# Supplementary Materials for Compulsory Indications in Hospital Prescribing Software Tested with Antibacterial Prescriptions

## Contents

**Appendix 1.** Grouping for Specific Medicines

Due to a known Medchart™ constraint, some amoxicillin and trimethoprim prescriptions had a compulsory indication introduced at the time of the intervention. This was because amoxicillin + clavulanic acid and trimethoprim + sulfamethoxazole medicine combinations were part of the intervention group. As a result, any amoxicillin or trimethoprim prescriptions created using the same form as amoxicillin + clavulanic acid and trimethoprim + sulfamethoxazole respectively also had compulsory indications introduced. To ensure appropriate classification of medicines into the intervention, positive control, and negative control groups, each possible combination of medicine, prescribing method, and medication form were tested using Medchart™ and the combination allocated to the appropriate group (intervention, positive control, or negative control). Hence, some amoxicillin and trimethoprim prescriptions are correctly included in the intervention group rather than the negative control group, as the compulsory field was introduced for these prescriptions at the time of intervention. A full list of combinations and their classifications for amoxicillin and trimethoprim can be reviewed below.

<u>Amoxicillin – Intervention Group Prescribing Combinations</u>

- Longhand - injection: powder form
- Medication on admission - injection: powder form
- Protocol - injection: powder form
- Quicklist - injection: powder form
- Transfer - injection: powder form
- Longhand - oral liquid: powder form
- Quicklist - oral liquid: powder form
- Transfer - oral liquid: powder form
- Longhand - tablet form
- Quicklist - tablet form
- Transfer - tablet form

<u>Trimethoprim – Intervention Group Prescribing Combinations</u>

- Longhand - oral liquid form
- Quicklist - oral liquid form
- Longhand - tablet form
- Medication on admission - tablet form
- Protocol - tablet form
- Quicklist - tablet form
- Transfer - tablet form

Similarly, tobramycin had a pre-existing compulsory indication field if prescribed for an inhalation route but had no compulsory indication if prescribed for a non-inhalation route. Therefore, all tobramycin prescriptions for an inhalation route were included in the positive control group, whereas all tobramycin prescriptions for a non-inhalation route were included in the negative control group.

A medicine ‘transferred’ from another system was classified into the same group as the longhand version of a prescription for the same form and medicine.

Any prescription completed using longhand prescribing where form was not specified did not have a compulsory indication introduced regardless of the intervention, positive control, or negative control group the medicine was allocated to. This is because prescribing without form renders the indication field non-compulsory. Such prescriptions were recorded as having an ‘unknown’ form in the data warehouse. 3.20% (337/10528) of all prescriptions in the dataset had an ‘unknown’ form, and 2.69% (67/2495) of all prescriptions with an assumed compulsory indication (positive control group before or after the compulsory field was introduced, or intervention group after the compulsory field was introduced) had an ‘unknown’ form. This was accepted as a limitation of the dataset and justifies why a small number of blanks were present after the intervention.

For some medicines an indication would be prepopulated into the free text field if prescribed by protocol. This indication could be edited by the prescriber. If the indication was prepopulated, but not required, the indication was considered non-compulsory. Non-compulsory indications were either classified into the negative control group before or after the compulsory field was introduced, or intervention group prior to the compulsory field being introduced. This is because the prepopulated text could be removed by the prescriber. The prepopulated text was not necessarily an indication and was classified as a 'indication present', 'other text', 'rubbish text' or 'blank' indication in a blinded manner, as per all other free text documented.

Independent to our study, yet concurrently with the intervention, the protocol 'Pick List, Adult, Anaesthetics, General' was updated to contain the prepopulated indication 'Surgical Antimicrobial prophylaxis'. The indication remained non-compulsory, and the prepopulated text could be removed by the prescriber prior to completing the prescription. The text 'Surgical Antimicrobial prophylaxis' was classified as 'indication present' and hence inclusion of prescriptions created using the protocol would result in biasing of the results after the intervention upwards. There were 851 prescriptions created using this protocol before the intervention, and 956 after the intervention. The protocol applied to six medicines: amoxicillin (n=61), amoxicillin + clavulanic acid (n=174), cefazolin (n=1050), cefuroxime (n=199), gentamicin (n=142), and metronidazole (n=181). Although only prescriptions created after the intervention were affected by the change in protocol, prescriptions from this protocol both before and after the intervention were excluded to prevent results being biased through higher proportions of the six listed medicines being present before the intervention compared to after the intervention.

**Appendix 2.** Generic medicine names in the 'intervention', 'pre-existing compulsory indication' and 'no pre-existing compulsory indication' group.

Intervention group (n=7): amoxicillin + clavulanic acid, ciprofloxacin, gentamicin, vancomycin, meropenem, piperacillin + tazobactam, and trimethoprim + sulfamethoxazole.

Pre-existing compulsory indication group (n=5): azithromycin, ceftaroline fosamil, clarithromycin, moxifloxacin, roxithromycin.

