PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adherence and Dosing Interval of Subcutaneous Anti-Tumour Necrosis Factor Biologics Among Patients with Inflammatory Arthritis: Analysis from a Canadian Administrative Database.
AUTHORS	Bhoi, Peter; Bessette, Louis; Bell, Mary; Tkaczyk, Cathy; Nantel, Francois; Maslova, Karina

VERSION 1 - REVIEW

REVIEWER	A/Prof Peter Wong Rural Clinical School Coffs Harbour University of New South Wales Australia and Mid-North Coast Arthritis Clinic Coffs Harbour New South Wales Australia
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	This study used a large administrative database of patients on a TNFi to determine adherence to various TNFi's over a 24-mth period. This is an important question as TNFi's remain first-line biologic agents for treatment of inflammatory arthritis. Methods: How complete is the data which IMS Brogan purchases from the national private drug plans and public drug databases and then "on-sells" to customers? I suspect busy clinicians aren't always as rigorous with data entry as they should be. Was data integrity checked by random audit? It might be helpful to reference other publications that have used data purchased from IMS Brogan. One of the major limitations of administrative databases is inability to link with clinical data. (The authors do mention this in the Discussion). I would be particularly interested in any clinical measures of disease activity, eg DAS28/SDAI for RA or BASDAI/ASDAS-CRP/ASDAS ESR for ank spond. Was better bDMARD adherence associated with improved clinical outcomes? Presumably if the drug is working, people are more likely to be using it as per the manufacturer's specified dosing interval? Is there an element of "channelling bias" in selecting patients who were on the TNFi for > 24 months? These would be expected to have excellent medication adherence – as observed in this study. The authors

	allude to this in the Discussion. Was there lower adherence in patients on a TNFi for < 24 mths? Results: "The final study population was 4035 patients". What percentage of the total number of patients in the overall source population does this represent? Does the data purchased from IMS Brogan contain all the source population data? Table 1: duplicated in the text. Table 2: Would have been more compelling if the patients receiving GLM had lower clinical disease activity than those on the other TNFi's. Unfortunately, such data isn't usually available from an administrative database. Fig 1 is superfluous as the data is contained in Table 2. The need for less frequent drug administration is usually associated with greater adherence, eg, in the treatment of osteoporosis and hypertension. The findings of this study therefore aren't particularly novel. The authors are to be commended for undertaking a sensitivity analysis to determine if line of therapy affected adherence. It did not. Was it possible to identify other factors predictive of greater drug adherence, eg socio-economic status as measured by postcode or literacy as assessed by highest level of education attained?

REVIEWER	Shahin Jamal University of British Columbia, Vancouver, Canada
REVIEW RETURNED	12-May-2017

GENERAL COMMENTS	Congratulations on a very interesting study and design. I am unclear about features of the study design and data interpretation which is making it hard for me to accept the results. 1. How are you defining the number of days on therapy (the denominator of your main outcome)? Are you assuming that dispensing of the drug on a particular date means the patient took it on that day? 2. How is Golimumab dispensed in Canada? Do patients receive one dose at a time or does a box contain a 2-3 month supply? The other biologics compared in this study are usually supplied one month at a time - Adalimumab is supplied as two doses in a box, Etanercept as four in a box, and Certolizumab as 2 in a box. If Golimumab comes in 2 doses in a box, this will bias your outcome measure. This needs to be clarified in the manuscript 3. Is there auto-drug dispensing by central pharmacy or do patients have to present to the pharmacy to pick up their prescriptions? Is there a difference between products? 4. I think it is difficult to compare average days between units on administrative data from dispensing data when the dosing interval is different between products. Has this been validated?

	5. There is good published data that retention is higher with later lines of therapy in RA. Do you think that doing a sensitivity analysis is sufficient to exclude this bias in your data?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

How complete is the data which IMS Brogan purchases from the national private drug plans and public drug databases and then "on-sells" to customers? I suspect busy clinicians aren't always as rigorous with data entry as they should be. Was data integrity checked by random audit? It might be helpful to reference other publications that have used data purchased from IMS Brogan.

