ETH zürich

D CHAB

Exploring the Applicability of the Prevalent New User Design in Rare Diseases

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ETH Zurich

Basel Epidemiology Seminar
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Disclosure statement

I, Maria Luisa Marques de Sá Faquetti, hereby declare that I have no financial or other potential conflicts of interest to disclose in relation to this presentation.

Overview

1. Background information
2. The prevalent new user design & JAK inhibitors case study
3. Is the prevalent new user design an option in rare diseases?

Selection bias: A critical issue in observational studies

Despite the growing importance of observational studies in generating real-world evidence, the indiscriminate inclusion of patients in these studies can result in significant bias.

Selection bias

Occurs when individuals or groups in a study differ systematically from the population of interest leading to a systematic error in an association or outcome.

Often introduced by the investigators during the design if:

- The application of inclusion/exclusion criteria is different between study groups.
- The selection of exposed and unexposed (comparison) groups is somehow related to the outcome of interest.

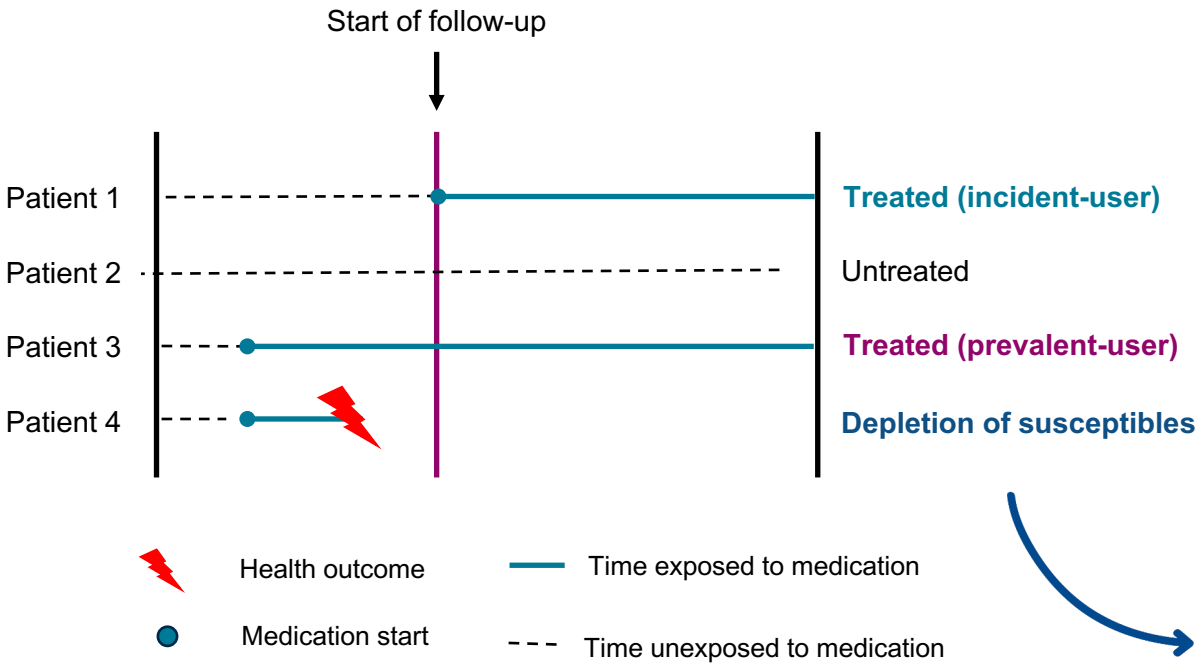
Understanding and mitigating selection bias strengthens the validity and reliability of observational studies.

Lund J.L, et al. *Curr Epidemiol Rep*. 2015.

Catalogue of Bias Collaboration, Nunan D, Bankhead C, Aronson JK. Selection bias. *Catalogue of Bias*. 2017.

Prevalent-user bias and depletion of susceptibles

Prevalent-user bias occurs when a study includes patients who are not experiencing their first prescription.



Prevalent-users might be fundamentally different from incident-users:

Michael

Emma

When patients more susceptible to adverse effects discontinue the treatment, leaving behind a population less likely to experience these effects.

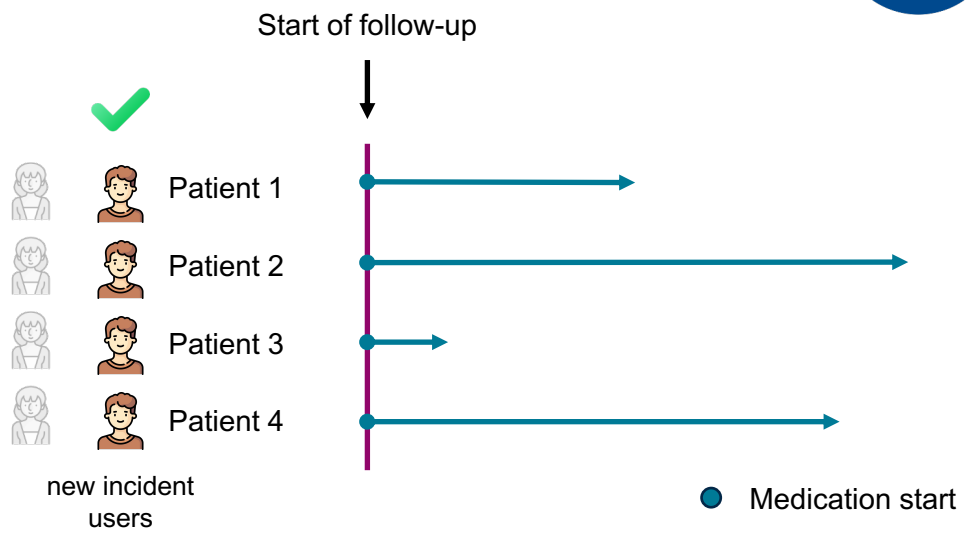
Lund J.L, et al. *Curr Epidemiol Rep*. 2015.

Ali A.K. *J Pharm Research*. 2013

Avoiding prevalent user bias

New-user design

- Include only new incident users
- Aligns individuals at a uniform point in time to start follow-up (e.g., at first use).



