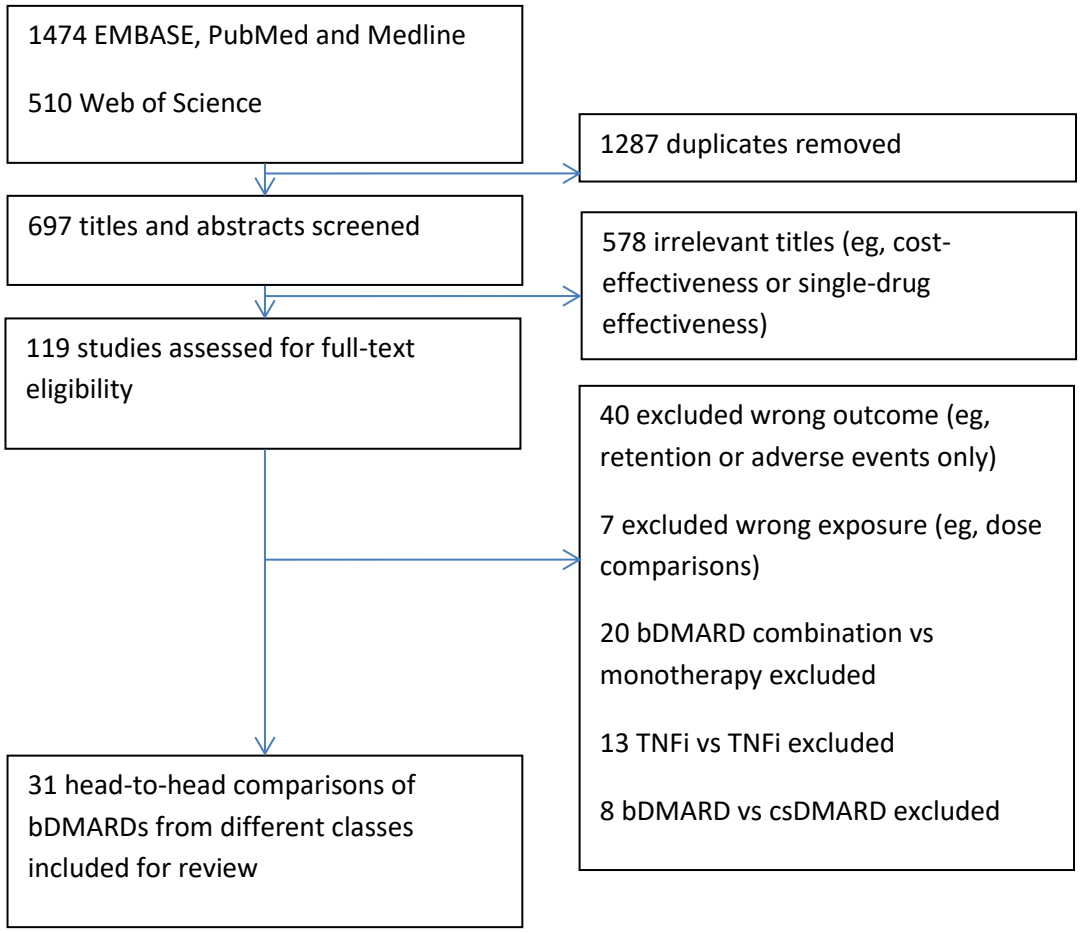
Supplementary materials

Improving rheumatoid arthritis comparative effectiveness research through causal inference principles: systematic review using a target trial emulation framework

Sizheng S Zhao, Houchen Lyu, Daniel H Solomon, Kazuki Yoshida

Search terms: Rheumatoid arthritis AND (Observational OR regist* OR real-world) AND (Comparative effectiveness OR effectiveness OR propensity) NOT (review OR cost-effective* OR JIA OR juvenile idiopathic arthritis).



Supplementary figure S1. Study selection flowchart.

We focused on design rather than reporting recommendations, as it precedes and impacts study conduct and reporting. Study design guidance from the Patient-Centred Outcomes Research Institute (PCORI) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) share many overlapping areas with each other and with target trial emulation [1–4]. Target trial emulation is unique in explicitly writing down two protocols, whereas the target trial is rarely characterised in other recommendations (supplementary Table S1). Note that this review used the target trial emulation framework retrospectively to appraise studies, and does not demonstrate its prospective implementation for design; worked examples of the latter and detailed descriptions can be found in references [3,5–7].