No pre-existing compulsory indication group (n=72): amikacin, amoxicillin, avibactam, aztreonam, bedaquiline, benzathine penicillin (as benzathine benzylpenicillin tetrahydrate), benzylpenicillin, cefaclor, cefalexin, cefazolin, cefazolin + heparin sodium, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftolozane + tazobactam, ceftriaxone, cefuroxime, chloramphenicol, cilastatin, ciprofloxacin + hydrocortisone, clindamycin, clindamycin hydrochloride, clofazimine, colistimethate, cycloserine, dapsone, daptomycin, demeclocycline, doxycycline, ertapenem, erythromycin, erythromycin (as ethtlsuccinate, lactobionate, and stearate), ethambutol, fidaxomicin, flucloxacillin, fosfomycin, fusidate sodium, imipenem + cilastatin, isoniazid, isoniazid + rifampicin, levofloxacin, linezolid, lymecycline, methenamine, metronidazole, minocycline, nitrofurantoin, norfloxacin, ornidazole, para-aminosalicylic acid, paromomycin, phenoxymethylpenicillin, pivmecillinam hydrochloride, pivmecillinam, procaine benzylpenicillin, protionamide, pyrazinamide, rifabutin, rifampicin, spiramycin, streptomycin sulfate, streptomycin, sulfadiazine, sulfadiazine silver, teicoplanin, tetracycline, ticarcillin, tigecycline, tobramycin, trimethoprim, vancomycin + heparin sodium.

**Appendix 3.** Definitions and explanations of relevant prescribing terms used.

- Prescriptions were medicines prescribed in the ePA system as a scheduled prescription administered once or more to the patient, or as a PRN medicine 'live' for one hour or more. This excluded prescriptions that were technically live in the system but updated or ceased before affecting patient care.
- Every prescription in the ePA system has an indication field. Indications were extracted from the hospital ePA data. The text or absence of text (blank) was extracted for each field for analysis.
- The text in the indication field for the complete data set was allocated to four categories: 'indication present', 'other text', 'rubbish text' and 'blank'. Free text was classified using the guidelines in Supplementary Appendix 4.
- Frequencies were calculated as the proportion of prescriptions with the defined classification of interest in each group (intervention, positive control, or negative control group).
- An admission was an episode of hospital care starting from admission from the community and ending at discharge back to the community. Individual patients may have had more than one admission. At

each admission all medicines are re-prescribed. The rate of readmissions was similar in both time periods.

- Prescription created datetime was the datetime the prescriber created (opened) the order in the hospital ePA system.
- Prescription commenced datetime was the datetime the first dose of the prescription was intended to be administered when the prescription was created.
- Datetime of first administration was the time the administration record for the first dose of the prescription was entered. This was further classified as administered, delayed, withheld, or not given.
- Duration of inpatient stay was the difference in time in days between datetime of inpatient stay admission and datetime of inpatient stay discharge.
- Datetime since admission was the difference in time between time of inpatient stay admission and time the prescription was created.
- A 'medicine' referred to all products for a particular medicine including all forms and routes of administration.
- Antibacterial medicines were defined as all medicines in the antibacterial chapter (5.1) of the New Zealand Formulary (https://nzf.org.nz).

**Appendix 4.** Examples of working guidance for classification of indications as 'indication present', 'other text', 'rubbish text', or 'blank'.

There was a clear spectrum of indication validity, with cases on a scale of valid indication to no valid indication. There were numerous indications where validity was difficult to determine. We focused on ensuring classification was consistent and our data therefore reliable. Abbreviations were accepted if they were in common usage or standard abbreviations. Common usage was interpreted liberally based on current local practice. Spelling errors were accepted. Discussion and precedent, consistency within the database, were primary factors for classification. During the process terms were reclassified as needed for consistency within the data base.

- Indication present (n = 2999)
- Other text (n = 1716)
- Rubbish text (n = 13)
- Blank (n = 5800)

Drug Classes

Drug classes describing the disease or condition the medicines of that class are being used to treat, were accepted as indications. For example, 'antihypertensive' was accepted as a synonym for hypertension and hence accepted as an indication. Similarly, 'analgesia', 'antiemetic', 'antidepressant', 'antihypertensive', 'anxiolytic', and 'antiepileptic' were accepted as indications. A drug class such as thiazide diuretic or prokinetic was not taken as a synonym for an indication. 'Anticoagulant' was not accepted as an indication as it is not a synonym for atrial fibrillation or venous thromboembolism. The exception to this was where the reason for requiring anticoagulation was clearly specified such as 'anticoagulation bedbound' and 'anticoagulation for flight'. Similarly, 'antihistamine' and 'anticholinergic' were not accepted as indications.

Bridging, where the medicine being bridged to was specified, was accepted as an indication. This included 'bridging clexane', bridging warfarin' and more generally 'anticoagulant bridging'. 'Bridging until INR X' (where the X indicated a specific target value) was also accepted as an indication. To maintain consistency with the prophylaxis rules below, 'cover' was not accepted as a synonym for bridging, and therefore 'warfarin cover' and 'dabigatran cover' were not accepted as indications.

Medicine reversal was accepted as an indication where the medicine being reversed was specified. Hence 'dabigatran reversal pre-op' was considered an indication.

'Stress dose' was accepted as an indication for steroid use and hence the following text inputs were accepted as indications: 'stress dose steroids', 'stress dosing', 'perioperative steroids', 'perioperative steroid cover', 'rescue dose of steroid', 'stress dose for infection', and 'weaning from stress dose'.