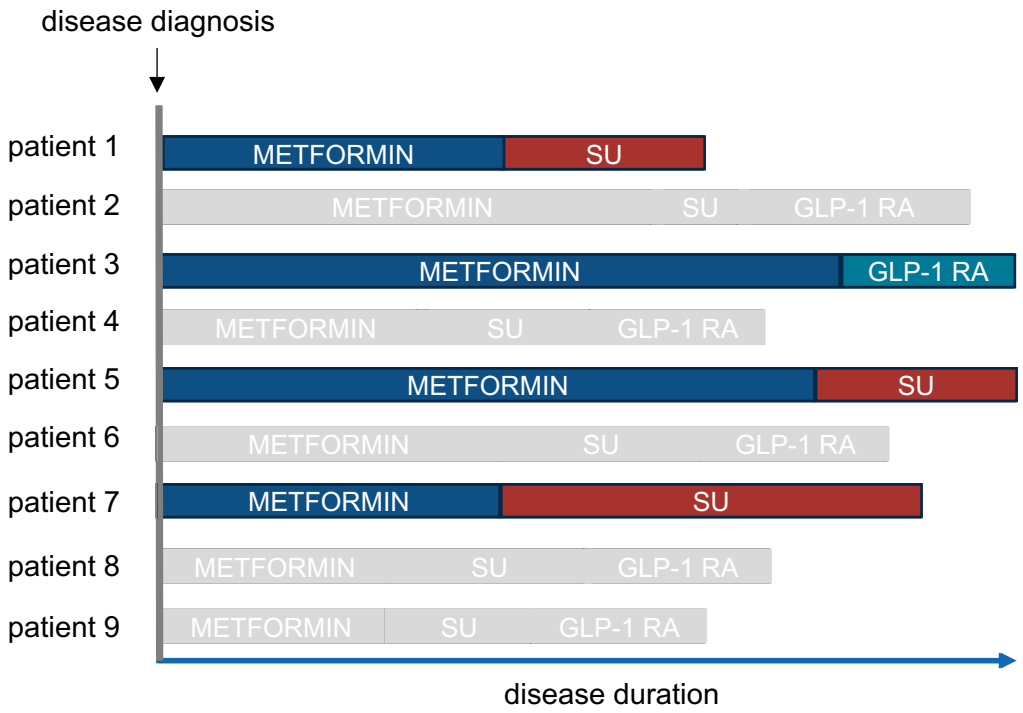
Considerations on the new-user design

- It **requires large sample sizes** to capture sufficient incident users.
- **Calendar time** considerations (e.g., treatment practices, drug availability, and guidelines can change over time).

Lund J.L, et al. *Curr Epidemiol Rep*. 2015.
Ali A.K. *J Pharm Research*. 2013

Complex scenarios in pharmacoepidemiology

Conditions requiring dynamic, multi-staged treatment (e.g., type 2 diabetes mellitus).



Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

Published date: February 2022. Last updated: August 2022. This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.

Suissa S., et al. *Pharmacoepidemiol Drug Saf*. 2017.

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3. Is the prevalent new user design an option in rare diseases?

Prevalent new-user design

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 459–468
Published online 9 September 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4107

ORIGINAL REPORT

Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores

Samy Suissa[1,2,3]*, Erica E. M. Moodie[1] and Sophie Dell'Aniello[2,3]

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[2] *McGill Pharmacoepidemiology Research Unit, McGill University, Montreal, Quebec, Canada*
[3] *Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada*

ABSTRACT

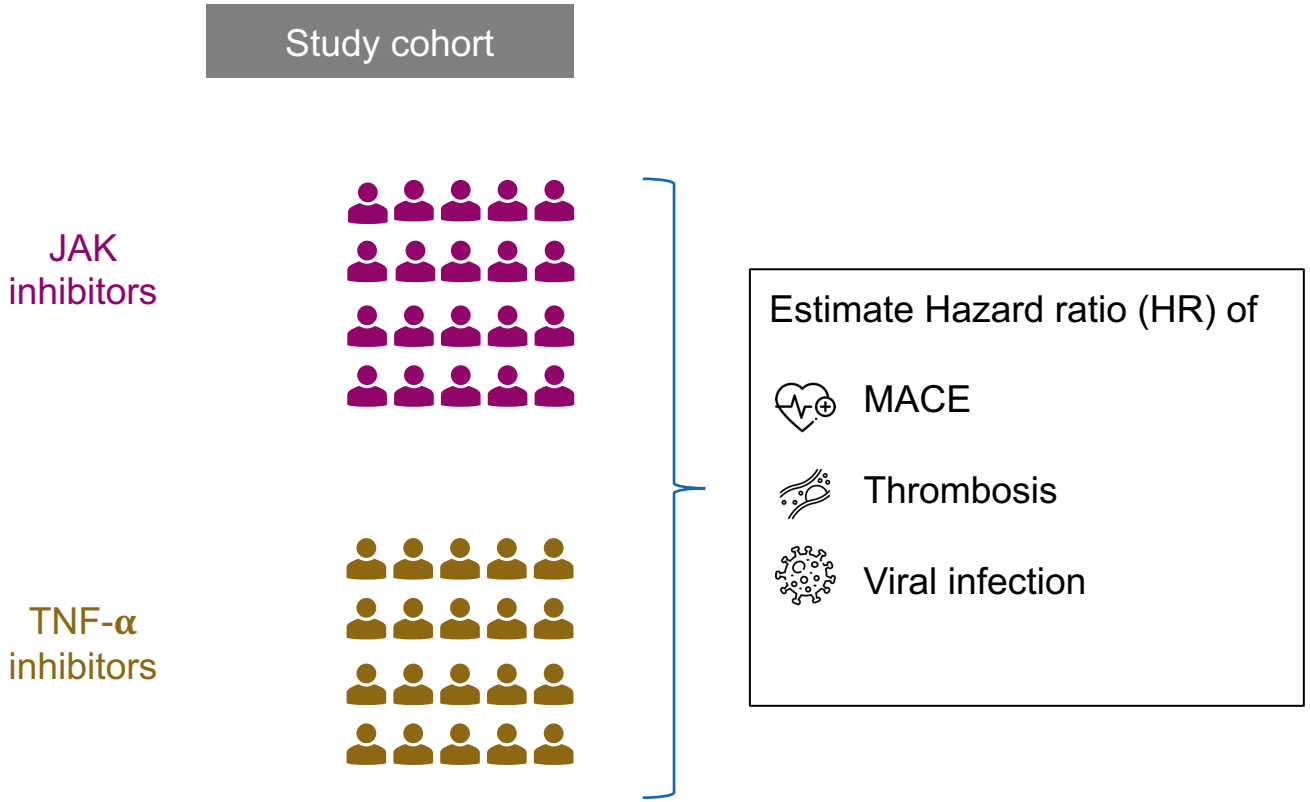
Purpose Studies of the real-world comparative effectiveness of drugs conducted using computerized healthcare databases typically involve an incident new-user cohort design for head-to-head comparisons between two medications, using exclusively treatment-naïve patients. However, the desired contrast often involves one new drug compared with an older drug, of which many users of the new drug may have

- Introduced for comparative drug effect studies, where **incident new users are scarce** and the **comparator drug is not contemporaneous**

Suissa S., et al. *Pharmacoepidemiol Drug Saf*. 2017.

