 times more likely to be overridden than antibiotic prescriptions. Prescriptions for immunoglobulins (OR 4.36 [3.59-5.35], p<0.001) were more than 4 times and opioids (OR 2.07 [1.94-2.20], p<0.001) were more

than 2 times as likely to be overridden than antibiotics. Prescriptions categorised as 'other' (OR 1.52 [1.40-1.64], p<0.001) were 52% more likely to be overridden as compared to antibiotics.

Those patients who were classified as outpatients (OR 4.27 [4.02-4.54], p<0.001) were strongly associated with prescription warning overrides and were over 4 times more likely to have override records as compared to inpatients. While the 'Both Inpatient and Outpatient' category (OR 1.63 [1.00-2.79], p=0.059), was on the borderline of statistical significance for the association with overrides, prescriptions for patients in this category were 63% more likely to be overridden than for those in the inpatient category.

'Rash, Itching or Hives & Other' (OR 1.71 [1.46-1.99], p<0.001) and 'other' (OR 1.54 [1.32-1.79], p<0.001) drug-allergy reactions were strongly associated (p<0.001) with overrides. Prescriptions with drug-allergy reaction warnings relating to the former were 71% more likely to be overridden than Anaphylaxis, while the latter were 54% more likely to be overridden. 'Shortness of Breath & Other' reactions were 60%, 'Shortness of Breath' 45%, and 'Swelling & Other' were 41% more likely to be overridden than anaphylaxis.

Warnings categorised at an importance level of 'Very High' (OR 0.65 [0.62-0.68], p<0.001) were 35% less likely to be overridden than those categorised as 'High'.

Allergies (OR 0.92 [0.87-0.97], p=0.003) were 8% less likely to be overridden than Adverse Reactions/Drug Intolerances.

3.2.2 Adjusted analysis

In the adjusted model in Table 4, prescription in males (adjOR 1.07 [1.01-1.14], p=0.026) had a 7% increased likelihood of overrides than females when compared to the unadjusted model.

After adjustment no statistically significant association was observed between patient age and decisions to override prescription warnings.

Even after adjustment, medically qualified prescribers (consultants, registrars, junior doctors, other doctors), registered nurses and allied health professionals were less likely to override prescription warnings as compared to pharmacists. However, the adjusted odds ratios shifted slightly towards 1 as compared to the unadjusted odds ratios in all these cases. Technicians were more likely to override prescription warnings as compared to pharmacists in the adjusted analysis, with a reduced adjusted odds ratio (62.17 as compared to the unadjusted odds ratio of 83.50).

Most provider specialities were less likely to override prescription warnings as compared to pharmacy departments, however, some of the associations were no longer statistically significant and the adjusted odds ratios shifted slightly towards 1. The exception was Neonatology Paediatrics (adjOR 1.36 [0.82-2.29], p=0.241) where prescribers were 36% more likely to override warnings as compared to those within Pharmacy, although this association was not statistically significant.

The odds ratios comparing various prescription drug classes to antibiotics increased for all categories in the adjusted model, with all except Antihistamines (adjOR 1.02 [0.82-1.28], p=0.856) being statistically significant (p<0.001). Prescriptions for steroids/corticosteroids, immunoglobulins and opioids were between ~3.5 and ~5 times more likely to be overridden than prescription for antibiotics.

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In the adjusted model the odds ratios for context were lower than in the unadjusted model, decreasing by approximately half. Outpatients (adjOR 2.09 [1.94-2.25], p<0.001) were over two times more likely to have prescriptions overridden than inpatients.

As compared to a drug-allergy reaction flag relating to anaphylaxis, all other types of reactions were more likely to be associated with overrides. Notably, warnings relating to 'Rash, Itching or Hives & Other' (adjOR 1.40 [1.16-1.69], p<0.001) were 40% more likely and those relating to 'Shortness of Breath' (adjOR 1.72 (1.29-2.32), p<0.001) were 72% more likely to be associated with an override than anaphylaxis.

Flags relating to 'Drug Class Match' (adjOR 0.50 [0.35-0.72], p<0.001) and 'Ingredient Match' (adjOR 0.26 [0.18-0.37], p<0.001) were less likely to be associated with an override as compared to cross-sensitive match even after adjustment for other factors, with the odds ratios decreasing in the adjusted model.

After adjustment there was no longer a significant association observed by importance level, however, 'Very High' as compared to 'High' presented an increased adjusted odds ratio (adjOR 1.07 [0.74-1.54], p=0.74) when compared to the unadjusted odds ratio (OR 0.65 [0.62-0.68], p<0.001).

In the adjusted model, allergies (adjOR 0.88 [0.82-0.94], p<0.001) were significantly less likely to be overridden than adverse reactions/drug intolerances.

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Table 4. Presents the counts, percentages, unadjusted odds ratios, adjusted odds ratios, confidence intervals and associated p-values in relation to overrides.

Variable	Total count	Override count (%)	Removed count (%)	Unadjusted OR (95% CI), p-value	Adjusted OR (95% CI), p-value
	n=43119	n=32520	n=10599		
Sex					
Female	29540	21987 (74.43)	7553 (25.57)	1.0	1.0
Male	13579	10533 (77.57)	3046 (22.43)	1.19 (1.13-1.25), <**0.001**	1.07 (1.01-1.14), 0.026
By age group (years)					
0-5	70	56 (80.00)	14 (20.00)	1.0	1.0
6-15	729	620 (85.05)	109 (14.95)	1.42 (0.74-2.58), 0.316	0.85 (0.39-1.75), 0.676
16-25	4094	3093 (75.55)	1001 (24.45)	0.77 (0.41-1.35), 0.301	0.54 (0.25-1.06), 0.086
26-35	5712	4115 (72.04)	1597 (27.96)	0.64 (0.34-1.13), 0.300	0.49 (0.23-0.96), 0.047
36-45	5466	4040 (73.91)	1426 (26.09)	0.71 (0.38-1.24), 0.300	0.52 (0.24-1.02), 0.069
46-55	7504	5693 (75.87)	1811 (24.13)	0.79 (0.42-1.37), 0.300	0.49 (0.23-0.97), 0.051
56-65	6761	5172 (76.50)	1589 (23.50)	0.81 (0.44-1.43), 0.300	0.56 (0.26-1.10), 0.107
66-80	9321	7011 (75.22)	2310 (24.78)	0.76 (0.41-1.33), 0.300	0.52 (0.24-1.02), 0.068
80+	3460	2718 (78.55)	742 (21.45)	0.92 (0.49-1.61), 0.302	0.57 (0.27-1.13), 0.120
Missing data	.	.	.	.*	.*
Provider Type					
Pharmacist	10352	9951 (96.13)	401 (3.87)	1.0	1.0
Registered Nurse	3073	2672 (86.95)	401 (13.05)	0.27 (0.23-0.31), <**0.001**	0.62 (0.41-0.93), 0.022
Other Doctor	400	292 (73.00)	108 (27.00)	0.11 (0.09 0.14), <**0.001**	0.23 (0.14-0.37), **<0.001**
Other	3	3 (100.00)	0 (0.00)	.*	.*
Consultant	6247	3063 (49.03)	3184 (50.97)	0.04 (0.04-0.04), <**0.001**	0.17 (0.12-0.26), **<0.001**
Registrar	16098	10644 (66.12)	5454 (33.88)	0.08 (0.07-0.09), <**0.001**	0.21 (0.14-0.30), **<0.001**
Allied Health Professional	822	685 (83.33)	137 (16.67)	0.20 (0.16-0.25), <**0.001**	0.62 (0.42-0.92), 0.016
Junior Doctor	2867	2052 (71.57)	815 (28.43)	0.10 (0.09-0.12), <**0.001**	0.22 (0.14-0.33), **<0.001**
Technician	2073	2072 (99.95)	1 (0.05)	83.50 (18.88-1466.32), <**0.001**	62.17 (13.84-1097.84), **<0.001**
Pre-Registration Pharmacist	55	55 (100.00)	0 (0.00)	.*	.*
Consultant Dental Surgeon	3	3 (100.00)	0 (0.00)	.*	.*
Pre-registration Nurse	19	17 (89.47)	2 (10.53)	0.34 (0.10-2.17), 0.153	1.62 (0.40-10.96), 0.548
Missing data	1107	1011 (91.33)	96 (8.67)	0.42 (0.34-0.54), <**0.001**	0.55 (0.35-0.85), 0.008