Supplementary Table S1. Comparison of design principles from target trial emulation and other sources.			
	Hernan et al. Target Trial Emulation [6,8]	**PCORI Methodology Standards for Causal Inference Methods**	**ISPOR Good Research Practices for CER** [2]
Objective	Explicitly specifying the target trial so that causal analyses of observational data can be evaluated with respect to how well they emulate it. - Organizes analytic approaches dispersed throughout the literature - Provides a structured process for critical appraisal of observational studies - Helps avoid common methodologic pitfalls	Set standards required for the conduct of scientifically valid patient-centred outcomes research that focuses on causal inference.	Ensure internal validity and improve causal inference from observational studies
Conceptualization	Specify the aims of the target and emulated trials, e.g., using the PICOTS framework	Specify the causal model underlying the research question, informed by the PICOTS framework. Determine whether and how the study can handle bias and confounding and the extent to which valid estimates of the effects of an intervention can be generated.	Define causal diagrams (directed acyclic graphs (DAGs)) before starting analysis, to declare a priori assumptions about causal relationships between variables under study and consider whether the observed data are sufficient to control for confounding.
Eligibility	Define clear eligibility criteria that would be used in a hypothetical target trial. Criteria cannot include post-baseline events (e.g., patients with insufficient follow-up), which may introduce bias.	Specify eligibility criteria for inclusion in the study population and analysis, based on information at baseline. If patients are excluded, address potential for and impact of selection bias on validity of results.	Eligibility criteria can be used to create homogenous study cohorts with the primary intention of reducing confounding, particularly when there are variables that influence prescribing decisions that are not available in the data.
Treatment strategies	The emulated target trial will typically be a pragmatic trial (e.g., cannot emulate a placebo-controlled trial with tight monitoring and enforcement of adherence to the study protocol). Eligible individuals who did not start interventions of interest are considered ineligible. Individuals are then assigned to the trial (treatment) strategy or strategies (note that multiple assignment is explicitly allowed).	No recommendation regarding treatment strategies, except to describe intervention and comparators as per PICOTS framework.	No recommendation regarding treatment strategies, except that exposure misclassification should be considered at the design stage, including how they could influence the acceptance or rejection of the null hypothesis.

	Comparisons of initiators avoid biases.		
Assignment procedures	Only pragmatic target trials can be emulated (i.e., without blind assignment). To emulate random assignment of interventions at baseline, we need to adjust for all confounding factors required to ensure comparability (exchangeability) of the groups defined by initiation of the treatment strategies. Confounding bias may be reduced by using active comparators and tested using "reverse target trials" (i.e., users are assigned to continue or stop the treatment) or control outcomes with no expected causal effect.	No specific recommendations about assignment. Considerations for using propensity scores and instrumental variables are given.	Confounding should be considered at the conceptual stage, and whether the observed data are sufficient to control for confounding. Confounding may be reduced using new-user and active comparator designs, propensity score trimming, and/or sensitivity analysis exploring outcomes with no expected causal effect.
Follow-up period	Successful target trial emulation requires a proper definition of start of follow-up, which should align with meeting eligibility criteria and treatment assignment. This may not be straightforward, but solutions are available. End should be clearly defined (e.g., at loss to follow-up or 1 year after baseline).	No specific recommendations except to measure potential confounders before start of exposure	No specific recommendations except that the exposure time-window should not be based on the actual drug intake, but rather on the time period during which the medication may cause the outcome and the duration of the disease process.
Outcome	Outcomes begin to be measured after start of follow-up. Note that it may not be possible to emulate target trial with systematic and blind outcome ascertainment (i.e., without knowledge of treatment history) using observational data, except when outcome ascertainment cannot be affected by treatment history (e.g., death ascertained from an independent data source).	Define the timing of the outcome assessment relative to the initiation and duration of exposure, to reduce potential sources of bias arising from inappropriate study design choices (e.g., immortal time bias)	No recommendation regarding the timing of outcome assessment. However, outcome misclassification should be considered at the design stage, including how they could influence the acceptance or rejection of the null hypothesis.
Causal contrast(s)	Intention-to-treat effect (i.e., effect of being assigned to the treatment strategies	No specific recommendations	No specific recommendations

of interest	regardless of whether it is followed) or the per-protocol effect (i.e., effect of following the treatment strategies).		
Analysis	An intention-to-treat analysis is rarely possible using observational data. Often the closest analogue is a comparison of initiators of the different treatment strategies, assuming adequate adjustment for baseline confounders. To estimate the per-protocol effect, adjustment for baseline and post-baseline (e.g., adjusting for loss to follow-up) confounding is necessary.	No equivalent recommendations	No equivalent recommendations
Additional stages			Conclusions should be compared to equivalent randomised trials; caution should be applied if it conflicts with trial evidence or if effect sizes are small

