Title: Rituximab and Pyoderma Gangrenosum. An investigation of disproportionality using a systems biology-informed approach in the FAERS Database.

Running Title: An investigation of risk using a systems biology approach in the FAERS Database.

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Drug names in FAERS are not standardised. Fuzzy string matching of drug names (whether they be generic or branded), drug synonyms and misspellings which may include superfluous text is therefore required to ensure appropriate capture of AEs related to drugs of interest. The R package fuzzyfaers performs fuzzy string matching of drug names using as sequence of steps outlined in Figure A1.

Initially, for a given drug of interest, the comprehensive and freely available data provided by OHDSI (Observational Health Data Sciences and Informatics) common data model (CDM) vocabulary files are used to find drug synonyms automatically. OMOP Common Data Model – OHDSI. Then the FAERS data are queried to find potential valid drug representations. Potential matches are extracted from the database if they meet any of the following non-restrictive criteria for any of the synonyms of the drug: (a) within a soundex distance of two, (b) the first three letters are contained anywhere in the potential match, or (c) the last three letters are contained anywhere in the potential match. This list of potential matches containing many false positives are then read into R [3] allowing more a sophisticated assessment of drug name matches using a classification boundary based on regular expressions and full Damerau-Levenshtein distance [4]. An example of accepted and rejected potential matches is provided in Figure A2. From this list of drug matches, a manual review of the match statuses is undertaken (importantly, blinded to the AEs they are associated with) to finalise the records extracted from FAERS for the given drug.

Expert intervention is required to validate matches and non-matches found by fuzzyfaers (made more efficient by ordering by frequency and fuzzy matching similarity) prior to analysis of the captured data.

The instructions to install fuzzyfaers and the related infrastructure is available at https://github.com/tystan/fuzzyfaers

Figure A1: Schematic of the fuzzy matching process to obtain FAERS records associated with a given drug
Figure A2: Example fuzzy matching classification boundary based on regular expression matching and full Damerau-Levenshtein distance for “Abatacept” prior to manual verification.
Appendix B: Comparator medicines.

Table B1: Comparator medicines for main analysis.

| Chemical: mAbs    | Pharmacological: CD20s | Indication                      |
|-------------------|------------------------|---------------------------------|
| abciximab         | obinutuzumab           | abatacept, alemtuzumab, acalabrutinib |
| adalimumab        | ocrelizumab            | acetaminophen, amifampridine, axicabtagene ciloleucel |
| alemtuzumab       | ofatumumab             | adalimumab, anthralin, bendamustine |
| basiliximab       | rituximab              | anakinra, apremilast, bortezomib |
| bevacizumab       | tositumomab            | anthralin, baclofen, brentuximab vedotin |
| certolizumab pegol |                        | apremilast, cladribine, carboplatin |
| cetuximab         | baricitinib            | corticosterin, cisplatin         |
| daclizumab        | canakinumab            | daclizumab, cyclophosphamide    |
| golimumab         | celecoxib              | dalfampridine, cytarabine       |
| infliximab        | certolizumab pegol    | dimethyl fumarate, dexamethasone |
| ixekizumab        | corticostatin          | dirosmel fumarate, doxorubicin  |
| natalizumab       | cyclosporine           | fingolimod, filgrastim          |
| obinutuzumab      | denosumab              | gabapentin, fludarabine          |
| ocrelizumab       | illofosin               | glatiramer, gemcitabine         |
| ofatumumab        | etanercept             | glatiramer, idelalisib          |
| omalizumab        | golimumab              | glatiramer acetate, ibrutinib   |
| palivizumab       | hydroxychloroquine     | immunoglobulin g, idelalisib    |
| ranibizumab       | ibuprofen              | interferon beta-1a, felenalidomide |
| sarilumab         | infliximab             | interferon beta-1b, methotrexate |
| tocilizumab       | ixekizumab             | methylprednisolone, nivolumab   |
| trastuzumab       | teflunomide            | mitoxantrone, obinutuzumab      |
| ustekinumab       | meloxicam              | natalizumab, ofatumumab         |
|                   | methotrexate           | ocrelizumab, oxaliplatin        |
|                   | methylprednisolone     | peginterferon beta-1a, pegfilgrastim |
| naproxen           | pregabalin             | polatuzumab vedotin             |
| prednisolone      | siponimod              | prednisolone                    |
| prednisone        | teriflunomide          | prednisone                      |
| pregabalin        | procarbazine           |                                |
| sarilumab         | tisagenlecleucel       |                                |
| secukinumab       | venetoclax             |                                |
| simethicone       | vincristine            |                                |
| sulfasalazin      |                        |                                |
### Table of Treatment Agents

|                |               |               |
|----------------|---------------|---------------|
|                | tacrolimus    |               |
|                | teriparatide  |               |
|                | tocilizumab   |               |
|                | tofacitinib   |               |
|                | upadacitinib  |               |
|                | ustekinumab   |               |

Numbers were too small (<3) for stratification by chemical or pharmacological characteristics for CD20s in RA, MS, or NHL.