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Variable	Total count	Override count (%)	Removed count (%)	Unadjusted OR (95% CI), p-value	Adjusted OR (95% CI), p-value
	n=43119	n=32520	n=10599		
Provider Specialty					
Pharmacy	12353	11948 (96.72)	405 (3.28)	1.0	1.0
General Medicine & Other Medical Specialty	12003	9233 (76.92)	2770 (23.08)	0.11 (0.10-0.13), **<0.001**	0.65 (0.44-0.97), 0.035
Anaesthesiology & Emergency Medicine	9959	4486 (45.04)	5473 (54.96)	0.03 (0.03-0.03), **<0.001**	0.21 (0.14-0.32), **<0.001**
General Surgery & Other Surgical Specialty	2594	1904 (73.40)	690 (26.60)	0.09 (0.08-0.11), **<0.001**	0.43 (0.29-0.66), **<0.001**
General Practice	511	378 (73.97)	133 (26.03)	0.10 (0.08-0.12), **<0.001**	0.53 (0.33-0.83), 0.006
Obstetrics Gynaecology	878	467 (53.19)	411 (46.81)	0.04 (0.03-0.05), **<0.001**	0.22 (0.14-0.34), **<0.001**
Oncology & Palliative Care	1917	1543 (80.49)	374 (19.51)	0.14 (0.12-0.16), **<0.001**	0.76 (0.50-1.16), 0.20
Neonatology Paediatrics	326	276 (84.66)	50 (15.34)	0.19 (0.14-0.26), **<0.001**	1.36 (0.82-2.29), 0.241
Other Non-medical Specialty	56	29 (51.79)	27 (48.21)	0.04 (0.02-0.06), **<0.001**	0.086 (0.04-0.17), **<0.001**
Missing data	2522	2256 (89.45)	266 (10.55)	0.29 (0.25-0.34), **<0.001**	0.77 (0.52-1.14), 0.184
Description					
Antibiotic	6456	4542 (70.35)	1914 (29.65)	1.0	1.0
NSAID	4257	1920 (45.10)	2337 (54.90)	0.35 (0.32-0.38), **<0.001**	0.68 (0.62-0.76), **<0.001**
Steroid	746	670 (89.81)	76 (10.19)	3.71 (2.93-4.77), **<0.001**	5.00 (3.85-6.59), **<0.001**
Anti-emetic	1585	743 (46.88)	842 (53.12)	0.37 (0.33-0.42), **<0.001**	0.78 (0.67-0.90), **<0.001**
Corticosteroid	817	711 (87.03)	106 (12.97)	2.83 (2.30-3.51), **<0.001**	3.44 (2.74-4.35), **<0.001**
Immunoglobulin	1293	1179 (91.18)	114 (8.82)	4.36 (3.59-5.35), **<0.001**	4.97 (3.99-6.24), **<0.001**
Opioid	20434	16972 (83.06)	3462 (16.94)	2.07 (1.94-2.20), **<0.001**	3.82 (3.52-4.14), **<0.001**
Antihistamine	501	282 (56.29)	219 (43.71)	0.54 (0.45-0.65), **<0.001**	1.02 (0.82-1.28), 0.856
Other	7030	5501 (78.25)	1529 (21.75)	1.52 (1.40-1.64), **<0.001**	1.99 (1.81-2.19), **<0.001**
Context					
Inpatient	27998	19321 (69.01)	8677 (30.99)	1.0	1.0
Outpatient	14476	13098 (90.48)	1378 (9.52)	4.27 (4.02-4.54), **<0.001**	2.09 (1.94-2.25), **<0.001**
Both Inpatient and Outpatient	88	69 (78.41)	19 (21.59)	1.63 (1.00-2.79), 0.059	0.72 (0.40-1.35), 0.287
Missing data	557	32 (5.75)	525 (94.25)	0.03 (0.02-0.04), **<0.001**	0.04 (0.02-0.06), **<0.001**
D-A Reactions					
Anaphylaxis	819	525 (64.10)	294 (35.90)	1.0	1.0
Anaphylaxis & Other	40	4 (10.00)	36 (90.00)	0.06 (0.02-0.16), **<0.001**	0.10 (0.02-0.33), **<0.001**
GI Intolerance& Other	553	341 (61.66)	212 (38.34)	0.90 (0.72-1.13), 0.35847	1.18 (0.90-1.57), 0.24
Other	8400	6161 (73.35)	2239 (26.65)	1.54 (1.32-1.79), **<0.001**	1.25 (1.04-1.51), 0.019

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Variable	Total count	Override count (%)	Removed count (%)	Unadjusted OR (95% CI), p-value	Adjusted OR (95% CI), p-value
	n=43119	n=32520	n=10599		
Rash, Itching or Hives & Other	5781	4353 (75.30)	1428 (24.70)	1.71 (1.46-1.99), **<0.001**	1.40 (1.16-1.69), **<0.001**
Shortness of Breath	642	463 (72.12)	179 (27.88)	1.45 (1.16-1.81), 0.00118	1.72 (1.29-2.32), **<0.001**
Shortness of Breath & Other	154	114 (74.03)	40 (25.97)	1.60 (1.09-2.37), 0.01803	1.93 (1.22-3.09), 0.006
Swelling & Other	634	454 (71.61)	180 (28.39)	1.41 (1.13-1.77), 0.00252	1.29 (0.98-1.70), 0.072
Missing data	26096	20105 (77.04)	5991 (22.96)	1.88 (1.62-2.17), **<0.001**	1.36 (1.13-1.62), **<0.001**
Severity					
Cross-sensitive Class Match	17569	14034 (79.88)	3535 (20.12)	1.0	1.0
Drug Class Match	18059	13901 (76.98)	4158 (23.02)	0.84 (0.80-0.89), **<0.001**	0.50 (0.35-0.72), **<0.001**
Ingredient Match	7489	4583 (61.2)	2906 (38.8)	0.40 (0.37-0.42), **<0.001**	0.26 (0.18-0.37), **<0.001**
Missing data	2	.	.	.*	.*
Importance Level					
High	16884	13616 (80.64)	3268 (19.36)	1.0	1.0
Very High	25051	18269 (72.93)	6782 (27.07)	0.65 (0.62-0.68), **<0.001**	1.07 (0.74-1.54), 0.74
Missing data	1182	633 (53.55)	549 (46.45)	0.28 (0.25-0.31), **<0.001**	0.86 (0.68-1.08), 0.19
Drug Allergy Contra-indication Group					
Adverse Reactions/Drug Intolerances	8458	6483 (76.65)	1975 (23.35)	1.0	1.0
Allergies	34659	26035 (75.12)	8624 (24.88)	0.92 (0.87-0.97), 0.003	0.88 (0.82-0.94), **<0.001**
Missing data	2	.	.	.*	.*

*Could not be calculated due to zero counts in one of the columns
Note: p-values indicating statistical significance are highlighted in bold.

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4.0 Discussion

This study highlights that prescriber overrides in response to alert warnings are significantly associated with provider type, provider speciality, description, context, drug-allergy reactions, drug-allergy contraindication group, severity, along with patient sex and age. As mentioned earlier, overrides related to those alerts that were not adhered to by prescribers for a number of reasons, as presented in Table 3. Alert warnings are given importance levels, which for overrides in this study are 7% more likely for the very high (adjOR 1.07 [0.74-1.54], p=0.74) importance level of alert than for high.