Pain

'Pain' was considered an indication, and therefore synonyms of pain such as 'discomfort', 'sore', 'irritation' (e.g., discomfort with NG tube, or skin irritation), 'inflammation', 'burning', and 'stinging' were also accepted. 'Neuropathic', where pain was not specified, was not considered an indication and 'redness' without another accepted term was not accepted as an indication.

# followed by the bone fractured, or the word 'fracture' were accepted as an indication, as we assumed that the medicine was for pain and analgesia. We accept this might not have been the case for all medicines with this indication. 'Dislocation' was also accepted as an indication by the same assumption.

Nausea and vomiting

Both 'nausea' and 'vomiting' were accepted as indications. Commonly used acronyms such as 'CINV' and 'NV' were also accepted. 'Highly emetogenic' was also accepted, to remain consistent with accepting nausea and antiemetics, but 'minimal emetogenicity' and 'low emetogenicity' were not considered indications, as text containing a negative prefix (such as 'no nausea') was not accepted as an indication.

Vaccines and OCP

Vaccines were accepted as a separate category for which the indication was defined by the product. Any indication including the word 'vaccine', 'vaccination', or 'immunisation', was accepted.

Similarly, 'oral contraceptive' was accepted as a separate category for which the indication was defined by the product. If the indication implied the medicine was for 'contraception', 'OCP', 'COC', 'COCP', or the 'progesterone only pill', the indication was accepted.

Cancer and Chemotherapy

A specific type of cancer specified e.g., 'AML' or 'gynae cancer' was accepted as an indication, as was 'metastasis'. 'Reduce tumour bulk' was also accepted as it was considered specific enough to describe the exact purpose of the medicine, whereas 'tumour burden' and 'tumour suppression' were not accepted, as these words were not considered specific enough in intent or cancer type.

'Chemotherapy', 'CHOP', and 'chemotherapy prophylaxis' were too vague regarding purpose of the medicine, or were too generic describing the medicine being given rather than the indication or purpose for which the medicine was being given. None of these three text inputs were accepted.

Infection and Fever

For an infection to be accepted as an indication, either a site or type of infection had to be specified. For example, 'pneumonia' (infection of the lungs) and 'UTI' (urinary tract infection) would both be accepted as indications. 'Sepsis' was accepted as an indication as it indicates a bacteraemia (infection with the site blood specified) with an extreme inflammatory response. Nonspecific text such as 'infection' was not accepted as an indication. When considering the site of an infection, 'wound' was considered a synonym for skin (and therefore when used with the word infection, it was assumed to mean cellulitis), and post-op or surgical was considered a synonym for the surgical site wound. Hence, 'infected wound', 'post-op infection', and 'PPM infection' were accepted as indications. 'Infection' did have to be specified, so 'dirty wound', 'contaminated wound', 'malodourous wound', and 'oozing wound' were not accepted as indications to remain consistent with our classification of injuries and wounds.

Drains were considered a specific site for infection. 'Purulent' and 'pus' were considered synonyms of infection, and if paired with a site or type, were accepted as an indication. A 'collection' was also considered a synonym for infection so 'pelvic collection' was accepted as an indication.

If the treatment was clearly empiric, and hence the type or site of the infection was unknown, it was accepted as an indication. This included text such as 'infection of unknown origin', or 'empiric antibiotic treatment'. Empiric anti-infective treatment is more readily used when a patient is immunosuppressed, so if the text indicated immunosuppression and concurrent anti-infective use, it was assumed use of the medicine was empiric. An example of this was the accepted indications 'antiviral when immunosuppressed' and 'rising inflammatory markers whilst immunocompromised'. In contrast, 'raised inflammatory markers likely infection'

was categorised as other text, as there is no site or type of infection given, and there is no suggestion of immunosuppression. To remain consistent with the infection-based classifications, ‘cover’ was not accepted as a synonym for prophylaxis, so text such as ‘chest cover’ was not accepted as an indication.

Indications implying use to prevent immunosuppression or treat immunosuppression were accepted. This included ‘preventing neutropenia’ and ‘low neutrophils’. ‘Immunosuppressed’ alone was not accepted as an indication as it remains unclear whether the medicine is to induce immunosuppression (as in transplant treatment) or because of immunosuppression (as prophylactic infection prevention).

‘Fungal infection’, ‘polymicrobial infection’, and ‘viral infection’ were not accepted as indications as they are not specific enough to be considered a ‘type’ of infection. Similarly, ‘antifungal’ was not considered an indication. However, if a valid site was given (e.g., fungal infection between toes) then the indication was accepted. Therefore, the word ‘thrush’ required a site to be accepted as an indication.

‘Raised CRP’ and ‘raised inflammatory markers’ were considered other text, as these are not lab tests you can directly change with a medicine. In line with fever and infection guidelines, a site or type of likely infection had to be specified, or it had to be specified the person was immunocompromised, had a low neutrophil count, or were likely immunosuppressed. Where more than two sites of infection were described, and it was not clear to be empiric treatment, it was not accepted as an indication (e.g., CRP chest urine skin).

