institute of health informatics

# Graduate Programme in Health Data Science

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**Allergy Related Clinical Prescribing Alerts (ARCPA):**

**Description and Impact**

**By**

**\*\*\*\*\***

**31st August 2021**

**A Dissertation submitted in part fulfilment of the**

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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

# 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.

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.

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 |

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.

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.

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  n=43119 | Override count (%)  n=32520 | Removed count (%)  n=10599 | Unadjusted  OR (95% CI), p-value | Adjusted  OR (95% CI), p-value |
| --- | --- | --- | --- | --- | --- |
| 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 |
| 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 |
| 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.

# 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 ask-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.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| D-A reaction | D-A reaction  count  **(A)**  (n=53057 ) | D-A reaction percentage  (%) | Overridden | | | Removed | | |
| **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** |

## 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 |
| 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 |

## 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 |
|  | 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 |
|  | 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 |

## 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 |

## 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 |
|  | 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 |
| **P**harmacy | 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 |
|  | 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 |

## 9.6 Appendix 6

Table 8. Recoding lists

**Github link:**

<https://github.com/dbgmx/Dissertation_recoding_list>

## 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](https://github.com/dbgmx/Dissertation_Python_Pandas_script) 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>

## 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)

## 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)))