The IMS Brogan database is a pharmacy-based database. Patient data is entered once the patient fills out his first prescription and it gets billed to their drug plan. All private drug plans in Canada and a few public ones go through that system. There is no data entry from the physician.

There have been several studies in other therapeutic areas that have been published using the IMS Brogan database. Some examples are listed below:

• Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: a descriptive study. Pringsheim T, Gardner DM. CMAJ Open. 2014 Oct 1;2(4):E225-32. doi: 10.9778/cmajo.20140009. eCollection 2014 Oct.

• Differences in self-monitored, blood glucose test strip utilization by therapy for type 2 diabetes mellitus. Tavares R, Duclos M, Brabant MJ, Checchin D, Bosnic N, Turvey K, Terres JA. Acta Diabetol. 2016 Jun;53(3):483-92. doi: 10.1007/s00592-015-0823-z. Epub 2016 Mar 14.

• Concomitant Use of Non-Steroidal Anti-Inflammatory Drugs (Nsaids) And Proton Pump Inhibitors (Ppis) in Newly Diagnosed Patients With Osteoarthritis (Oa), Rheumatoid Arthritis (Ra) or Ankylosing Spondylitis (As). Dziarmaga A, Reidel K, White R, Tarride JE, Corner N. Value Health. 2014 Nov;17(7): A390. doi: 10.1016/j.jval.2014.08.2666. Epub 2014 Oct 26.

• The pharmacoepidemiology of selective serotonin reuptake inhibitors for children and adolescents in Canada from 2005 to 2009: a database analysis. Lam D, Gorman DA, Patten S, Pringsheim T. Paediatr Drugs. 2013 Aug;15(4):319-27. doi: 10.1007/s40272-013-0014-8.

One of the major limitations of administrative databases is inability to link with clinical data. (The authors do mention this in the Discussion). I would be particularly interested in any clinical measures of disease activity, eg DAS28/SDAI for RA or BASDAI/ASDAS-CRP/ASDAS ESR for ank spond. Was better bDMARD adherence associated with improved clinical outcomes? Presumably if the drug is working, people are more likely to be using it as per the manufacturer's specified dosing interval? Is there an element of "channelling bias" in selecting patients who were on the TNFi for > 24 months? These would be expected to have excellent medication adherence – as observed in this study. The authors allude to this in the Discussion. Was there lower adherence in patients on a TNFi for < 24 mths?

We agree with the reviewer that this is a major limitation of administrative databases and we did not have access to any clinical measure of clinical activity. As stated, we did mention this limitation in the discussion. To our knowledge, the only study that could link non-adherence to biological DMARDs to clinical outcomes was that of Bluett et al (2015; Ref. 4 in manuscript). As stated in the discussion, "… patients who were ever non-adherent to their SC TNFi were significantly less likely to achieve a good EULAR response and significantly more likely to have no response after 6 months of treatment."

We initially selected a 24 months' window to ensure that we had an adequate follow-up period to measure adherence and to remove any potential bias due to primary non-response to therapy (this statement was added to the discussion). We did not measure a shorter time window.

We agree with the reviewer that this could lead to a channeling bias and explain the high rates of adherence (added in the limitation section of the discussion) although the adherence rate was similar to other published studies with SC biologic DMARDs (Ref. 7 and 10).