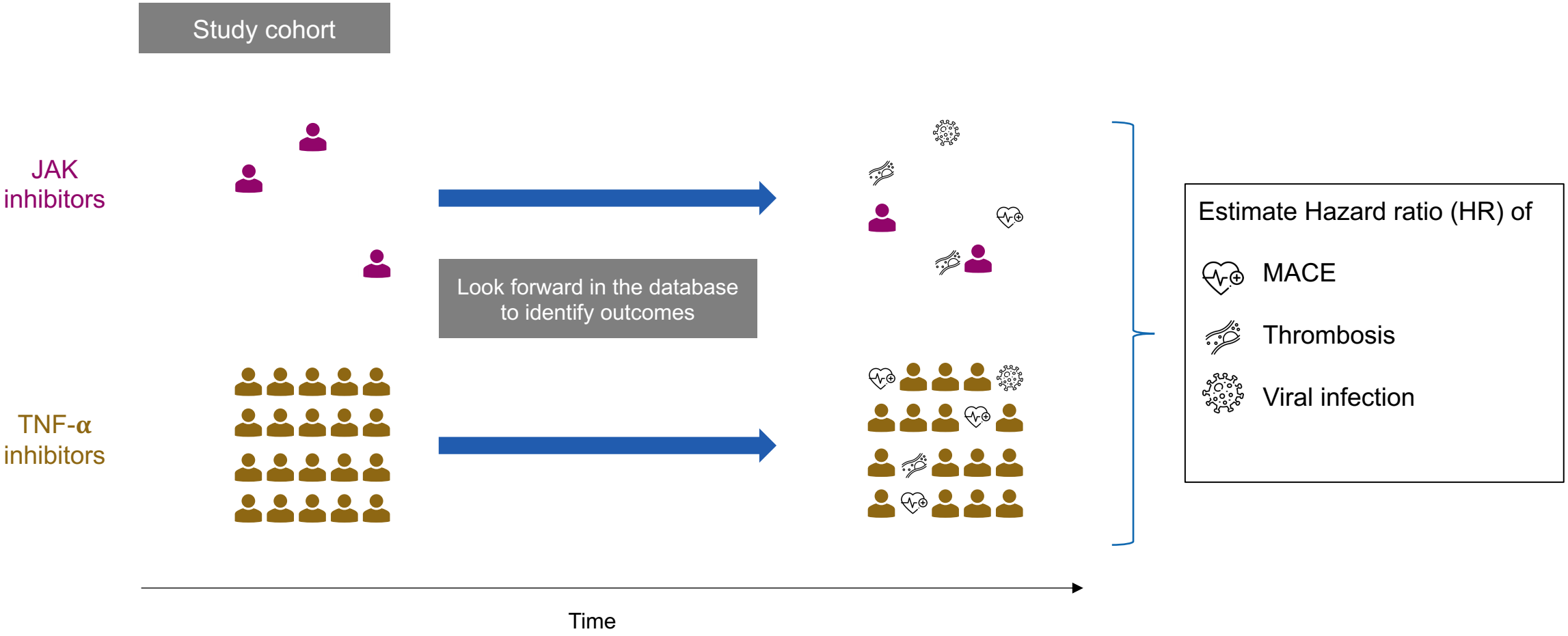
Prevalent new-user design: A case study on JAK inhibitors

2



Faquetti M.L. & Vallejo-Yagüe E., *et al.* Plos One. 2023.

Prevalent new-user design: A case study on JAK inhibitors



Faquetti M.L. & Vallejo-Yagüe E., *et al.* Plos One. 2023.

Prevalent new-user design: A case study on JAK inhibitors

2

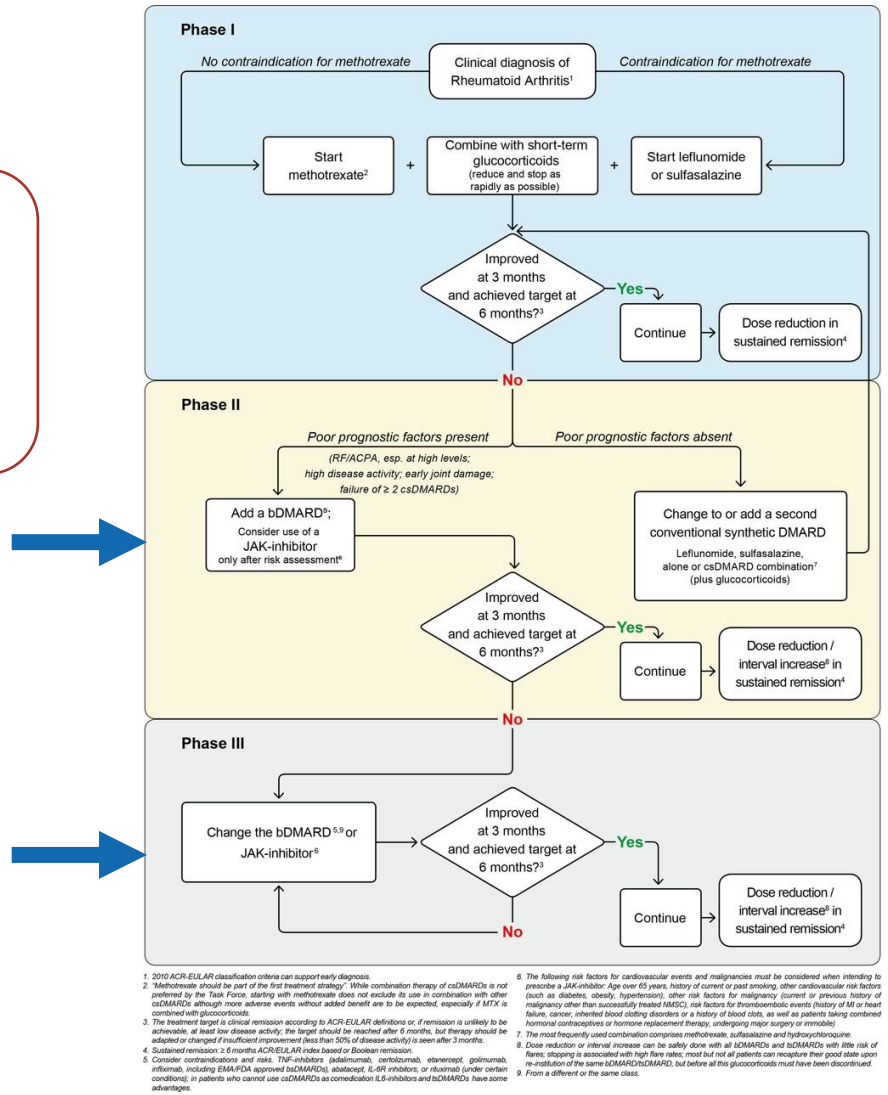
Study cohort

JAK inhibitors

TNF-α inhibitors

Problem

A new-user design would exclude a significant number of patients



Smolen JS, *et al*. *Ann Rheum Dis*. 2023;82(1):3-18.

Faquetti M.L. & Vallejo-Yagüe E., *et al.* Plos One. 2023.