‘Chorio’ was considered a site not a condition. It is not a suitable acronym for chorioamnionitis, as there are other conditions starting with the prefix chorio, such as choriocarcinoma.

Fever or pyrexia alone is a symptom that can be medically treated, and hence ‘fever’ and ‘pyrexia’ without other text were accepted as indications. ‘Fever post plasma exchange’ and ‘fever during chemo’ were also accepted, as fever was the symptom being treated. As per the lab guidelines below, a specific temperature value defined was accepted as an indication.

If an infection was implied, but a site or type not specified (as per the above guidelines), then it was classified as other text. For example, ‘fever raised WCC’ was not accepted as it was not clear what was being treated. However, as per the above guidelines, the text was accepted as an indication if use of the medicine was clearly empiric such as in ‘fever unknown source’ and ‘PUO’. A fever after a procedure was considered proxy for empiric infection treatment and so ‘post TRUS fever’, ‘post-partum fever’ and ‘febrile in the setting of a new wire’ were all accepted as indications. If it was stipulated the patient was immunocompromised, this was accepted as proxy for empiric treatment and hence ‘fever neutropenic’ and ‘fever low WBC’ were accepted. Where it remained ambiguous, it was not accepted, such as for ‘fever with raised WCC’, ‘fever take blood cultures please’, and ‘fever non-neutropenic’. In these last three cases it was unclear whether the symptoms of fever or whether an infection of no specific site was being treated.

If the word fever was coupled with another accepted indication, the text would be accepted (e.g., ‘fever with haematuria’, where haematuria is an accepted indication, or ‘febrile diarrhoea’, where diarrhoea is an accepted indication). ‘Fever urine’, ‘haem fever’, and ‘consolidation and fever’ were not accepted as indications as a specific site was not provided.

‘Post op fever’ was not accepted as an indication as it was considered too generic. As above, the specific procedure was required to be documented. This is consistent with not accepting ‘post op antibiotics’ or ‘post op prophylaxis’ as an indication.

<u>Reactions and Pre-medication</u>

Pre-medication was accepted as an indication where the medicine or procedure it was pre-emptively treating was documented with reasonable specificity. It was accepted that a specific medicine or regime would be documented, such as asparaginase, or Folfox premed, but generic regimes (such as ‘premed for chemotherapy’) was not accepted as an indication as it is too vague. ‘Peg premed’ was not accepted, as peg could be an abbreviation for several different medical words.

Premed for CT contrast was considered an indication, as the medication is acting as prophylaxis for an immunological reaction. This is consistent with accepting anaphylaxis, hayfever, and allergy to contrast as indications. ‘CT scan’ or ‘CT prophylaxis’ without specifying that the medicine was for contrast prophylaxis was not accepted as an indication, in line with not accepting procedures as indications.

Where the text described a specific reaction or allergy being prevented, it was accepted as an indication. Therefore 'platelet reaction', 'prevention of contrast reaction', 'X drug reaction' (where X represents a specific medicine such as penicillin), 'contrast reaction', and 'dressing reaction' were all accepted. In contrast, 'drug reaction' was not accepted and 'skin reaction' was not accepted, as both are too generic. 'Reaction prophylaxis' was also not accepted due to lack of specificity, as it was not clear what was causing the reaction.

Prophylaxis or premed prior to RBC transfusion was accepted as an indication, as it is clear the treatment is to prevent a reaction occurring from the transfusion. If it was unclear whether the indication was to prevent a reaction, it was considered other text, such as 'administer with RBC'. Text indicating the medicine was for during or after the RBC transfusion was considered other text, as it did not imply prevention of an allergic based reaction. For example, 'after RBC transfusion', 'after platelet transfusion', 'platelets', 'platelet transfusion' (with no 'premed' included), 'prior to third unit of blood', 'RBC transfusion' (with no 'premed' included), and 'between RBC units' were all considered other text.

Transfusion incompatibility was considered an accepted indication so 'Rh positive' and 'ABO incompatibility' were accepted.

Prophylaxis

Prophylaxis was accepted as an indication where the type of prophylaxis was specified (e.g., 'antibiotic prophylaxis', 'infection prophylaxis', 'DVT prophylaxis', or 'infection prevention'). 'Prevention for X' (where the X would normally be accepted as an indication) was accepted as an indication. Generic text such as 'prophylaxis' was not accepted as an indication. Post-op was not considered an acceptable prefix for specifying type of prophylaxis, as there are several types of post-operative prophylaxis. Hence, 'post op prophylaxis', 'intraoperative dose', 'intraoperative antibiotics', and 'post op antibiotics' (not specified as prophylaxis) were not accepted as indications. 'Cover' was not accepted as a synonym for prophylaxis as it is too non-specific. Therefore, 'cover for infection' was considered 'other text'. As per the classification rules used for reactions and pre-medications, chemotherapy was considered too vague as a reason for prophylaxis and so 'prophylaxis on chemo' was classified as other text.