Supplementary Table S2. Summary of observational study designs for each component of the target trial emulation framework. Design limitations are underlined and summarised in the final column.								
Study	1.Eligibility criteria	2.Treatment strategies	3.Assignment procedures	4.Follow-up period	5.Outcome	6.Causal contrast of interest	7.Analysis plan	Summary of design issues identified
Blom 2011 [9]	ACR criteria RA failing 2 TNFi with DAS28≥3.2. with ≥12m follow-up Analysis implicitly excluded those without follow-up at each time point.	1) RTX 2) Any TNFi as 3rd bDMARD	Unadjusted comparison: Statistical selection of confounders found no significant univariate association with treatment arm.	12 months Follow-up schedule at discretion of rheumatologist	Course of DAS28 every 3m over 12m	ITT – clearly declared	Linear mixed effect model. No covariate adjustment. Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Confounding by indication. 3. Solely statistical selection of confounders.
Boyadzhieva 2018 [10]	ACR criteria RA with no prior bDMARD use and DAS28>5.1 Analysis implicitly excluded those without follow-up	1) RTX 2) TCZ 3) any TNFi as 1st bDMARD Discontinuation censored	Unadjusted pairwise comparisons	12 months	CDAI, SDAI, DAS28 at 6 and 12 months	Per-protocol	t-test Complete-case analysis	1. Naïve PP with potential for selection bias. 2. Confounding by indication.
Choy 2017 [11]	ACR criteria RA with no prior bDMARD use Analysis implicitly excluded those without follow-up at 24wks	1) TCZ (IV) 2) any TNFi as 1st bDMARD Discontinuation censored	Pre-defined confounders	12 months	Change in DAS28 at 24wks Sample size justified	Per-protocol	ANCOVA; sensitivity analysis adjusting for propensity score. Complete-case analysis; MI as sensitivity analysis	1. Naïve PP analysis with potential for selection bias.
Emery 2015 [12]	RA failing 1 TNFi With follow-up DAS28 at 6m	1) RTX 2) Any TNFi as 2nd bDMARD	Statistical selection of confounders for association with treatment arm. Post baseline variables included (use of co-medications in the first 6m of the study).	12 months with visits as indicated by routine clinical practice regardless of treatment discontinuation.	Mean change in DAS28 between baseline and 6±2 months Sample size justified	ITT; "as observed" sensitivity analysis	ANCOVA for treatment strategies adjusting for baseline DAS28 and unbalanced baseline characteristics; sensitivity analysis adjusting for propensity score. Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Naïve ITT with potential for selection bias. 3. Solely statistical selection of confounders.