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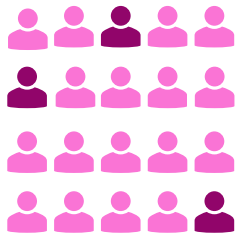
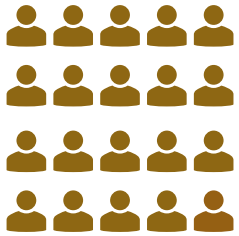


TNF-α inhibitors



Solution

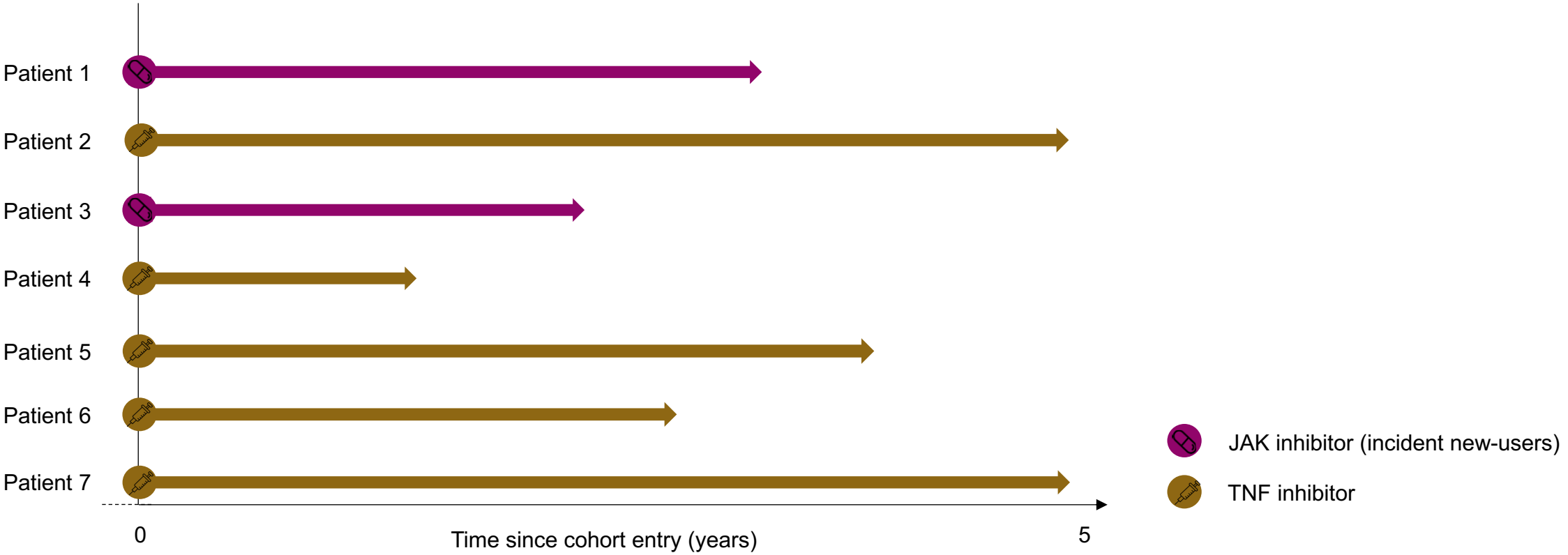
The prevalent new-user design allows the inclusion of incident new users and prevalent new users

Faquetti M.L. & Vallejo-Yagüe E., *et al.* Plos One. 2023.

Prevalent new-user design: A case study on JAK inhibitors

2

1) Base cohort



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Prevalent new-user design: A case study on JAK inhibitors

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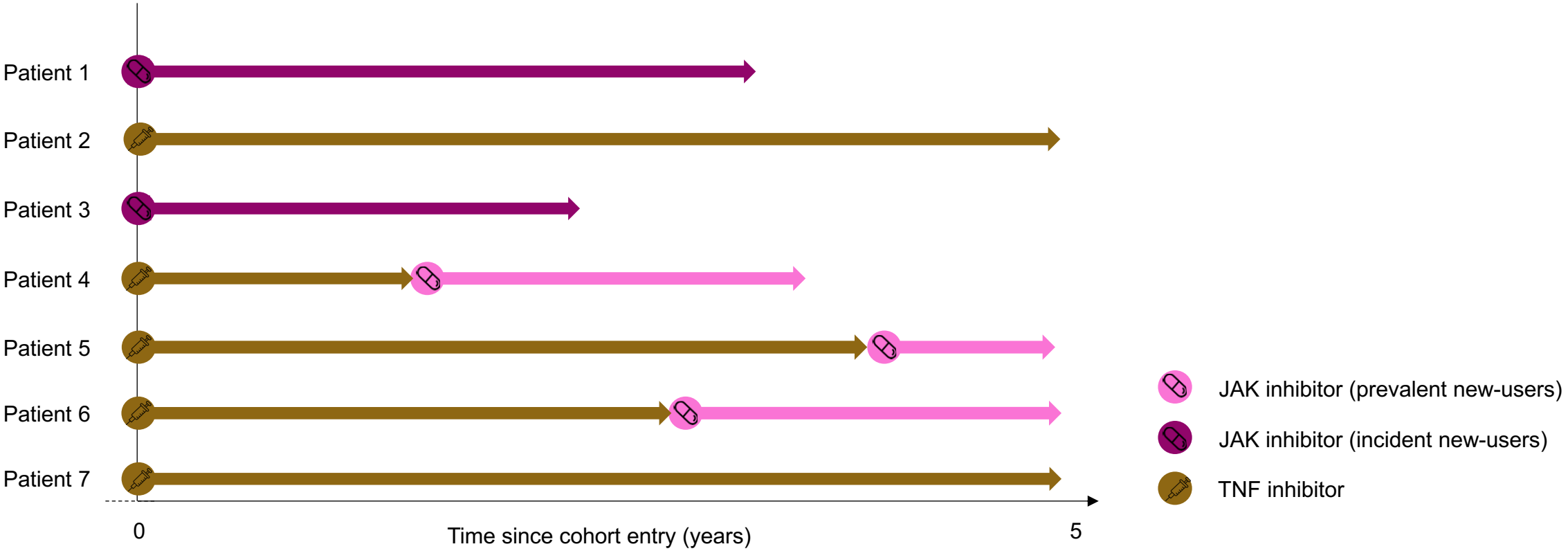
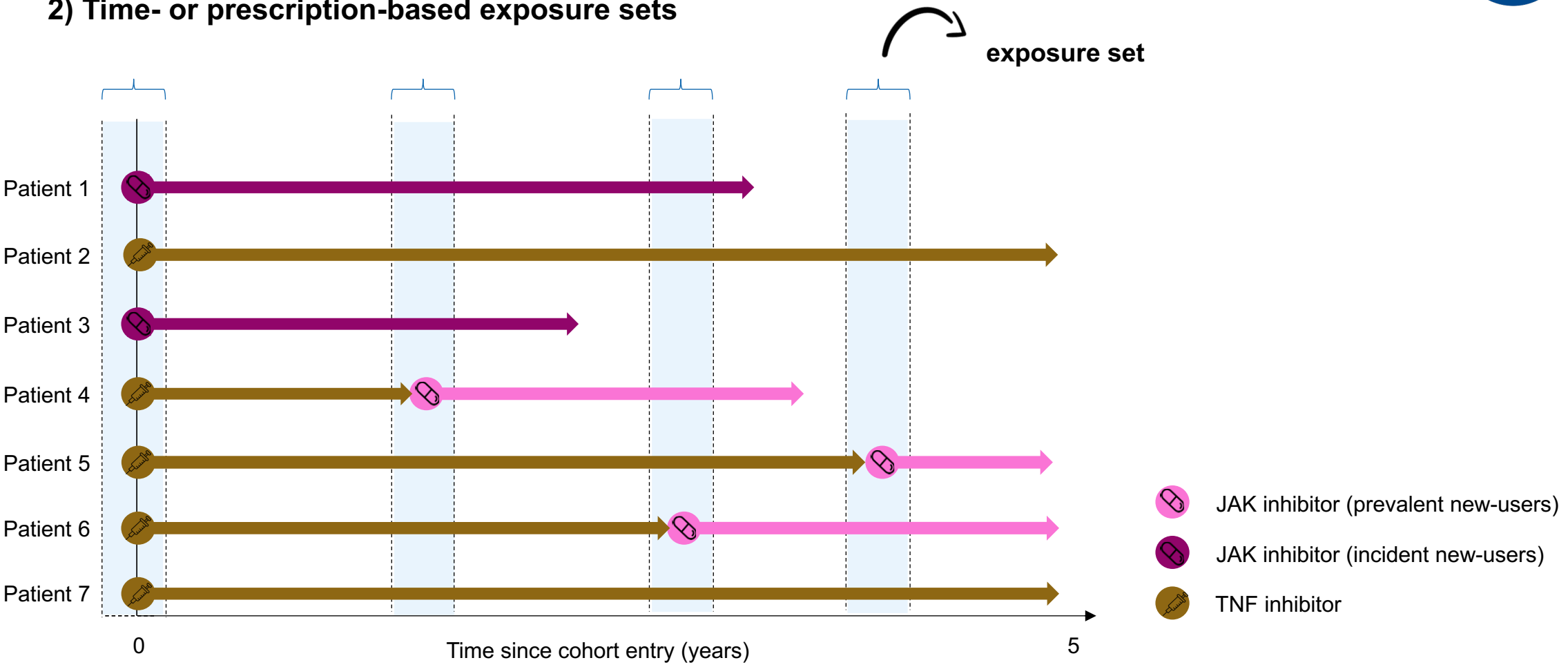