Prophylaxis in specific situations was accepted as an indication. This included 'CSF leak prophylaxis', 'preterm labour prophylaxis', and 'transplant prophylaxis'. All three of these situations described require specific protocols to be followed and hence the situation is the indication for medicine use. 'Prevent preterm labour' was also considered an indication as it is a valid reason for use of tocolytics, and 'PROM' was considered an indication as it is a valid reason for use of antibiotics in labour. However, 'preterm labour' without specifying whether use was to prevent preterm labour, or because of preterm labour, was not considered an indication. Similarly, 'SROM' was not considered an indication, as spontaneous rupture of membranes is normal rather than a specific indication for medicine-based treatment.

Procedures, Wounds, Catheters

Procedures were typically classified as other text, as a 'procedure' cannot typically be treated or completed using a medication, and hence the specific medicine purpose would be unclear. This included minor procedures such as biopsies which were categorised as other text. Hence, 'ORIF', 'hysterectomy', 'PPM insertion', and 'CT scan' were also classified as other text. A type of wound without additional information regarding the specific reason for use of the medicine (such as infection, or pain) was also considered other text. For example, 'laceration to toe', 'ulcer', and 'excoriated skin' were classified as other text as they are synonyms for 'wound'.

There were a few exceptions to the above rules. 'Drain flush' and 'blocked catheter' were accepted as indications as they can be directly treated with an infusion or injection of a product. The flush must be specified to be for a drain, catheter, or similar, and 'flush' alone was not accepted as an indication. E.g., 'unblock CVAD' (central venous access device) was accepted as an indication. A 'lock' such as an ethanol lock, Hickmann lock, or line lock was also accepted as an indication. 'Anal fissure' was accepted as an indication, but 'anal tear' was not accepted as it is not a specific diagnosis and considered more consistent with classification of 'wound' and '3$^{rd}$ degree tear'.

Catheter insertions were considered a procedure and therefore classified as other text unless there was additional information provided to justify use of the medicine (such as pain, or blocked catheter). Therefore, 'IDC insert', 'if required for ICD post op', 'IDCU', and 'catheterisation' were all considered other text.

Text related to stage of labour such as '3rd stage', or 'active labour' was not accepted as an indication. This is because labour was considered as a procedure, where specific explanation of the use of the medicine was required rather than documenting a generic stage of the procedure. Similarly, a type of tear such as 'third degree tear was not accepted, as this was considered a type of wound, and hence classified as other text to be consistent with the above rules.

Indications that a medicine was being used for organ transplant were accepted. This included the indications 'renal transplant', 'liver transplant', and 'lung transplant'. Similarly, removal of an organ which will result in immunosuppression or a lifelong requirement for hormone replacement, was accepted as an indication, such as 'adrenalectomy' and 'post splenectomy'.

Blood and Bleeding

To maintain consistency with classification of infection indications and classification of gastrointestinal medicine indications, for bleeding to be accepted as an indication, a site had to be provided. Therefore, 'haematuria', 'haematemesis', and 'PPH' (as an accepted abbreviation of post-partum haemorrhage) were accepted as indications. As drain was considered a site for infection, 'bleeding around the line' was accepted. Haematoma was not a site of bleeding and required a specific site to be documented to be considered an indication. 'Delivery of placenta with ongoing bleeding' was accepted as the placenta/uterus was the proxy site of bleeding. 'RPOC' was also considered an accepted indication. 'Intraoperative haemostasis' was accepted as an indication, as similarly to our method of infection classification, post-op or surgical was considered a synonym for the surgical site wound. However, 'haemostasis' without a specified site was not accepted as an indication. Because, in theory, all wounds bleed, 'wound bleeding' and synonyms of this such as 'ulcer bleeding' were not accepted as indications unless the site of the wound was more specifically described (e.g., surgical site wound, or bleeding tonsils). Bleeding with an antiplatelet or anticoagulant specified was accepted as an indication as it was assumed the treatment was for reversal of the antithrombotic agent. Similarly, bleeding with low platelets, low Hb, or low iron specified was accepted as an indication.

Cardiovascular Risk and Cardiovascular Medications and Hydration

Whether the medicine was clear for reducing cardiovascular event risk, it was accepted as an indication. This included 'CVS risk', 'cardiac secondary prevention', and 'high lipids' all being accepted as indications. If the type of secondary prevention was not specified, it was classified as other text.

'DVT', 'PE', 'VTE', 'HF', 'ACS', 'MI', and 'TIA' were all considered widely known and understood acronyms for accepted indications. Similarly, 'VTE prophylaxis' and 'DVT prophylaxis' were accepted as indications. 'Angina' and 'stroke' were also accepted as indications. 'CTCA' (CT coronary angiogram) was a procedure classified as other text.

'Heart failure', as well as specific types of heart failure (such as 'PEFHF') were accepted as indications. Similarly, 'fluid overload', 'oedema', and 'fluid build-up' were accepted as indications, as these were considered appropriate indications for diuretic use. Less specific terms where it remained unclear whether there was too much, or too little fluid meant the information was classified as other text, such as 'deal with fluid', 'fluid', 'fluid balance', and 'fluid breathing'. In accordance with accepting fluid overload as an indication, 'dehydration', 'hydration', and 'hyperhydration' were accepted as indications.

'Burn' was accepted as an indication, to maintain consistency with accepting 'pain'. Similarly, 'heartburn' was accepted as an indication. If the site of a seroma was documented, it was also considered an indication.