Finckh 2007 [13]	RA failing ≥1 TNFi With ≥1 follow-up at 12m Excluded patients wishing to switch due to personal preference or have lymphoma	1) RTX 2) any TNFi as 2nd or 3rd bDMARD censored observations after interruption of TNFi treatment or re-treatment with RTX	Statistical selection of confounders using stepwise selection for association with treatment arm. Baseline disease activity not included.	Indefinite	Change in DAS28 over time	Per-protocol	Linear mixed effect model Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Naïve PP with potential for selection bias. 3. Solely statistical selection of confounders. 4. Undefined follow-up period.
Finckh 2010 [14]	RA failing ≥1 TNFi With ≥1 follow-up at 12m Excluded patients with lymphoma	1) RTX 2) any TNFi as 2nd or 3rd bDMARD censored observations after interruption of TNFi treatment or re-treatment with RTX	Pre-defined confounders	Indefinite	Change in DAS28 over time	Per-protocol	Linear mixed models with PS stratification. Complete-case analysis	1. Naïve PP with potential for selection bias. 2. Undefined follow-up period.
Finckh 2012 [15]	RA failing ≥1 TNFi With ≥1 follow-up radiograph Excluded bio-naïve and those with lymphoma.	1) RTX 2) any TNFi as 2nd, 3rd or 4th bDMARD Discontinuation censored	Pre-defined confounders	Indefinite	Change in Ratigen erosion score over time	ITT – clearly declared; per-protocol as sensitivity analysis	Linear mixed effect model Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Naïve ITT/PP with potential for selection bias. 3. Undefined follow-up period.
Frisell 2019 [16]	RA with no prior bDMARD use or failing 1 TNFi within 1 year	1) ABA 2) RTX 3) TCZ 4) any TNFi Stratified analysis as 1st bDMARD; separate analysis as 2nd bDMARD. Biosimilar switch and discontinuation	Confounders selected if differed significantly between treatments, significant predictors of response, or expert opinion.	12m	Proportion on therapy *and* with good response (good EULAR response AND HAQ improvement >0.2 AND 0 swollen/tender joints AND CDAI remission) at 3 and 12m	Per-protocol Sensitivity analyses using complete case and extreme imputation (as good or poor responders) declared as ITT	Linear models. Missing outcomes multiple imputation.	1. Naïve PP with potential for selection bias.

		due to remission permitted. Other discontinuation and emigration were censored.			(equivalent to LUNDEX)			
Gomez-Reino 2012 [17]	RA failing ≥1 TNFi With follow-up at 6, 9, 12m	1) RTX 2) any TNFi as 2nd or subsequent bDMARD.	Pre-defined confounders	12 months	Change in DAS28 and HAQ at 6, 9 and 12m compared to baseline	ITT	Linear mixed models with PS stratification Complete-case analysis of different subsets at each time point	1. Naïve ITT with potential for selection bias.
Gottenberg 2019 [18]	ACR criteria RA with no prior ABA/RTX/TCZ use or failing any number of prior TNFi, with ≥24 month follow-up contraindications to any of the three bDMARDs	1) ABA (IV) 2) RTX 3) TCZ (IV) as 2nd or subsequent bDMARD	Pre-defined confounders	24 months	EULAR response at 6, 12, 24m	ITT	Weighted GEE. worst case (non-response) imputation for missing	1. Post-baseline data in eligibility criteria.
Grøn 2019 [19]	RA with no prior bDMARD use	1) ABA 2) CZP 3) INF (CT-P13) as 1st bDMARD	Pre-defined confounders	12 months	DAS28 remission at 6 and 12m	ITT – clearly declared	Logistic regression. Missing outcome imputed with best (all responded) and worst case (non-response) scenario.	None
Harrold 2015 [20]	RA failing ≥1 TNFi but no prior bDMARD of other classes, not in CDAI remission at baseline. With follow-up assessments at 6 or 12m	1) ABA 2) any TNFi as 2nd or subsequent bDMARD	Pre-defined confounders	12 months	Change in CDAI at 6m and 12m	ITT	Generalised linear latent and mixed models with PS matching Discontinuation imputed using LOCF.	1. Naïve ITT with potential for selection bias.

Harrold 2015 [21]	RA failing ≥1 TNFi, with CDAI>10. With ≥1 assessment between baseline and 1yr and follow-up at 1y Excluded lymphoma.	1) RTX 2) any TNFi as 2nd or subsequent bDMARD; separate analysis stratified by number of prior bDMARDs	Statistical selection of confounders for propensity score trimming, then pre-defined confounder for outcome models	12 months	CDAI low disease activity or remission at 12m	ITT	Logistic regression Discontinuation imputed as non-response.	1. Naïve ITT with potential for selection bias.
Harrold 2016 [22]	RA failing ≥1 TNFi, have not used ABA/TCZ with CDAI>10. With follow-up CDAI at 6m	1) ABA 2) TCZ Stratified analysis as 2nd bDMARD; separate analysis as 3rd or subsequent bDMARD	Pre-defined confounders	6 months	Change in CDAI at 6m	ITT	Linear regression with PS matching. Discontinuation imputed using LOCF and nonresponse.	1. Naïve ITT with potential for selection bias.
Harrold 2018 [23]	RA failing ≥1 TNFi, CDAI>10 With follow-up at 6m	1) TCZ monotherapy 2) any TNFi+MTX dual therapy as 2nd or subsequent bDMARD Discontinuation censored	Pre-defined confounders	6 months	Change in CDAI	ITT	Mixed effect models with PS trimmed population. Imputation with LOCF and non-response after artificial censoring.	1. Post-baseline data in eligibility criteria. 2. Naïve ITT with potential for selection bias.
Harrold 2019 [24]	ACPA positive RA with no prior TNFi use, or failing any number of TNFis, With follow-up at 6m	1) ABA 2) any TNFi Stratified analysis by number of prior TNFi Discontinuation censored.	Pre-defined confounders	6 months	Change in CDAI at 6 months	Per-protocol	Test of mean difference in PS matched group CDAI at switch was carried forward to 6m	1. Potential for selection bias
Iannone 2018 [25]	RA with no prior bDMARD use or failing any number of bDMARDs Analysis implicitly excluded those without follow-up at each time point	1) ABA 2) TCZ 3) any TNFi as 1st or subsequent bDMARD	Active comparator with similar indications. No further attempt for confounding adjustment.	24 months	DAS28 remission at 6, 12, 18, 24 months	ITT	chi-squared test Complete-case analysis	1. Heterogenous eligibility (bDMARD naïve and experienced). 2. Naïve ITT with potential for selection bias. 3. Confounding by indication.