Faquetti M.L. & Vallejo-Yagüe E., *et al.* Plos One. 2023.

Prevalent new-user design: A case study on JAK inhibitors

2

2) Time- or prescription-based exposure sets



Faquetti M.L. & Vallejo-Yagüe E., *et al.* Plos One. 2023.

Prevalent new-user design: A case study on JAK inhibitors

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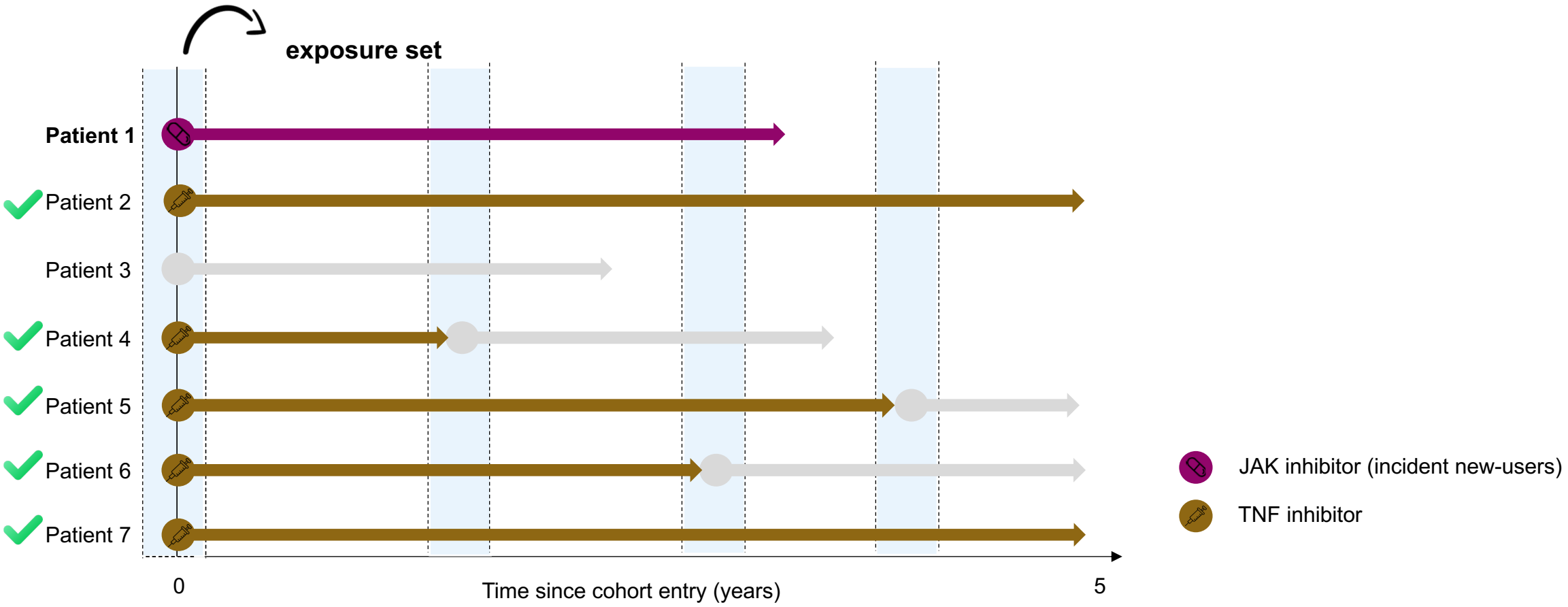
2) Time- or prescription-based exposure sets