These findings are broadly in line with those reported from similar studies conducted in other settings but there were some differences. Similar to this study, Isaac et al. reported that after adjustment for age, there was no statistically significant association between patient age and decisions to accept the alert warnings leading to removal of the original prescription (Isaac et al., 2009). While after adjusting for sex, no association was found between patient sex and prescriber decisions in response to alert warnings (adjOR 1.01[0.97-1.05], p=0.69), unlike this study where prescriptions in males were slightly more likely to be overridden. The Isaac et al. study differed from this study, in terms of having a larger sample size (233,537 alert records) and being set in the United States hospital system. One hypothesis is that there may also be differences in the patient case mix and sociodemographic characteristics in a London hospital setting which could explain the differences in findings.

In the adjusted model, medically qualified provider types (professions) such as registrar, other doctor, junior doctor and consultant were significantly less likely to override prescription warnings as compared to pharmacists, who are considered medicines experts. One could hypothesise that consultants and registrars may override more based on prescribing experience, while junior doctors may override less, due to the lack of extensive prescribing experience, although the confidence intervals overlap, suggesting that there might be no difference of the likelihood of overrides across provider types. Technicians' likelihood of overriding a warning was multiples higher than any other provider type including pharmacists and this could possibly be due to broad definition of technician in the dataset that does not stratify by different types of technician such as ambulance technician or prescribing technician. However, as most technicians (>99%) were found to be based in a pharmacy speciality it is likely they are prescribing technicians.

In the adjusted model, prescribers based in specialties such as 'Anaesthesiology & Emergency Medicine', 'General Surgery & Other Surgical Specialty', 'Obstetrics Gynaecology' and 'Other Non-medical Specialty' were significantly less likely to override warnings than prescribers based in pharmacy. By comparison, Isaac et al reported that when compared to 'Family medicine', removals (alert accepts) for obstetrics-gynecology (adjOR 1.28 [0.83-1.97], p=.) were ~28% more likely, while in the Surgery or surgical subspecialty (adj OR 1.16 (0.89-1.50), p.) they were ~16% more likely and thus, less likely to have overrides (Isaac et al., 2009). This reduced likelihood of overrides is consistent with the two clinical specialty settings often associated with more invasive medical procedures. In the case of overrides in this study, one could hypothesise that pharmacists are the point of reference at the medicines dispensing stage after the treating consultants and doctors have initially determined the patients' medical treatment and thus share prescribing information. Whilst registrars are responsible for ensuring that inpatient details are correct on the EHR and thus would have more accurate patient sourced information on possible allergic responses on which to base an override decision. This prescribing custody for each patient may be of importance, as registrars (10,644) and

pharmacists (n=9,951) are responsible for the most overrides by far in the UCLH dataset used in this study. Furthermore, patients representing multiple prescription entries in the dataset may have had a chain of prescribing custody shared between multiple prescribers who would be regularly checking the severity of prescriptions prior to use on the patient. This may result in various levels of override likelihood by different prescribers for the same patient and thus highlight variation in how drug-allergy or as suggested by Legat et al, drug intolerance alert warnings might be interrupted and dealt with by different professions (Légat et al., 2018). This analysis was not carried out in this study.

Of the prescription (description) categories, all but antihistamine prescriptions are of statistical significance in relation to override decisions. Anti-emetic and NSAID prescriptions were less likely to be overridden than antibiotics. NSAIDs which are commonly used to reduce inflammation and reduce pain, while anti-emetic prescriptions are used to ease vomiting and nausea. Alerts for stronger drugs such as opioids, steroids and corticosteroids, which are used as strong anti-inflammatory or pain relief medications, and immunoglobulins (antibodies derived from blood plasma) which are used to protect patients against illness (for *e.g.*, hepatitis) are more likely to be overridden than antibiotics. In an assessment carried out by the prescriber; patients with minor drug-allergy reactions to a stronger drug such as an opioid or antibiotic may have the drug prescribed anyway, as the benefits may outweigh the risks.

In terms of patient context, while inpatients are more numerous in the data-frame (n=27,998), prescriptions for outpatients are more likely to be overridden, which may indicate direct discussion between the prescriber and outpatients to determine the true level of allergic response or intolerance of the patient to a particular drug. This hypothesis is supported by the 'Both Inpatient and Outpatient' category begin less likely to be overridden than the 'Inpatient' category as the patient when presenting as an outpatient may have had a longer lead up to admission as an inpatient and therefore more discussion with prescribers about their drug-allergy reaction.

In terms of drug-allergy reaction, both anaphylaxis and shortness of breath are of most importance as these indicate serious and possibly life-threatening ADEs. While the 'Anaphylaxis and Other' related warning is less likely to be overridden than the warning for anaphylaxis alone, the less severe reactions like shortness of breath and rash related categories were more likely to be overridden. This pattern is to be expected with anaphylaxis begin treated with greater caution overall. All anaphylaxis cases represented ~2% of the data-frame (n=43,119), whilst all shortness of breath cases accounting for ~1.8% and the milder conditions of 'Rash, Itching or Hives & Other' represented 13.4%. By comparison, Topaz et al carried out a study on 611,192 data entries and reported 'Hives or rash' as the most likely drug-allergy reaction, with anaphylaxis at 4.3% and shortness of breath at 1.3% of the total number of drug-allergy alerts, with the latter two reactions considered potentially life-threatening (Topaz et al., 2016). As in this study and in that of Topaz et al, the most drug-allergen reactions were mild which may be a possible reason for higher number of prescriber overrides (n=32,520).

Cross-sensitive class matches were more likely to be overridden than either drug class (adjOR 0.50 [0.35-0.72], $p<0.001$) or ingredient matches (adjOR 0.26 [0.18-0.37], $p<0.001$). In this study, cross-sensitive class matches were 40.74%, drug class matches were 41.88% and ingredient matches accounted for 17.37% of the data-frame (n=43,119). Overrides accounted for 79.88% of cross-sensitive class matches, 76.98% of drug class matches and 61.2% of ingredient matches. As a comparison, Nanji et al reported that of the 157,483 records explored, ~52% (n=82,889) were overrides and found that of those alerts; ~24% of drug-class (Cross-

sensitive class) matches were overrides, ~60% of drug-drug (ingredient) matches were overrides and ~70% of class-class matches were overrides while patient allergies of ~77% were overrides (Nanji et al., 2014).

Both importance levels: 'high' and 'very high' are of comparable likelihood of occurrence reflecting patients' drug allergy reactions. In absolute terms, high overrides occurred a total number of 13616 times and very high 18269 times. The classification of warnings as high or very high were not correlated with drug-allergy reaction types (for e.g., anaphylaxis). This indicates subjective judgement made by individual prescribers, possible based on the patients' health condition.

Although allergy related overrides were more numerous, the adjusted odds ratios for the 'Drug Allergy Contra-indication Group' category indicated that potential allergic response warning overrides were less likely than 'Adverse Reactions/Drug Intolerances' reactions which is to be expected, as allergic response can potentially lead to more severe outcomes such as anaphylaxis (NICE, 2014c)("Anaphylaxis Campaign," 2020). Generally, it can be observed that prescriptions likely to cause adverse reactions or intolerances were more likely to be overridden and mostly by registrars and pharmacists.

By way of comparison, an investigation at an affiliate Harvard Medical School in Boston, USA by Slight et al on 158,023 drug-allergy events split into two contextual cohorts; 131,615 inpatients and 26,408 outpatients was found to consist of 83% overrides (Slight et al., 2017). Slight et al reported that patients from both contexts who had previously taken a particular drug were most associated with overrides (Slight et al., 2017). This may be possibly due to the prescriber consulting with the patient on their medical history prior to prescribing and not relying solely on details present on the EHR database (Frew, 2011)(Weingart et al., 2003). Slight et al also found that for inpatients >70% of overrides were for anaphylaxis alert warnings, while this was the case for 56% of outpatients (Slight et al., 2017). One could hypothesis that this could be more likely than for outpatients as inpatients are in a clinical setting and thus under closer clinical observation; therefore, overrides are more likely as the benefits of a drug may outweigh the potential risks and any potential adverse events can be flagged and managed early in those circumstances.