Jørgensen 2015 [26]	RA with no prior bDMARD use or failing 1 or 2 bDMARDs Analysis implicitly excluded those without follow-up	monotherapy of 1) ABA 2) RTX 3) TCZ 4) any TNFi Both monotherapy initiators and those who stopped combination therapy were included. Later stratified by incident/prevalent users. Discontinuation censored	Unadjusted proportions. Several baseline characteristics unbalanced between treatment groups, including the number of prior bDMARDs	6 months	CDAI remission at 6m using LUNDEX	Causal contrast undefinable due to unclear treatment initiation. Per-protocol (in incident users) – clearly declared	LUNDEX - No statistical comparison Complete-case analysis	1. Confounding by indication. 2. Causal contrast unclear. 3. Naïve PP with potential for selection bias.
Jørgensen 2017 [27]	RA with no prior bDMARD use or failing any number of bDMARDs Analysis implicitly excluded those without follow-up	monotherapy of 1) ABA 2) RTX 3) TCZ 4) any TNFi As 1st or subsequent bDMARD Discontinuation censored	Unadjusted pairwise comparisons. Several baseline characteristics unbalanced between treatment groups, including the number of prior bDMARDs	6 months	EQ5D at 6 months	Per-protocol – clearly declared	Kruskal Wallis test Complete-case analysis	1. Heterogenous eligibility. 2. Confounding by indication. 3. Naïve PP with potential for selection bias.
Kekow 2012 [28]	RA failing 1 TNFi, DAS28≥3.2 With follow-up DAS28 at 6m	1) RTX 2) any TNFi as 2nd bDMARD	Unadjusted pairwise comparison	6 months	Change in DAS28 at 6m	ITT	t-test Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Naïve ITT with potential for selection bias.
Kihara 2017 [29]	RA with no prior bDMARD use with DAS28>5.2	1) TCZ (IV) 2) any TNFi as 1st bDMARD	Statistical selection of confounders for association with treatment arm and potential predictors of outcome	6 months	EULAR and DAS28 remission at 6m	ITT	Weighted generalised linear models. Multiple imputation for missing data.	none