Urinary Related Indications

A stone where the type or site was specified, such as 'renal stone', 'gallstone', or 'bladder stone', as accepted as an indication. This is consistent with accepting infections where the type or site is specified. If the specific type or site of stone was not included, the indication was not accepted, such as 'passage of stone' or 'infected stone'.

Indications related to specific urinary issues were accepted if it was clear whether there was too much urine or too little urine. This included accepting 'reduce urine output overnight', 'urinary frequency', 'urinary hesitancy', 'urinary incontinency', 'difficulty passing urine', 'urinary leak', 'urinary flow'. Where it remained unclear whether there was too much or too little urine, the indication was classified as other text, such as 'urinary

symptoms' and 'urinary issues'. 'Urinary retention' was not accepted as an indication, because it implies treatment with IDC use, which itself is a procedure and hence not accepted as an indication.

'Irritable bladder', 'overactive bladder', 'bladder spasms', 'reflex bladder', 'unstable bladder', 'poor bladder compliance', 'bladder leakages', and 'strengthen bladder' were all accepted as indications as it was implied that urinary urgency and incontinence were occurring. 'Bladder control', 'regular bladder', and 'spinal bladder' were not accepted as indications as again, it was not clear whether the issue was lack of urinary flow, or urinary urgency and incontinence. 'Bladder irritation' was accepted as an indication as 'irritation' is considered a synonym for pain. To maintain consistency with the above classification, synonyms of pain are accepted as indications.

Bowel Motions

Any text which indicates the medicine was for preparation for a gastrointestinal camera-based procedure, it was accepted. This was because procedures such as a colonoscopy are common indications for laxatives and no more specific indication would be required. Therefore, 'prep for flexisig', 'colonogram', 'pill cam', 'colonoscopy', 'CT colonography', 'CTC', 'inadequate bowel prep', 'bowel prep', and 'bowels not running clear' were all accepted as indications.

Where the text indicated too high or too low stool output, the indication was accepted to maintain consistency with the rules stipulated for urinary output. Similarly, quantification of bowel motions was accepted as an indication, as logic dictates quantification of bowel motions is more specific information than constipation or diarrhoea (which were both accepted as indications). Hence, 'BNO', '2-3 BM a day', 'soft bowel motions', 'thickened stoma output', 'stool softener', 'stool bulking', 'bowel stimulation', 'flaccid bowel', 'bowel motility', 'reflex bowels', 'bowel leak', and 'loose bowels' were all accepted as indications.

Text that did not indicate whether the medicine was to slow or quicken stool output was not accepted as an indication. This included 'bowels', 'bowel regime', 'bowel cares', 'regulate bowels', and 'regular bowels'.

Gastrointestinal Medications

'Ileus' was accepted as an indication, as it was deemed this condition of the gastrointestinal tract was of equivalent specificity to conditions such as pneumonia for the respiratory tract. Bleeding from the upper gastrointestinal tract was also categorised as an indication, including UGIB, GI or duodenal ulcer. Non-specific gastrointestinal symptoms were categorised as other text, such as 'GI upset' and 'GI symptoms'.

If being used for peptic ulcer prophylaxis whilst concurrently on another medicine, the indication had to include specifically the words 'GI prophylaxis' or 'GI protection' to be considered an indication. 'While taking X' (where X was the concurrent medicine) was not considered an indication, and similarly, 'NSAID prophylaxis' and 'prednisone prophylaxis' were not accepted, as the prophylaxis was not specified to be for the gastrointestinal system.

Perforations of the gastrointestinal tract specifically were accepted. This included 'perforated duodenum', 'perf sigmoid', 'perforated gallbladder', and 'perforated appendix'. However, perforation outside the gastrointestinal tract was considered a form of wound and not an indication (for example 'perforation of the eye').

Respiratory Medicines

Text including the word 'secretion' was accepted as an indication. This is because the term is commonly used in the palliative care setting where secretions are a symptom being treated with medication. Sputum was treated similarly and was accepted as an indication if it was specified that the sputum was being cleared or removed. The words 'cleared', 'collected', 'induced', 'excoriated', and 'nebulised' were all accepted when used together with the word sputum. If it remained unclear whether the sputum was being cleared (i.e., 'sputum spec', 'sputum sample', 'growth on sputum', or 'sputum culture') then the text was not accepted. 'Chest physio' was not accepted as an indication as is describes a procedure rather than condition or reason for medicine use. 'Airways disease' was considered non-specific and hence not accepted as an indication. 'Respiratory distress' was accepted as an indication, and if a medicine was clearly for resuscitation, the text was accepted as an indication.

Withdrawal, Toxicity, and Smoking

Any text implying the medicine was for smoking cessation, such as ‘smoking’, ‘decreasing smoking’, ‘current smoker’, and ‘keen for smoking cessation’ was considered an indication. ‘Nicotine replacement therapy’ (including ‘NRT’) was similarly accepted as an indication. Where it was implied the text related to smoking was additional information wrongly included in the indication field, rather than the indication for a medicine, it was classified as other text. This included examples ‘ex-smoker’ and ‘laparotomy smoker BMI’.