In Table 3, of the override reasons in given for overriding (61.29% of cases), the suggested prescription was considered inappropriate by the prescribers for 21.21% of the alerts. More specifically, two of the reasons, 'Does not apply to patient' and 'inaccurate warning' strongly suggest that the related warnings were unsuitable for those patients. It may happen in many cases that prescribers view written paper records and/or speak to the patient before entering prescribing details on to the EHR and so may override warnings with a level of confidence. This may explain a portion of the 23.24% of override reasons which were recorded as 'Benefit outweighs risk'. Override reasons may also relate to the patients' health status and the negative effects of a prescription being considered less severe than the symptoms of the medical condition they are prescribed to combat. In 4.56% of cases, the override reason included a note signposting to a 'see comments' section, which suggests more detailed explanation for these overrides is available on the EHR system. However, these were not available for analysis.

4.1 Potential recommendations

Based on findings of this study it is not possible to make definitive recommendations on policies relating to prescriber alert warnings. With overrides representing 61.29% of total alerts in the dataset and 21.21% of the override reasons for all alert warnings (overrides and removals) being either 'Does not apply to patient' or 'Inaccurate warning', there is some support for alert fatigue amongst prescribers. However, more analysis is needed before any potential alert warning system suggestions to reduce alert fatigue could be safely considered.

Key recommendations from this study are related to avenues for future research that could provide further insight into appropriateness of warnings (for *e.g.*, overrides, removals) in association with prescriptions, prescribers, hospital settings, phases of care and override reasons. These are discussed a later section.

4.2 Study limitations

In some instances, due to the nature of the UCLH Epic EHR system (not detailed in this study), the selection of a warning cancellation by a prescriber is accompanied by an additional removed action. As this represents <5% of the total warnings and cannot be determined from the dataset, these events have been ignored for the purposes of this study.

Missing values were present in provider type (2.35%), provider specialty (6.11%) and importance level (8.96%) variables. Another limitation is that a significant proportion of Drug-Allergy reactions 59.42% (n=31,524) and override reasons 38.71% (n=20,537) values were missing in the dataset.

Another limitation is that there are no details on potential patient comorbidities which could have provided insights into alert warning decisions.

Information on the patient outcome was not provided therefore this study was concerned with the prescriber's action on whether to accept a prescription or override with it after the UCLH Epic system raised an alert warning. As suggested in (Isaac et al., 2009), a limitation of a study of this type includes dependence on individual prescriber experience from which decisions can be based. Another limitation is the use of a single dataset from one hospital system which would reduce the generalisability of the findings.

The dataset consists of data from June 2019 to March 2021, which includes both pre-covid and covid period data from UCLH which may reduce the overall generalisability to non-pandemic periods.

4.3 Future work

Further to this study, analysis to determine if any differences exist in warning status outcomes depending on the time of the year the warnings occur could be explored. For example, if overrides are more or less likely in the months of August or September when new junior doctors enter the hospital.

The use of natural language learning (NLP) for the delineation of allergic and non-allergic medication intolerance by exploration of the free text inputs by prescribers is a possible direction to expand on. However, this may require an expanded dataset to include more free text components than presented in the current dataset.

The use of NLP can further be used to extract clinical information from medical notes (for *e.g.*, free text) to assess reasons for alert response by prescribers that may be embedded in text spread across multiple locations in the data-frame (Goss et al., 2013). An exemplar of this is provided in the work by Goss et al., which applied NLP to identify and encode allergy details from clinical notes to ascertain true allergic reactions (Goss et al., 2013).

Using this dataset, the possibility exists to use clustering techniques (such as k-means) for identifying how different drug classes cluster with other factors to further the understanding of combinations of factors that may influence prescribers' decisions in response to warnings.

A qualitative analysis of prescribers within different hospital departments may provide further insights as to the potential override reasons and how these could be used to optimise future warnings.

Exploring the impact of phase of care on prescriber decisions to override warnings might also provide insights into override reasons. Additionally, more detailed analysis could be carried out in relation to hospital, department and interaction settings in order to more fully understand the situational determinants of overrides decisions.

In this study each observation was treated as independent, discounting instances where there were multiple prescriptions for the same patient. Therefore, a further investigation of prescribers' decisions in response to alert warnings on a per patient basis, would provide insights into clinical circumstances that may influence prescribing decisions that could lead to the overriding of alert warnings.

Further work could include a stratified analysis of pre-covid and covid period data taken from the dataset to investigate differences that may exist.

An additional point of investigation would be the layout and ease of use of the prescriber user interface that the EHR utilises (Olakotan, 2020) and to what extent this influences the way different prescribers complete the EHR options in other to reduce missing data fields. More completed data fields can aid in decision making of other prescribers leading to a potential reduction in overrides.

In general, all future work should aim to improve alert warning accuracy by optimising alerts for each patients' medical needs and safety, and thus limit the number of overrides due to alert inappropriateness.

5.0 Conclusion

Alert fatigue has been considered a problem for EHR users as it can lead to seemingly unnecessary alerts arising and the subsequent increased risk of alerts warnings being overridden as a matter of course. However, there is evidence that suggests alert fatigue amongst provider types. This study presented a quantitative analysis of alert warnings and their association with provider type, provider speciality, description, context, drug-allergy reactions, drug-allergy contraindication group, severity, along-with the patients' sex and age.

As hospital interactions between prescribers and patients are a complex matter dependant on the situational circumstances, prescriber experience, patients' medical history and current condition, it is difficult to make any definite statements based on this study alone, as to how warning thresholds could be modified to reduce alert fatigue. The importance of prescribers consulting with patients rather than relying on maintained databases to determine drug allergy or drug intolerance should continue to be recognised (Frew, 2011).

6.0 Ethical Issues

As part of this project the student prepared a Data Protection Impact Assessment (DPIA) form which was submitted to the UCLH Information Governance Team for review and approval. The DPIA form assessed the risk of data use of individual patients' data and attempted to identify and reduce those risks ("Information Commissioner's Office (DPIA)," 2021).

The student was provided with anonymised UCLH patient data for the project. All data was anonymised prior to the student receiving the large dataset and did not contain patient identifiers (*i.e.,* name, NHS number, exact date of birth).

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9.0 Appendix

9.1 Appendix 1

Table 3. D-A reaction sub-categories by count and percentage along with the associated override and removed count and percentage.