Lauper 2018 [30]	RA failing ≥1 bDMARD	1) TCZ 2) any TNFi as 2nd or subsequent bDMARD	Pre-defined confounders	Indefinite	Change in CDAI over time	ITT	Linear mixed models. Single imputation for missing outcome	1. Naïve ITT with potential for selection bias. 2. Undefined follow-up period.
			Unadjusted proportions	1 year for binary outcome	Binary CDAI threshold at 1 year using LUNDEX	ITT	No statistical comparison	1. Confounding by indication.
Leffers 2011 [31]	ACR criteria RA with no prior bDMARDs use or failing ≥1 bDMARDs With ≥1 follow-up at 48w	1) ABA 2) TCZ as 1st or subsequent bDMARD Discontinuation censored	No statistical comparison made	Indefinite	Change in DAS28 over time	Per-protocol	No statistical comparison Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Heterogenous eligibility (bDMARD naïve and experienced). 3. Naïve PP with potential for selection bias. 4. Undefined follow-up period.
Li 2017 [32]	RA failing etanercept as the 1st bDMARD With continued use of study drug ≥1y and follow-up visit at ≥1y	1) ABA 2) TCZ 3) any TNFi as 2nd bDMARD	Pre-defined confounders	Undefined period, at least 1 year	EULAR responses and change in CDAI	ITT	Linear and logistic regression Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Naïve ITT with potential for selection bias. 3. Undefined follow-up period.
Pascart 2016 [33]	ACR criteria RA failing any number of bDMARDs as long as the last one was ABA/RTX/TCZ Analysis implicitly excluded those without follow-up	1) ABA 2) TCZ 3) RTX as 2nd or subsequent bDMARD	Baseline DAS28 adjusted	12 months	Percentage change in DAS28 at 6 and 12m	ITT	ANCOVA Complete-case analysis	1. Naïve ITT with potential for selection bias. 2. Confounding by indication.
Romao 2015 [34]	ACR criteria RA with no prior bDMARD use or failing any number of bDMARDs, continuing treatment for ≥6m With follow-up at 6m	1) TCZ 2) any TNFi Stratified analysis as 1st bDMARD; separate analysis as 2nd or subsequent bDMARD	Stepwise then change-in-outcome selection of confounders for association with outcome; PS (pre-defined variables without	6 months	DAS28 remission at 6 months	ITT	Logistic regression. PS use for matching and outcome regression. Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Naïve ITT with potential for selection bias.

			significant missing data)					
Santos-Faria 2019 [35]	RA failing 1 TNFi with baseline assessments Analysis implicitly excluded those without follow-up	1) RTX 2) TCZ 3) any TNFi as 2nd bDMARD Discontinuation censored	Unadjusted proportions	24 months	Remission/low disease activity using CDAI, SDAI, DAS28 at 6, 12, 24m using LUNDEX	Per-protocol	LUNDEX - No statistical comparison Complete-case analysis	1. Naïve PP with potential for selection bias. 2. Confounding by indication.
Soliman 2012 [36]	RA failing 1 TNFi With follow-up DAS28 and/or HAQ at 6m	1) RTX 2) any TNFi as 2nd bDMARD	Selection for baseline characteristics that differed (presumed statistically) between the two treatment arms	6 months	EULAR response and HAQ improvement at 6m. Further switches within 6 months constituted composite failure. Sample size justified.	ITT	Logistic models adjusting for PS Complete-case analysis	1. Post-baseline data in eligibility criteria. 2. Naïve ITT with potential for selection bias. 3. Solely statistical selection of confounders.
Torrente-Segarra 2016 [37]	ACR criteria RA failing 1 TNFi Analysis implicitly excluded those without follow-up	1) RTX 2) any TNFi as 2nd bDMARD	Active comparator with similar indications. No further attempt for confounding adjustment.	6 months	DAS28 and EULAR response at 6m	?Per-protocol	'Cochran test' Unclear if discontinuation was counted as non-response Complete-case analysis	1. Confounding by indication. 2. Causal contrast unclear.
Walker 2016 [38]	RA failing RTX starting the subsequent bDMARD within 6 months of last RTX infusion With 6m follow-up	1) ABA 2) TCZ 3) any TNFi After any number (1 to >4) of prior bDMARDs as long as the most recent was RTX	Pre-defined confounders	6 months	Change in DAS28, CDAI, HAQ at 6m	ITT	Linear regression Complete-case analysis	1. Heterogenous eligibility (bDMARD naïve and experienced). 2. Naïve ITT with potential for selection bias.

Yoshida 2011 [39]	RA with no prior bDMARD use or failing 1 to 2 bDMARDs With follow-up at 6m	1) TCZ 2) any TNFi Stratified analysis as 1st bDMARD; separate analysis as 2nd or 3rd bDMARD Discontinuation censored	Statistical selection of confounders	6 months	DAS28 remission and Boolean remission at 6m	Per-protocol	Linear mixed models. LOCF for those with follow-up <6 months.	1. Post-baseline data in eligibility criteria. 2. Naïve PP with potential for selection bias. 3. Solely statistical selection of confounders.
For item 2, treatment strategies implied initiation of listed drugs; almost all studies permitted concurrent use of other non-bDMARDs. Where discontinuation was censored, this implied that analysis was for per-protocol effect.								

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