‘Opioid dependence’, ‘opioid withdrawal’, ‘OST’ (opioid substitution therapy), and ‘opioid toxicity’ were all accepted as indications. Similarly, ‘alcohol withdrawal’, ‘alcohol misuse’, ‘alcohol detox’, and the abbreviation ‘AWS’ for alcohol withdrawal (scale), were accepted as indications. However, ‘CIWA’ alone was not accepted as an indication (as it is a scoring system) and indications containing CIWA were only accepted if they included another accepted indication such as ‘ETOH withdrawal’. ‘Addiction’ was also accepted as an indication.

Psychiatric Medications

‘Extrapyramidal side effects’ and ‘EPSE’ were accepted as indications. Similarly, more specific symptoms of EPSE or Parkinson’s Disease were accepted as indications, such as ‘tremor’ or ‘stiffness’.

Nutrition and Feeding

To maintain consistency with accepting low BMI and low weight, the indications ‘malnutrition’, ‘nutrition supplement’, ‘low food intake’, ‘reduced oral intake’, and ‘frailty’ were accepted.

‘Refeeding’ and ‘refeeding syndrome’ were accepted as indications.

Any indication that implied suppression of lactation, ceasing lactation, and avoidance of breast feeding was accepted as an indication. Similarly, ‘breast feeding supplement’ was accepted as an indication.

Skin Treatments

Where the medicine was indicated to be a substitute for an over-the-counter product, such as ‘soap substitute’, ‘moisturiser’ or ‘emollient’, it was accepted as an indication. Similarly, conditions treated with moisturiser and emollient were accepted as indications such as ‘cracked heels’, ‘heel fissure’, ‘dry skin’, and ‘itchy skin’. ‘Ectropion’ was also accepted as an indication, with the assumption that the medicine was for lubrication of the eye.

Laboratory Results and Values

In general lab results that could be directly impacted with a single medicine were accepted if it was specified whether they were too high, too low, or if an exact value was given. If the value was given for the target level to be achieved through medicine treatment, this was also accepted as an indication. For example, blood potassium (K) levels can be directly impacted by prescribing and administering oral potassium, and hence texts that stipulated potassium was too high, too low, or gave an exact value (e.g., K 3.4), were accepted as indications. The same principal applied for other minerals such as calcium, magnesium, phosphate, sodium, etc. Ferritin level was accepted as the associated lab test for iron replacement therapy and INR accepted as the associated lab test for anticoagulant use. A target level for the INR was also accepted as an indication, as was ‘subtherapeutic INR’ as proxy for low INR level, and ‘INR reversal’ to maintain consistency with allowing reversal of a specific medicine as an indication. The texts ‘for INR’ and ‘deranged INR’ were not accepted as indications was it was not clear whether the INR was too high or too low. A level of Hb (haemoglobin) documented as also accepted as an indication, as it can be directly influenced/treated through blood transfusion.

Further example of the above rules includes ‘LFT derangement’ not being accepted as an indication because LFT is a collection of tests that cannot be directly changed through a single medicine. Derangement also does not stipulate whether the level was too high or too low. In contrast ‘raised ammonia’ and ‘TSH>10’ were accepted as indications. Raised D-dimer was not accepted as it cannot be directly changed. A specific level of HbA1c or blood sugar was accepted as an indication as it is directly influenced by blood glucose level, but ‘BSL’ or ‘blood sugar level’ without stipulating a value or whether too high or too low was not accepted as an indication.

Replacement and supplementation were accepted as proxy for too high or too low levels of specific minerals. Therefore ‘K replacement’ and ‘K supplementation’ were accepted as indications.

As ‘tachycardia’, ‘bradycardia’, ‘hypertension’, and ‘hypotension’ were accepted as indications, specific values for heart rate or blood pressure, or indication of too high or too low heart rate or blood pressure, were accepted as indications. Similarly, a specific heart rate of blood pressure that was being targeted by use of the medicine was accepted as an indication.