			Overridden			Removed		
D-A reaction	D-A reaction count **(A)** (n=53057)	D-A reaction percentage (%)	**Count (B)**	**(B) / n=53057 (%)**	**(B) / (A) (%)**	**Count (C)**	**(C) / n=53057 (%)**	**(C) / (A) (%)**
Missing data	31524	59.42	20105	37.89	**63.78**	5991	11.29	**19**
Other (see comments)	10584	19.95	6161	11.61	**58.21**	2239	4.22	**21.15**
Rash, itching or hives	6661	12.55	3942	7.43	**59.18**	1238	2.33	**18.59**
Anaphylaxis	1025	1.93	525	0.99	**51.22**	294	0.55	**28.68**
Shortness of breath	832	1.57	463	0.87	**55.65**	179	0.34	**21.51**
Swelling	747	1.41	430	0.81	**57.56**	168	0.32	**22.49**
Rash, itching or hives, Swelling	513	0.97	324	0.61	**63.16**	135	0.25	**26.32**
Diarrhoea	394	0.74	239	0.45	**60.66**	72	0.14	**18.27**
Rash, itching or hives, Other (see comments)	175	0.33	84	0.16	**48**	49	0.09	**28**
Gastrointestinal bleeding	168	0.32	38	0.07	**22.62**	99	0.19	**58.93**
Rash, itching or hives, Shortness of breath	130	0.25	94	0.18	**72.31**	20	0.04	**15.38**
Diarrhoea, Rash, itching or hives, Swelling	64	0.12	31	0.06	**48.44**	20	0.04	**31.25**
Rash, itching or hives, Diarrhoea	41	0.08	22	0.04	**53.66**	12	0.02	**29.27**
Swelling, Other (see comments)	38	0.07	23	0.04	**60.53**	8	0.02	**21.05**
Anaphylaxis, Swelling	25	0.05	0	0.00	**0**	22	0.04	**88**
Shortness of breath, Other (see comments)	22	0.04	15	0.03	**68.18**	6	0.01	**27.27**
Shortness of breath, Swelling	18	0.03	5	0.01	**27.78**	8	0.02	**44.44**
Rash	14	0.03	3	0.01	**21.43**	2	0.00	**14.29**
Anaphylaxis, Other (see comments)	13	0.02	0	0.00	**0**	12	0.02	**92.31**
Diarrhoea, Other (see comments)	13	0.02	9	0.02	**69.23**	0	0.00	**0**
Anaphylaxis, Rash, itching or hives, Shortness of breath, Swelling	12	0.02	4	0.01	**33.33**	0	0.00	**0**
Other (see comments), Gastrointestinal bleeding	9	0.02	2	0.00	**22.22**	2	0.00	**22.22**
Rash, itching or hives, Shortness of breath, Swelling	8	0.02	0	0.00	**0**	6	0.01	**75**
Swelling, Rash, itching or hives	8	0.02	1	0.00	**12.5**	4	0.01	**50**
Rash, itching or hives, Gastrointestinal bleeding	6	0.01	0	0.00	**0**	6	0.01	**100**
Other (see comments), Rash, itching or hives	4	0.01	0	0.00	**0**	4	0.01	**100**
Swelling, Shortness of breath	3	0.01	0	0.00	**0**	0	0.00	**0**
Rash, itching or hives, Diarrhoea, Other (see comments)	2	0.00	0	0.00	**0**	0	0.00	**0**
Anaphylaxis, Rash, itching or hives	2	0.00	0	0.00	**0**	1	0.00	**50**
GI intolerance	1	0.00	0	0.00	**0**	1	0.00	**100**
Anaphylaxis, Rash, itching or hives, Swelling	1	0.00	0	0.00	**0**	1	0.00	**100**

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9.2 Appendix 2

Table 4. Provider Type and context by description count and percentage, override by and removed percentages.

Provider Type	Context	Total Warning Status counts n=53057	Overridden counts (% of Total Warning Status)	Removed counts (% of Total Warning Status)	Overridden / (Overridden + Removed) %	Removed / (Overridden + Removed) %
Consultant Dental Surgeon	Outpatient	10	3 (30.00)	0 (0.00)	100.00	0.00
Pre-Registration Pharmacist	Both Inpatient and Outpatient	3	0 (0.00)	0 (0.00)	0.00	0.00
	Inpatient	27	0 (0.00)	0 (0.00)	0.00	0.00
	Outpatient	89	55 (61.80)	0 (0.00)	100.00	0.00
Technician	Missing data	3	1 (33.33)	1 (33.33)	50.00	50.00
	Both Inpatient and Outpatient	25	0 (0.00)	0 (0.00)	0.00	0.00
	Inpatient	210	26 (12.38)	0 (0.00)	100.00	0.00
	Outpatient	2307	2045 (88.64)	0 (0.00)	100.00	0.00
Allied Health Professional	Missing data	85	2 (2.35)	26 (30.59)	7.14	92.86
	Both Inpatient and Outpatient	1	1 (100.00)	0 (0.00)	100.00	0.00
	Inpatient	583	293 (50.26)	107 (18.35)	73.25	26.75
	Outpatient	422	389 (92.18)	4 (0.95)	98.98	1.02
Consultant	Missing data	1642	0 (0.00)	288 (17.54)	0.00	100.00
	Both Inpatient and Outpatient	6	4 (66.67)	0 (0.00)	100.00	0.00
	Inpatient	6237	2420 (38.80)	2658 (42.62)	47.66	52.34
	Outpatient	973	639 (65.67)	238 (24.46)	72.86	27.14
Junior Doctor	Both Inpatient and Outpatient	6	2 (33.33)	4 (66.67)	33.33	66.67
	Inpatient	1986	1156 (58.21)	663 (33.38)	63.55	36.45
	Outpatient	1184	894 (75.51)	148 (12.50)	85.80	14.20
Other	Inpatient	3	3 (100.00)	0 (0.00)	100.00	0.00
Other Doctor	Inpatient	287	185 (64.46)	76 (26.48)	70.88	29.12
	Outpatient	158	107 (67.72)	32 (20.25)	76.98	23.02
Pharmacist	Missing data	90	25 (27.78)	0 (0.00)	100.00	0.00
	Both Inpatient and Outpatient	68	43 (63.24)	9 (13.24)	82.69	17.31
	Inpatient	5768	4930 (85.47)	267 (4.63)	94.86	5.14
	Outpatient	5415	4953 (91.47)	125 (2.31)	97.54	2.46
Pre-Registration Nurse	Inpatient	27	16 (59.26)	2 (7.41)	88.89	11.11
	Outpatient	2	1 (50.00)	0 (0.00)	100.00	0.00
Registered Nurse	Missing data	28	4 (14.29)	9 (32.14)	30.77	69.23
	Both Inpatient and Outpatient	27	10 (37.04)	2 (7.41)	83.33	16.67
	Inpatient	4441	2210 (49.76)	270 (6.08)	89.11	10.89
	Outpatient	931	448 (48.12)	120 (12.89)	78.87	21.13
Registrar	Missing data	1148	0 (0.00)	199 (17.33)	0.00	100.00
	Both Inpatient and Outpatient	15	9 (60.00)	4 (26.67)	69.23	30.77
	Inpatient	13893	7868 (56.63)	4562 (32.84)	63.30	36.70
	Outpatient	3710	2767 (74.58)	689 (18.57)	80.06	19.94

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Missing data	Missing data	3	0 (0.00)	2 (66.67)	0.00	100.00
	Inpatient	356	214 (60.11)	72 (20.22)	74.83	25.17
	Outpatient	888	797 (89.75)	22 (2.48)	97.31	2.69

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9.3 Appendix 3

Table 5. Provider Type by description count and percentage, override and removed percentages (n=53,057).

Provider Type	Description	Total Warning Status counts n=53057	Overridden counts (% of Total Warning Status)	Removed counts (% of Total Warning Status)	Overridden / (Overridden + Removed) %	Removed / (Overridden + Removed) %
Consultant Dental Surgeon	Nsaid	2	0 (0.00)	0 (0.00)	0.00	0.00
	Anti-biotic	3	0 (0.00)	0 (0.00)	0.00	0.00
	Opioid	5	3 (60.00)	0 (0.00)	100.00	0.00
Pre-Registration Pharmacist	Nsaid	9	6 (66.67)	0 (0.00)	100.00	0.00
	Anti-emetic	3	1 (33.33)	0 (0.00)	100.00	0.00
	Anti-biotic	6	5 (83.33)	0 (0.00)	100.00	0.00
	Anti-histamine	2	1 (50.00)	0 (0.00)	100.00	0.00
	Opioid	74	29 (39.19)	0 (0.00)	100.00	0.00
	Other	21	9 (42.86)	0 (0.00)	100.00	0.00
	Steroid	4	4 (100.00)	0 (0.00)	100.00	0.00
Technician	Nsaid	185	140 (75.68)	0 (0.00)	100.00	0.00
	Anti-emetic	39	31 (79.49)	0 (0.00)	100.00	0.00
	Anti-biotic	443	388 (87.58)	0 (0.00)	100.00	0.00
	Anti-histamine	16	9 (56.25)	0 (0.00)	100.00	0.00
	Corti-costeroid	46	43 (93.48)	0 (0.00)	100.00	0.00
	Immuno-globulin	13	12 (92.31)	0 (0.00)	100.00	0.00
	Opioid	1255	1088 (86.69)	0 (0.00)	100.00	0.00
	Other	512	329 (64.26)	1 (0.20)	99.70	0.30
	Steroid	36	32 (88.89)	0 (0.00)	100.00	0.00
Allied Health Professional	Nsaid	157	70 (44.59)	45 (28.66)	60.87	39.13
	Anti-emetic	20	4 (20.00)	12 (60.00)	25.00	75.00
	Anti-biotic	116	85 (73.28)	11 (9.48)	88.54	11.46
	Anti-histamine	4	4 (100.00)	0 (0.00)	100.00	0.00
	Corti-costeroid	7	6 (85.71)	1 (14.29)	85.71	14.29
	Immuno-globulin	91	44 (48.35)	0 (0.00)	100.00	0.00
	Opioid	367	249 (67.85)	22 (5.99)	91.88	8.12
	Other	318	216 (67.92)	44 (13.84)	83.08	16.92
	Steroid	11	7 (63.64)	2 (18.18)	77.78	22.22
Consultant	Nsaid	1618	167 (10.32)	1114 (68.85)	13.04	86.96
	Anti-emetic	549	104 (18.94)	401 (73.04)	20.59	79.41
	Anti-biotic	1004	281 (27.99)	208 (20.72)	57.46	42.54
	Anti-histamine	120	49 (40.83)	66 (55.00)	42.61	57.39
	Corti-costeroid	60	44 (73.33)	7 (11.67)	86.27	13.73
	Immuno--globulin	1	1 (100.00)	0 (0.00)	100.00	0.00
	Opioid	4478	1982 (44.26)	986 (22.02)	66.78	33.22
	Other	900	337(37.44)	398 (44.22)	45.85	54.15