Results:
“The final study population was 4035 patients”. What percentage of the total number of patients in the overall source population does this represent? Does the data purchased from IMS Brogan contain all the source population data?
The final study population of 4035 patients represents the totality of the source population data from IMS Brogan that conform to the following inclusion criteria:
• Index period: January 1, 2008 - June 30, 2011
• Follow-up period: Patients were followed from index date for 24 months through to June 30, 2014
• Only new-to-chemical patients using a target drug for the treatment of Rheumatoid Diseases (RD) during index periods were selected.
• In addition, only patients in the cohort with at least three prescriptions and retained on therapy at 24 months were selected
Table 1: duplicated in the text.
Removed table 1
Table 2: Would have been more compelling if the patients receiving GLM had lower clinical disease activity than those on the other TNFi’s. Unfortunately, such data isn’t usually available from an administrative database. Fig 1 is superfluous as the data is contained in Table 2. The need for less frequent drug administration is usually associated with greater adherence, eg, in the treatment of osteoporosis and hypertension. The findings of this study therefore aren't particularly novel.
Fig 1 was removed

The authors are to be commended for undertaking a sensitivity analysis to determine if line of therapy affected adherence. It did not.
Thank you

Was it possible to identify other factors predictive of greater drug adherence, eg socio-economic status as measured by postcode or literacy as assessed by highest level of education attained?
This data was, unfortunately, not available to us for this analysis.

Reviewer: 2
Congratulations on a very interesting study and design.
Thank you
I am unclear about features of the study design and data interpretation which is making it hard for me to accept the results.

1. How are you defining the number of days on therapy (the denominator of your main outcome)? Are you assuming that dispensing of the drug on a particular date means the patient took it on that day?
The compliance rate was calculated by dividing the “Estimated days’ supply in the defined period” by the “Number of days in the defined period”. However, "Days’ supply" information is not reliable for Biologic Drugs; thus, it was estimated based on total drug utilization in the defined period. This section was reworded to be more specific.
This is indeed the major limitation of every adherence study using the MPR (Mean Possession Ratio) as an endpoint. As we state in the discussion: “pharmacy refills do not necessarily mean that the medication was in fact taken by a patient”.
2. How is Golimumab dispensed in Canada? Do patients receive one dose at a time or does a box contain a 2-3 month supply? The other biologics compared in this study are usually supplied one month at a time - Adalimumab is supplied as two doses in a box, Etanercept as four in a box, and Certolizumab as 2 in a box. If Golimumab comes in 2 doses in a box, this will bias your outcome measure. This needs to be clarified in the manuscript
Golimumab comes in at one dose/box. Therefore, all four biologics are dispensed as one month of supply. This was clarified in the “Methods” section.

3. Is there auto-drug dispensing by central pharmacy or do patients have to present to the pharmacy to pick up their prescriptions? Is there a difference between products?
All products are distributed through an open distribution model. Therefore, patients either pick up their prescriptions at their local pharmacy or the local pharmacy delivers it to their home. To our knowledge, there is no auto-drug dispensing (at least not for GLM).
4. I think it is difficult to compare average days between units on administrative data from dispensing data when the dosing interval is different between products. Has this been validated?
Using the Mean Possession Ratio (MDR) is the standard method for studying medication adherence with administrative database and has been extensively validated (see Ref 11-2; 14-16 in the manuscript). An inverse relationship between dosing frequency and adherence has been reported in various studies with different medication classes (see Ref 31-33 in the manuscript)
5. There is good published data that retention is higher with later lines of therapy in RA. Do you think that doing a sensitivity analysis is sufficient to exclude this bias in your data?
We did not look at retention in this study and we agree with the reviewer that retention is better with later line of therapies, probably because patients are getting better access and are treated earlier with biologics as time goes by (we reported this trend in Thorne et al. Arthritis Care Res (Hoboken). 2014 Aug;66(8):1142-51. doi: 10.1002/acr.22290.). Therefore, this the reason we selected an index date from January 1, 2010 to June 30, 2012 where all four therapies are approved, listed and available to all patients.

VERSION 2 – REVIEW

REVIEWER	A/Prof Peter Wong Rheumatologist, Mid-North Coast Arthritis Clinic, Coffs Harbour, and Rural Clinical School, University of New South Wales, both in Australia.
REVIEW RETURNED	16-Jun-2017

GENERAL COMMENTS	The authors have satisfactorily addressed all my queries.