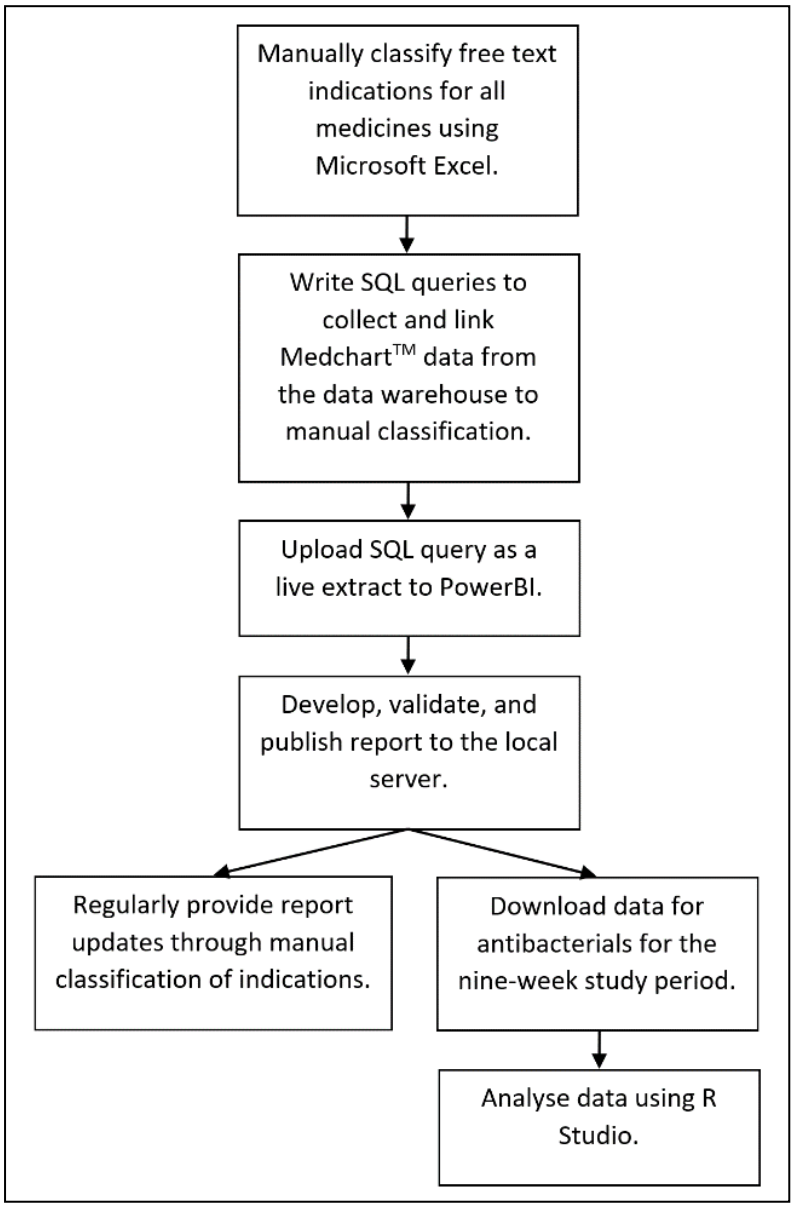
Weight that was specified to be too low was accepted as an indication. This included ‘low birth weight’, ‘low BMI’ and ‘underweight’. Similarly, weights that were too high due to antipsychotic use or specifically an increase in BMI as opposed to fluid weight such as ‘weight gain due to antipsychotic’, ‘weight management on olanzapine’, and ‘high BMI’ were accepted as indications. As an exception to previous rules, providing an exact value for weight was not accepted as an indication. This is because it does not indicate whether the weight it too high or too low, and more likely represents information used for dosing incorrectly documented in the indication field.

Text ‘weight increases by X’ and ‘if weight >/< X’ were not accepted as indications. Similarly, ‘weight gain’, ‘weight increasing’ and ‘weight increasing post IV fluid’ were not accepted as indications. ‘Weight’ alone was not accepted as an indication.

<u>Other</u>

- Text reading ‘reduced dose due to X’ was not accepted as an indication, even when X represented an accepted indication. This is because the reduction is dose would typically be due to a side effect, rather than reason for medicine use.
- ‘Wax’, ‘ear wax softening’, ‘ear wax extraction’, and ‘canal filled with wax’ were all accepted as indications.
- Scoring systems were not accepted as an indication. This is because whilst some scoring systems are well known, others are niche to a certain specialty and is becomes difficult to consistency determine whether a scoring system result would be universally recognised by prescribers. For example, ‘CURB65 2’ would not be accepted as an indication. An exception to this was ‘AWS’ which stands for ‘alcohol withdrawal scale’ and was accepted as an indication as it includes the words ‘alcohol withdrawal’.
- ‘Spinal decompression’ was accepted as an indication, as it was considered on par with ‘spinal stenosis’ and ‘spinal cord oedema’ which were also accepted indications.
- GTD (gestational trophoblastic disease) was not considered a well-known acronym and was not accepted as an indication.
- Sympathetic storm was accepted as an indication, as it is a common way of referring to paroxysmal sympathetic hyperactivity, autonomic storms, and hypothalamic dysregulation syndrome.
- ‘Corneal melt’ was accepted as an indication.
- ‘Coagulopathy’ alone was not considered specific enough to be an indication.
- ‘Electrolyte deficiency’ and ‘electrolyte replacement’ were not considered specific enough and hence were not accepted as indications.
- ‘Hyperstimulation’ was too non-specific and could relate to several syndromes/conditions and hence was considered other text.
- ‘PET’ was accepted as a commonly used abbreviation for preeclampsia.
- Behaviour alone wasn’t accepted as an indication, but most examples of ‘behaviour’ followed by a description of the type of behaviour were accepted as an indication e.g., ‘threatening behaviour’, or ‘disorganised behaviours’. ‘Difficult behaviour’ and ‘disturbed behaviour’ are two examples of exceptions to this ‘rule’ as they were not accepted as indications as both examples are too non-specific.
- ‘Enlarged prostate’ was accepted as it was considered lay terms for benign prostatic hypertrophy which was an accepted indication.
- ‘X Challenge’ accepted where X was a specific drug rather than a class of drugs. E.g., ‘amoxicillin challenge’ was accepted but ‘antibiotic challenge’ was not accepted as an indication as antibiotic describes a class of medicines rather than a specific drug.

**Appendix 5.** Flowchart visualising methodology of report development, data extraction, and statistical analysis.




*Abbreviations:* SQL: Structured Query Language