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	Steroid	128	98 (76.56)	4 (3.12)	96.08	3.92
Junior Doctor	Nsaid	310	151 (48.71)	119 (38.39)	55.93	44.07
	Anti-emetic	73	32 (43.84)	33 (45.21)	49.23	50.77
	Anti-biotic	553	277 (50.09)	226 (40.87)	55.07	44.93
	Anti-histamine	26	13 (50.00)	10 (38.46)	56.52	43.48
	Corti-costeroid	13	13 (100.00)	0 (0.00)	100.00	0.00
	Immuno-globulin	9	4 (44.44)	0 (0.00)	100.00	0.00
	Opioid	1511	1097 (72.60)	285 (18.86)	79.38	20.62
	Other	645	437 (67.75)	134 (20.78)	76.53	23.47
	Steroid	36	28 (77.78)	8 (22.22)	77.78	22.22
Other	Corti-costeroid	1	1 (100.00)	0 (0.00)	100.00	0.00
	Other	2	2 (100.00)	0 (0.00)	100.00	0.00
Other Doctor	Nsaid	36	20 (55.56)	13 (36.11)	60.61	39.39
	Anti-emetic	8	6 (75.00)	2 (25.00)	75.00	25.00
	Anti-biotic	82	34 (41.46)	36 (43.90)	48.57	51.43
	Anti-histamine	11	5 (45.45)	6 (54.55)	45.45	54.55
	Corti-costeroid	8	8 (100.00)	0 (0.00)	100.00	0.00
	Opioid	225	165 (73.33)	40 (17.78)	80.49	19.51
	Other	69	52 (75.36)	9 (13.04)	85.25	14.75
	Steroid	6	2 (33.33)	2 (33.33)	50.00	50.00
Pharmacist	Nsaid	649	545 (83.98)	40 (6.16)	93.16	6.84
	Anti-emetic	205	182 (88.78)	4 (1.95)	97.85	2.15
	Anti-biotic	1715	1470 (85.71)	94 (5.48)	93.99	6.01
	Anti-histamine	76	74 (97.37)	0 (0.00)	100.00	0.00
	Corti-costeroid	272	251 (92.28)	9 (3.31)	96.54	3.46
	Immune-globulin	844	671 (79.50)	47 (5.57)	93.45	6.55
	Opioid	5205	4760 (91.45)	104 (2.00)	97.86	2.14
	Other	2175	1824 (83.86)	100 (4.60)	94.80	5.20
	Steroid	200	174 (87.00)	3 (1.50)	98.31	1.69
Pre-Registration Nurse	Nsaid	3	0 (0.00)	2 (66.67)	0.00	100.00
	Anti-emetic	2	2 (100.00)	0 (0.00)	100.00	0.00
	Anti-biotic	3	2 (66.67)	0 (0.00)	100.00	0.00
	Anti-histamine	2	2 (100.00)	0 (0.00)	100.00	0.00
	Opioid	13	7 (53.85)	0 (0.00)	100.00	0.00
	Other	6	4 (66.67)	0 (0.00)	100.00	0.00
Registered Nurse	Nsaid	282	100 (35.46)	64 (22.70)	60.98	39.02
	Anti-emetic	130	73 (56.15)	21 (16.15)	77.66	22.34
	Anti-biotic	547	242 (44.24)	113 (20.66)	68.17	31.83
	Anti-histamine	77	42 (54.55)	13 (16.88)	76.36	23.64
	Corti-costeroid	50	27 (54.00)	8 (16.00)	77.14	22.86
	Immuno-globulin	884	297 (33.60)	5 (0.57)	98.34	1.66
	Opioid	2434	1362 (55.96)	86 (3.53)	94.06	5.94
	Other	925	479 (51.78)	81 (8.76)	85.54	14.46

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	Steroid	98	50 (51.02)	10 (10.20)	83.33	16.67
Registrar	Nsaid	1826	599 (32.80)	925 (50.66)	39.30	60.70
	Anti-emetic	683	267 (39.09)	362 (53.00)	42.45	57.55
	Anti-biotic	3295	1621 (49.20)	1195 (36.27)	57.56	42.44
	Anti-histamine	228	81 (35.53)	124 (54.39)	39.51	60.49
	Corti-costeroid	402	298 (74.13)	81 (20.15)	78.63	21.37
	Immuno-globulin	273	141 (51.65)	62 (22.71)	69.46	30.54
	Opioid	9163	5857 (63.92)	1914 (20.89)	75.37	24.63
	Other	2591	1552 (59.90)	749 (28.91)	67.45	32.55
	Steroid	305	228 (74.75)	42 (13.77)	84.44	15.56
Missing data	Nsaid	151	122 (80.79)	15 (9.93)	89.05	10.95
	Anti-emetic	50	41 (82.00)	7 (14.00)	85.42	14.58
	Anti-biotic	196	137 (69.90)	31 (15.82)	81.55	18.45
	Anti-histamine	2	2 (100.00)	0 (0.00)	100.00	0.00
	Corti-costeroid	21	20 (95.24)	0 (0.00)	100.00	0.00
	Immuno-globulin	15	9 (60.00)	0 (0.00)	100.00	0.00
	Opioid	447	373 (83.45)	25 (5.59)	93.72	6.28
	Other	307	260 (84.69)	13 (4.23)	95.24	4.76
	Steroid	58	47 (81.03)	5 (8.62)	90.38	9.62

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9.4 Appendix 4

Table 6. Provider Specialty by context counts and percentages, override and removed percentage (n=53,057).