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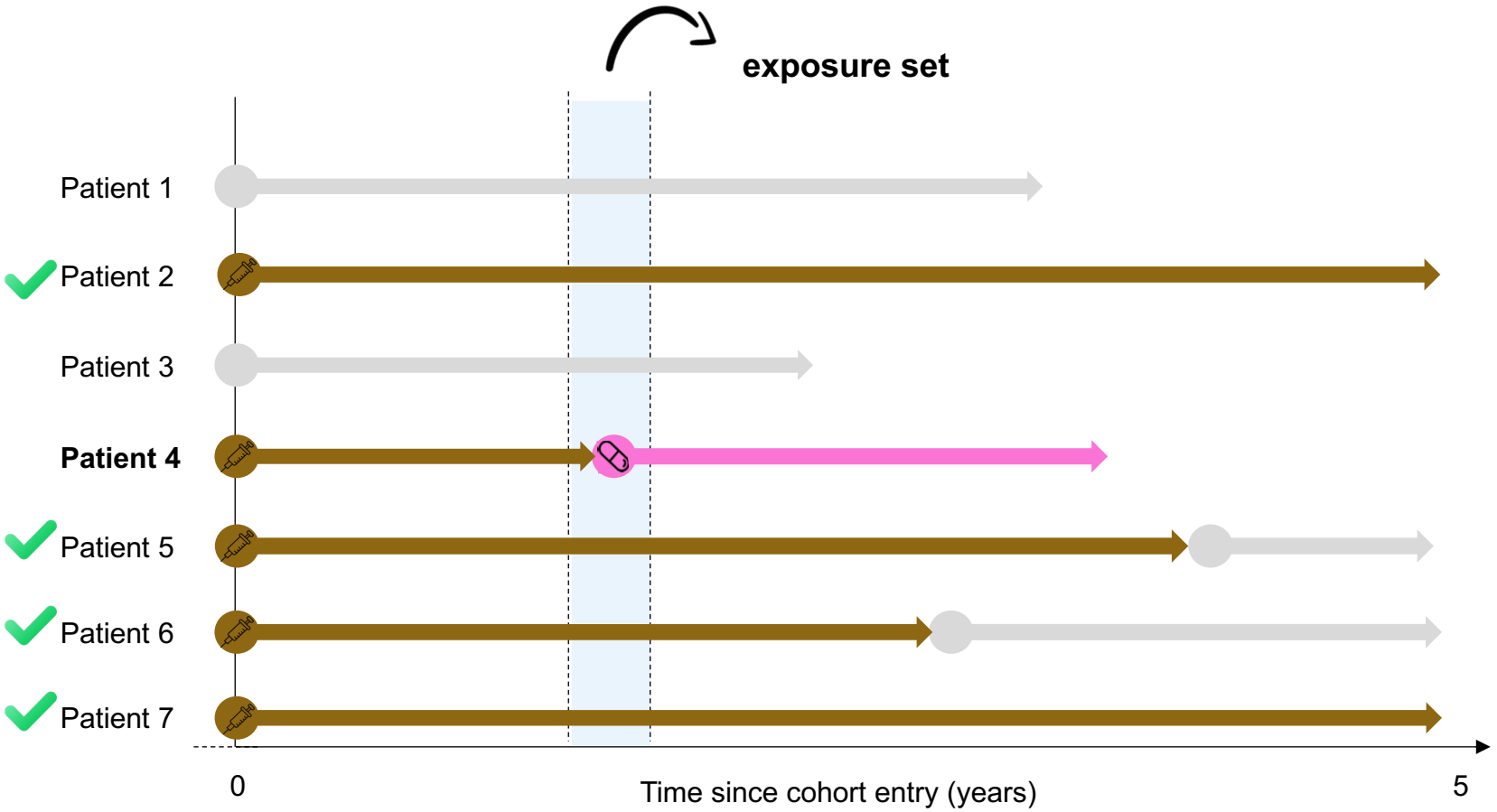
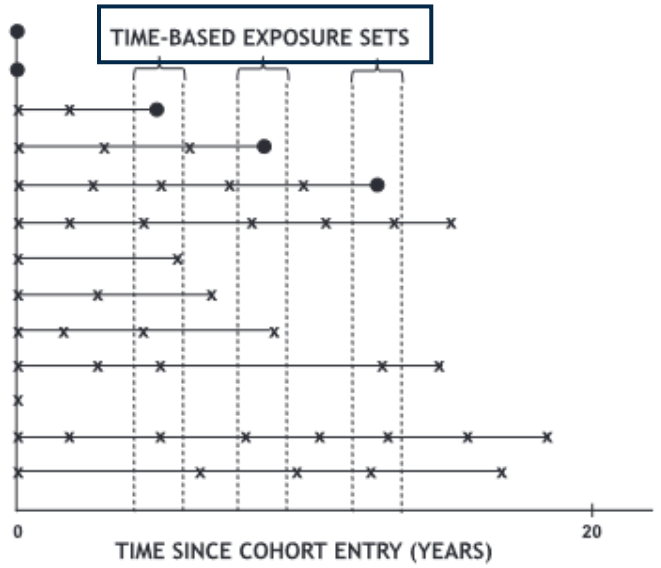
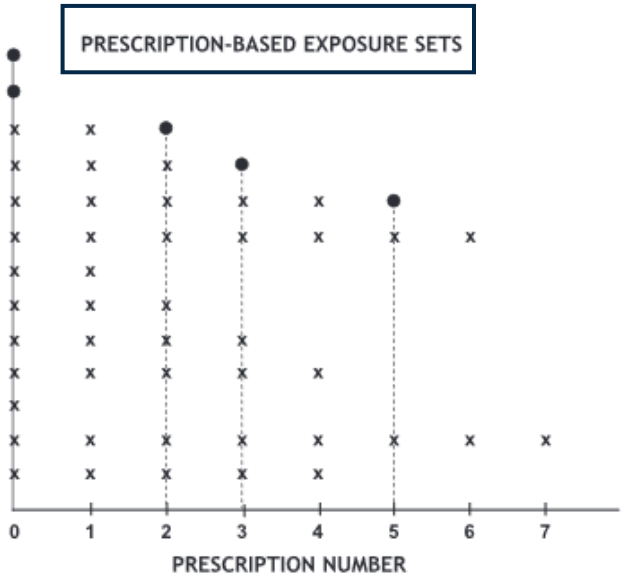






Faquetti M.L. & Vallejo-Yagüe E., *et al.* Plos One. 2023.

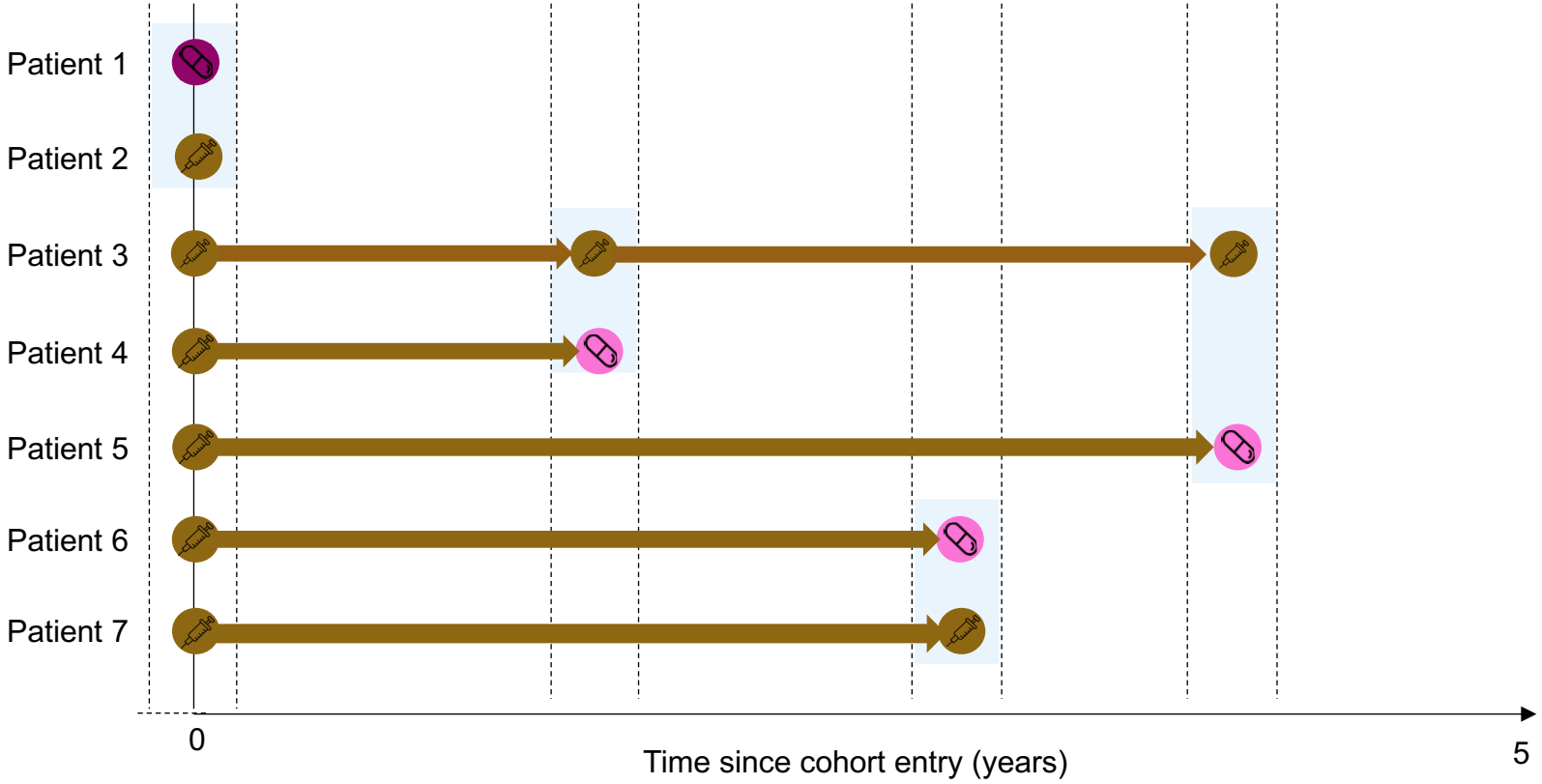
Figures adapted from Suissa S., et al. *Pharmacoepidemiol Drug Saf*. 2017.