Provider Specialty	Context	Total Warning Status counts n=53057	Overridden counts (% of Total Warning Status)	Removed counts (% of Total Warning Status)	Overridden / (Overridden + Removed) %	Removed / (Overridden + Removed) %
Anesthesiology & Emergency Medicine	Missing data	2809	0 (0.00)	494 (17.59)	0.00	100.00
	Both Inpatient and Outpatient	4	2 (50.00)	2 (50.00)	50.00	50.00
	Inpatient	10824	4094 (37.82)	4773 (44.10)	46.17	53.83
	Outpatient	750	390 (52.00)	204 (27.20)	65.66	34.34
General Medicine & Other Medical Specialty	Missing data	56	0 (0.00)	23 (41.07)	0.00	100.00
	Both Inpatient and Outpatient	20	8 (40.00)	6 (30.00)	57.14	42.86
	Inpatient	10154	6132 (60.39)	213 (21.06)	74.15	25.85
	Outpatient	4142	3093 (74.67)	603 (14.56)	83.69	16.31
General Surgery & Other Surgical Specialty	Missing data	9	0 (0.00)	1 (11.11)	0.00	100.00
	Both Inpatient and Outpatient	6	6 (100.00)	0 (0.00)	100.00	0.00
	Inpatient	1940	1092 (56.29)	551 (28.40)	66.46	33.54
	Outpatient	1083	806 (74.42)	138 (12.74)	85.38	14.62
General Practice	Inpatient	367	225 (61.31)	112 (30.52)	66.77	33.23
	Outpatient	194	153 (78.87)	21 (10.82)	87.93	12.07
Neonatology Paediatrics	Inpatient	292	226 (77.40)	40 (13.70)	84.96	15.04
	Outpatient	68	50 (73.53)	10 (14.71)	83.33	16.67
Obstetrics Gynaecology	Missing data	9	4 (44.44)	1 (11.11)	80.00	20.00
	Both Inpatient and Outpatient	5	4 (80.00)	0 (0.00)	100.00	0.00
	Inpatient	657	289 (43.99)	291 (44.29)	49.83	50.17
	Outpatient	315	170 (53.97)	119 (37.78)	58.82	41.18
Oncology & Palliative Care	Missing data	2	0 (0.00)	1 (50.00)	0.00	100.00
	Both Inpatient and Outpatient	6	2 (33.33)	2 (33.33)	50.00	50.00
	Inpatient	1662	1203 (72.38)	247 (14.86)	82.97	17.03
	Outpatient	498	338 (67.87)	124 (24.90)	73.16	26.84
Other Non-Medical Specialty	Inpatient	57	26 (45.61)	25 (43.86)	50.98	49.02
	Outpatient	7	3 (42.86)	2 (28.57)	60.00	40.00
Pharmacy	Missing data	97	28 (28.87)	0 (0.00)	100.00	0.00
	Both Inpatient and Outpatient	97	44 (45.36)	9 (9.28)	83.02	16.98
	Inpatient	6127	5069 (82.73)	269 (4.39)	94.96	5.04
	Outpatient	7557	6807 (90.08)	127 (1.68)	98.17	1.83
Missing Data	Missing data	17	0 (0.00)	5 (29.41)	0.00	100.00
	Both Inpatient and Outpatient	13	3 (23.08)	0 (0.00)	100.00	0.00
	Inpatient	1738	965 (55.52)	231 (13.29)	80.69	19.31
	Outpatient	1475	1288 (87.32)	30 (2.03)	97.72	2.28

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9.5 Appendix 5

Table 7. Provider Specialty by description counts and percentages, override and removed (n=53,057).

Provider Specialty	Description	Total Warning Status counts n=53057	Overridden counts (% of Total Warning Status)	Removed counts (% of Total Warning Status)	Overridden / (Overridden + Removed) %	Removed / (Overridden + Removed) %
Anesthesiology & emergency medicine	NSAID	2584	242 (9.37)	1760 (68.11)	12.09	87.91
	anti-emetic	666	46 (6.91)	594 (89.19)	7.19	92.81
	Anti-biotic	1748	390 (22.31)	531 (30.38)	42.35	57.65
	Anti-histamine	174	29 (16.67)	136 (78.16)	17.58	82.42
	Corti-costeroid	54	26 (48.15)	14 (25.93)	65.00	35.00
	Immuno-globulin	5	3 (60.00)	1 (20.00)	75.00	25.00
	opioid	7851	3398 (43.28)	1805 (22.99)	65.31	34.69
	other	1240	331 (26.69)	616 (49.68)	34.95	65.05
	steroid	65	21 (32.31)	16 (24.62)	56.76	43.24
General medicine & other medical specialty	NSAID	940	529 (56.28)	268 (28.51)	66.37	33.63
	anti-emetic	506	292 (57.71)	147 (29.05)	66.51	33.49
	Anti-biotic	2542	1524 (59.95)	745 (29.31)	67.17	32.83
	Anti-histamine	169	96 (56.80)	40 (23.67)	70.59	29.41
	Corti-costeroid	387	290 (74.94)	73 (18.86)	79.89	20.11
	Immuno-globulin	1053	392 (37.23)	56 (5.32)	87.50	12.50
	opioid	5666	4091 (72.20)	817 (14.42)	83.35	16.65
	other	2775	1770 (63.78)	585 (21.08)	75.16	24.84
	steroid	334	249 (74.55)	39 (11.68)	86.46	13.54
General surgery & other surgical specialty	NSAID	318	157 (49.37)	112 (35.22)	58.36	41.64
	anti-emetic	42	15 (35.71)	22 (52.38)	40.54	59.46
	Anti-biotic	396	175 (44.19)	166 (41.92)	51.32	48.68
	Anti-histamine	22	8 (36.36)	12 (54.55)	40.00	60.00
	Corti-costeroid	4	4 (100.00)	0 (0.00)	100.00	0.00
	Immuno-globulin	68	20 (29.41)	0 (0.00)	100.00	0.00
	opioid	1773	1230 (69.37)	316 (17.82)	79.56	20.44
	other	395	279 (70.63)	61 (15.44)	82.06	17.94
	steroid	20	16 (80.00)	1 (5.00)	94.12	5.88
General practice	NSAID	38	16 (42.11)	16 (42.11)	50.00	50.00
	anti-emetic	6	6 (100.00)	0 (0.00)	100.00	0.00
	Anti-biotic	102	45 (44.12)	50 (49.02)	47.37	52.63
	Anti-histamine	10	4 (40.00)	6 (60.00)	40.00	60.00
	Corti-costeroid	5	5 (100.00)	0 (0.00)	100.00	0.00
	opioid	308	233 (75.65)	45 (14.61)	83.81	16.19
	other	89	66 (74.16)	16 (17.98)	80.49	19.51
	steroid	3	3 (100.00)	0 (0.00)	100.00	0.00
Neonatology paediatrics	NSAID	8	7 (987.50)	1 (12.50)	87.50	12.50

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	anti-emetic	28	18 (64.29)	5 (17.86)	78.26	21.74
	Anti-biotic	97	71 (73.20)	20 (20.62)	78.02	21.98
	Anti-histamine	13	13 (100.00)	0 (0.00)	100.00	0.00
	Corti-costeroid	19	15 (78.95)	1 (5.26)	93.75	6.25
	opioid	111	86 (77.48)	12 (10.81)	87.76	12.24
	other	45	33 (73.33)	8 (17.78)	80.49	19.51
	steroid	39	33 (84.62)	3 (7.69)	91.67	8.33
Obstetrics gynaecology	NSAID	121	37 (30.58)	65 (53.72)	36.27	63.73
	anti-emetic	52	11 (21.15)	39 (75.00)	22.00	78.00
	Anti-biotic	220	67 (30.45)	138 (62.73)	32.68	67.32
	Anti-histamine	13	3 (23.08)	8 (61.54)	27.27	72.73
	Corti-costeroid	2	1 (50.00)	1 (50.00)	50.00	50.00
	Immuno-globulin	1	1 (100.00)	0 (0.00)	100.00	0.00
	opioid	466	274 (58.80)	135 (28.97)	66.99	33.01
	other	110	72 (65.45)	25 (22.73)	74.23	25.77
	steroid	1	1 (100.00)	0 (0.00)	100.00	0.00
Oncology & palliative care	NSAID	86	53 (61.63)	23 (26.74)	69.74	30.26
	anti-emetic	126	83 (65.87)	20 (15.87)	80.58	19.42
	Anti-biotic	262	141 (53.82)	107 (40.84)	56.85	43.15
	Anti-histamine	55	38 (69.09)	13 (23.64)	74.51	25.49
	Corti-costeroid	54	42 (77.78)	7 (12.96)	85.71	14.29
	Immuno-globulin	60	27 (45.00)	2 (3.33)	93.10	6.90
	opioid	1128	864 (76.60)	151 (13.39)	85.12	14.88
	other	311	223 (71.70)	47 (15.11)	82.59	17.41
	steroid	86	72 (83.72)	4 (4.65)	94.74	5.26
Other non-medical specialty	NSAID	1	0 (0.00)	1 (0.00)	0.00	0.00
	Anti-biotic	3	3 (100.00)	3 (0.00)	100.00	0.00
	opioid	2	0 (0.00)	2 (100.00)	0.00	100.00
	other	58	26 (44.83)	25 (43.10)	50.98	49.02
Pharmacy	NSAID	840	682 (81.19)	40 (4.76)	94.46	5.54
	anti-emetic	242	210 (86.78)	4 (1.65)	98.13	1.87
	Anti-biotic	2120	1822 (85.94)	94 (4.43)	95.09	4.91
	Anti-histamine	91	81 (89.01)	0 (0.00)	100.00	0.00
	Corti-costeroid	314	290 (92.36)	9 (2.87)	96.99	3.01
	Immuno-globulin	869	695 (79.98)	47 (5.41)	93.67	6.33
	opioid	6469	5815 (89.89)	104 (1.61)	98.24	1.76
	other	2707	2157 (79.68)	104 (3.84)	95.40	4.60
	steroid	226	196 (86.73)	3 (1.33)	98.49	1.51
Missing data	NSAID	292	197 (67.47)	52 (17.81)	79.12	20.88
	anti-emetic	94	62 (65.96)	11 (11.70)	84.93	15.07
	Anti-biotic	473	304 (64.27)	63 (13.32)	82.83	17.17
	Anti-histamine	17	10 (58.82)	4 (23.53)	71.43	28.57
	Corti-costeroid	41	38 (92.68)	1 (2.44)	97.44	2.56

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Immuno-globulin	74	41 (55.41)	8 (10.81)	83.67	16.33
opioid	1403	981 (69.92)	75 (5.35)	92.90	7.10
other	741	544 (73.41)	42 (5.67)	92.83	7.17
steroid	108	79 (73.15)	10 (9.26)	88.76	11.24

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9.6 Appendix 6

Table 8. Recoding lists

Github link:
https://github.com/dbgmx/Dissertation_recoding_list

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9.7 Appendix 7

Python (pandas) script – version 3.8.8.

A Github respository has been used to host the Python (Pandas) script used in part fulfilment of the MSc. Data Science for Research in Health and Biomedicine.

Included in the following Python Github link are:

1/. Dissertation_Python_Pandas_script as a word document.

2/. Dissertation_Python_Pandas_script as a pdf document.

Github link:
https://github.com/dbgmx/Dissertation_Python_Pandas_script

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9.8 Appendix 8

R Studio script – R Studio version 1.4.1106.

Github link:

https://github.com/dbgmx/Dissertation_R_script

```
## Load data
df_a <- read.csv("~/analysis_df.csv", header=FALSE)
View(df_a)

## Amend headers
names(df_a) <- df_a[1,]
df_a <- df_a[-1,]
head(df_a)
summary(df_a)

## Update types
df_a$warning_status <- as.numeric(df_a$warning_status)
df_a$provider_type_cat1 <- as.factor(df_a$provider_type_cat1)
df_a$provider_type_cat2 <- as.factor(df_a$provider_type_cat2)
df_a$provider_specialty_cat1 <- as.factor(df_a$provider_specialty_cat1)
df_a$provider_specialty_cat2 <- as.factor(df_a$provider_specialty_cat2)
df_a$description_cat1 <- as.factor(df_a$description_cat1)
df_a$context <- as.factor(df_a$context)
df_a$drug_allergy_reactions <- as.factor(df_a$drug_allergy_reactions)
df_a$age_range <- as.factor(df_a$age_range)
df_a$sex <- as.factor(df_a$sex)
df_a$severity <- as.factor(df_a$severity)
df_a$importance_level <- as.factor(df_a$importance_level)
df_a$drug_allergy_contraindication_group <- as.factor(df_a$drug_allergy_contraindication_group)
str(df_a)

## Install packages
install.packages('aod')
library(aod)

## Unadjusted logisic regression, ORs, CIs and Wald test for trend
## provider_type_cat1
mylogit1 <- glm(warning_status ~ provider_type_cat1, data = df_a, family = "binomial")
summary(mylogit1)
exp(cbind(OR = coef(mylogit1), confint(mylogit1)))

## provider_type_cat2
mylogit2 <- glm(warning_status ~ provider_type_cat2, data = df_a, family = "binomial")
summary(mylogit2)
exp(cbind(OR = coef(mylogit2), confint(mylogit2)))
wald.test(b = coef(mylogit2), Sigma = vcov(mylogit2), Terms = 1:12)

## provider_specialty_cat1
mylogit3 <- glm(warning_status ~ provider_specialty_cat1, data = df_a, family = "binomial")
summary(mylogit3)
exp(cbind(OR = coef(mylogit3), confint(mylogit3)))
wald.test(b = coef(mylogit3), Sigma = vcov(mylogit3), Terms = 1:9)

## provider_specialty_cat2
mylogit4 <- glm(warning_status ~ provider_specialty_cat2, data = df_a, family = "binomial")
summary(mylogit4)
exp(cbind(OR = coef(mylogit4), confint(mylogit4)))
wald.test(b = coef(mylogit4), Sigma = vcov(mylogit4), Terms = 1:16)

## description_cat1
mylogit5 <- glm(warning_status ~ description_cat1, data = df_a, family = "binomial")
summary(mylogit5)
exp(cbind(OR = coef(mylogit5), confint(mylogit5)))
wald.test(b = coef(mylogit5), Sigma = vcov(mylogit5), Terms = 1:9)

## context
mylogit6 <- glm(warning_status ~ context, data = df_a, family = "binomial")
summary(mylogit6)
exp(cbind(OR = coef(mylogit6), confint(mylogit6)))
wald.test(b = coef(mylogit6), Sigma = vcov(mylogit6), Terms = 1:3)
```


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```
## drug_allergy_reactions
mylogit7 <- glm(warning_status ~ drug_allergy_reactions, data = df_a, family = "binomial")
summary(mylogit7)
exp(cbind(OR = coef(mylogit7), confint(mylogit7)))
wald.test(b = coef(mylogit7), Sigma = vcov(mylogit7), Terms = 1:8)

## age_range
mylogit8 <- glm(warning_status ~ age_range, data = df_a, family = "binomial")
summary(mylogit8)
exp(cbind(OR = coef(mylogit8), confint(mylogit8)))
wald.test(b = coef(mylogit8), Sigma = vcov(mylogit8), Terms = 1:9)

## sex
mylogit9 <- glm(warning_status ~ sex, data = df_a, family = "binomial")
summary(mylogit9)
exp(cbind(OR = coef(mylogit9), confint(mylogit9)))
wald.test(b = coef(mylogit9), Sigma = vcov(mylogit9), Terms = 1:2)

## severity
mylogit10 <- glm(warning_status ~ severity, data = df_a, family = "binomial")
summary(mylogit10)
exp(cbind(OR = coef(mylogit10), confint(mylogit10)))
wald.test(b = coef(mylogit10), Sigma = vcov(mylogit10), Terms = 1:3)

## importance_level
mylogit11 <- glm(warning_status ~ importance_level, data = df_a, family = "binomial")
summary(mylogit11)
exp(cbind(OR = coef(mylogit11), confint(mylogit11)))
wald.test(b = coef(mylogit11), Sigma = vcov(mylogit11), Terms = 1:3)

## drug_allergy_contraindication_group
mylogit12 <- glm(warning_status ~ drug_allergy_contraindication_group, data = df_a, family = "binomial")
summary(mylogit12)
exp(cbind(OR = coef(mylogit12), confint(mylogit12)))
wald.test(b = coef(mylogit12), Sigma = vcov(mylogit12), Terms = 1:3)
str(df_a)

#####
## Adjusted regression - provider_type_cat2 + provider_specialty_cat1
mylogit_b <- glm(formula = warning_status ~ provider_type_cat2 + provider_specialty_cat1 + description_cat1 + context +
drug_allergy_reactions + age_range + sex + severity + importance_level + drug_allergy_contraindication_group, family = "binomial", data
= df_a)
summary(mylogit_b)
## odds ratios and 95% CI
exp(cbind(OR = coef(mylogit_b), confint(mylogit_b)))
```


*****