Prevalent new-user design: A case study on JAK inhibitors

2

3) Study cohort

Include the matched JAKis —TNFis pairs using time-conditional propensity score (TCPS) within each exposure set.



4) Statistical Analysis

Hazard ratios (HR) estimation using Cox proportional hazards models

JAK inhibitor (prevalent new-users)

JAK inhibitor (incident new-users)

TNF inhibitor

Overview

1. Background information
2. The prevalent new user design & JAK inhibitors case study
3. Is the prevalent new user design an option in rare diseases?

Challenges and opportunities for applying the prevalent new-user design in rare diseases

Opportunities

- Inclusion of a broader population
- Inclusion of patients already receiving treatment **helps to address small sample sizes** in rare diseases.
- Possible applications to investigate **drug-drug interactions and treatment intensification.**
- Allows comparison of different treatment lines (e.g., when the **comparator drug is not contemporaneous**).
- May be an option when **active comparator drug is lacking.**

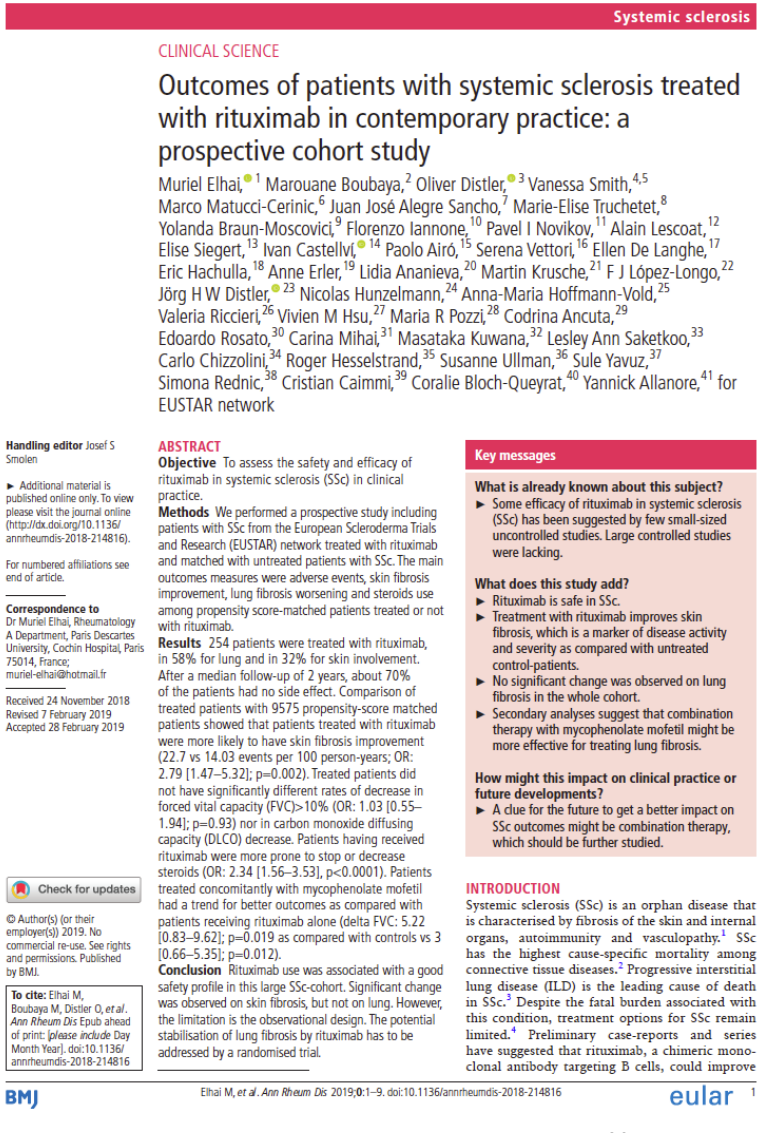
Prevalent new-user design: An option for rare diseases?

3

Considering the prevalent new-user design for follow-up studies on the safety of rituximab in systemic sclerosis

Prior study by Elhal and colleagues:

- Used rituximab second-line treatment
- No active comparator: rituximab users were matched to non-users
- Datasource: EUSTAR registry.
- Study outcomes: incidence of adverse events, improvements in skin fibrosis, worsening of lung fibrosis, and steroid use
- Findings: good safety profile, improvement in skin fibrosis but no improvement in the lung.
- Need for randomized trials to confirm lung fibrosis stabilization



Systemic sclerosis

CLINICAL SCIENCE

Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study

Muriel Elhai,[1] Marouane Boubaya,[2] Oliver Distler,[3] Vanessa Smith,[4,5] Marco Matucci-Cerinic,[6] Juan José Alegre Sancho,[7] Marie-Elise Truchetet,[8] Yolanda Braun-Moscovici,[9] Florenzo Iannone,[10] Pavel I Novikov,[11] Alain Lescoat,[12] Elise Siegert,[13] Ivan Castellvi,[14] Paolo Airó,[15] Serena Vettori,[16] Ellen De Langhe,[17] Eric Hachulla,[18] Anne Erler,[19] Lidia Ananieva,[20] Martin Krusche,[21] F J López-Longo,[22] Jörg H W Distler,[23] Nicolas Hunzelmann,[24] Anna-Maria Hoffmann-Vold,[25] Valeria Riccieri,[26] Vivien M Hsu,[27] Maria R Pozzi,[28] Codrina Ancuta,[29] Edoardo Rosato,[30] Carina Mihai,[31] Masataka Kuwana,[32] Lesley Ann Saketkoo,[33] Carlo Chizzolini,[34] Roger Hesselstrand,[35] Susanne Ullman,[36] Sule Yavuz,[37] Simona Rednic,[38] Cristian Caimmi,[39] Coralie Bloch-Queyrat,[40] Yannick Allanore,[41] for EUSTAR network

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ABSTRACT

Objective To assess the safety and efficacy of rituximab in systemic sclerosis (SSc) in clinical practice.

Methods We performed a prospective study including patients with SSc from the European Scleroderma Trials and Research (EUSTAR) network treated with rituximab and matched with untreated patients with SSc. The main outcomes measures were adverse events, skin fibrosis improvement, lung fibrosis worsening and steroids use among propensity score-matched patients treated or not with rituximab.

Results 254 patients were treated with rituximab, in 58% for lung and in 32% for skin involvement. After a median follow-up of 2 years, about 70% of the patients had no side effect. Comparison of treated patients with 9575 propensity-score matched patients showed that patients treated with rituximab were more likely to have skin fibrosis improvement (22.7 vs 14.03 events per 100 person-years; OR: 2.79 [1.47–5.32]; p=0.002). Treated patients did not have significantly different rates of decrease in forced vital capacity (FVC)>10% (OR: 1.03 [0.55–1.94]; p=0.93) nor in carbon monoxide diffusing capacity (DLCO) decrease. Patients having received rituximab were more prone to stop or decrease steroids (OR: 2.34 [1.56–3.53], p<0.0001). Patients treated concomitantly with mycophenolate mofetil had a trend for better outcomes as compared with patients receiving rituximab alone (delta FVC: 5.22 [0.83–9.62]; p=0.019 as compared with controls vs 3 [0.66–5.35]; p=0.012).

Conclusion Rituximab use was associated with a good safety profile in this large SSc-cohort. Significant change was observed on skin fibrosis, but not on lung. However, the limitation is the observational design. The potential stabilisation of lung fibrosis by rituximab has to be addressed by a randomised trial.

Key messages

What is already known about this subject?
- Some efficacy of rituximab in systemic sclerosis (SSc) has been suggested by few small-sized uncontrolled studies. Large controlled studies were lacking.

What does this study add?
- Rituximab is safe in SSc.
- Treatment with rituximab improves skin fibrosis, which is a marker of disease activity and severity as compared with untreated control-patients.
- No significant change was observed on lung fibrosis in the whole cohort.
- Secondary analyses suggest that combination therapy with mycophenolate mofetil might be more effective for treating lung fibrosis.

How might this impact on clinical practice or future developments?
- A clue for the future to get a better impact on SSc outcomes might be combination therapy, which should be further studied.

INTRODUCTION

Systemic sclerosis (SSc) is an orphan disease that is characterised by fibrosis of the skin and internal organs, autoimmunity and vasculopathy.[1] SSc has the highest cause-specific mortality among connective tissue diseases.[2] Progressive interstitial lung disease (ILD) is the leading cause of death in SSc.[3] Despite the fatal burden associated with this condition, treatment options for SSc remain limited.[4] Preliminary case-reports and series have suggested that rituximab, a chimeric monoclonal antibody targeting B cells, could improve

Fernandez-Codina, *et al*. Arthritis rheum. 2018.

Elhai M, *et al*. Ann Rheum Dis. 2019.

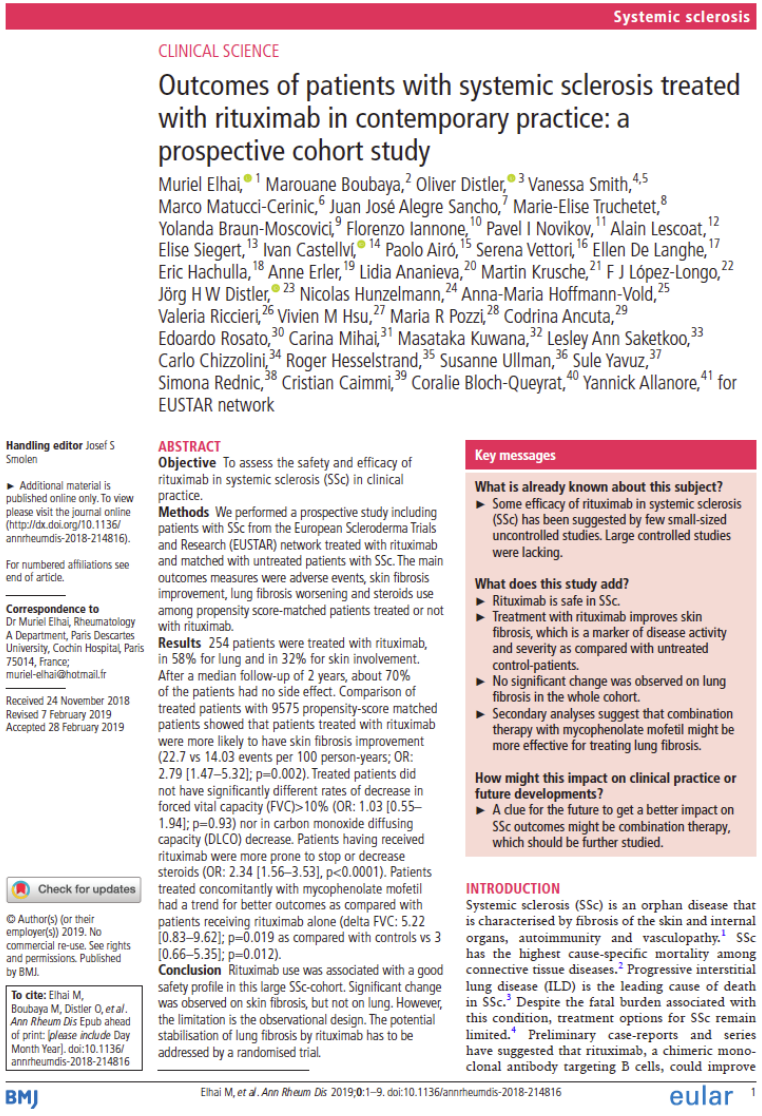
Prevalent new-user design: An option for rare diseases?

3

Considering the prevalent new-user design for follow-up studies on the safety of rituximab in systemic sclerosis

Prevalent new-user design:

- Apply this study design to investigate rituximab's safety and effectiveness in systemic sclerosis, adding to the current evidence.
- Compare outcome rates in patients starting rituximab as a second-line treatment compared to those continuing a first-line treatment.
- Provide a comprehensive assessment of rituximab's impact on systemic sclerosis in real-world clinical settings.
- Improve RWE in systemic sclerosis



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Challenges and opportunities for applying the prevalent new-user design in rare diseases

3

Challenges

In the Study design:

- Residual **confounding by indication** is possible.

- Adding a drug in treatment intensification studies may indicate a more severe disease, necessitating **careful assessment of recent clinical data to control for confounding**.

- **Effect modification** by prior use of the comparator drug requires distinguishing between incident and prevalent cohorts.

Challenges and opportunities for applying the prevalent new-user design in rare diseases

3

Challenges

In the data source selection:

- The **data source must provide information at the time of the drug switch or add-on** (exposure set TCPS matching).

- Limited **quality data** impedes long-term outcome tracking.

Challenges and opportunities for applying the prevalent new-user design in rare diseases

3

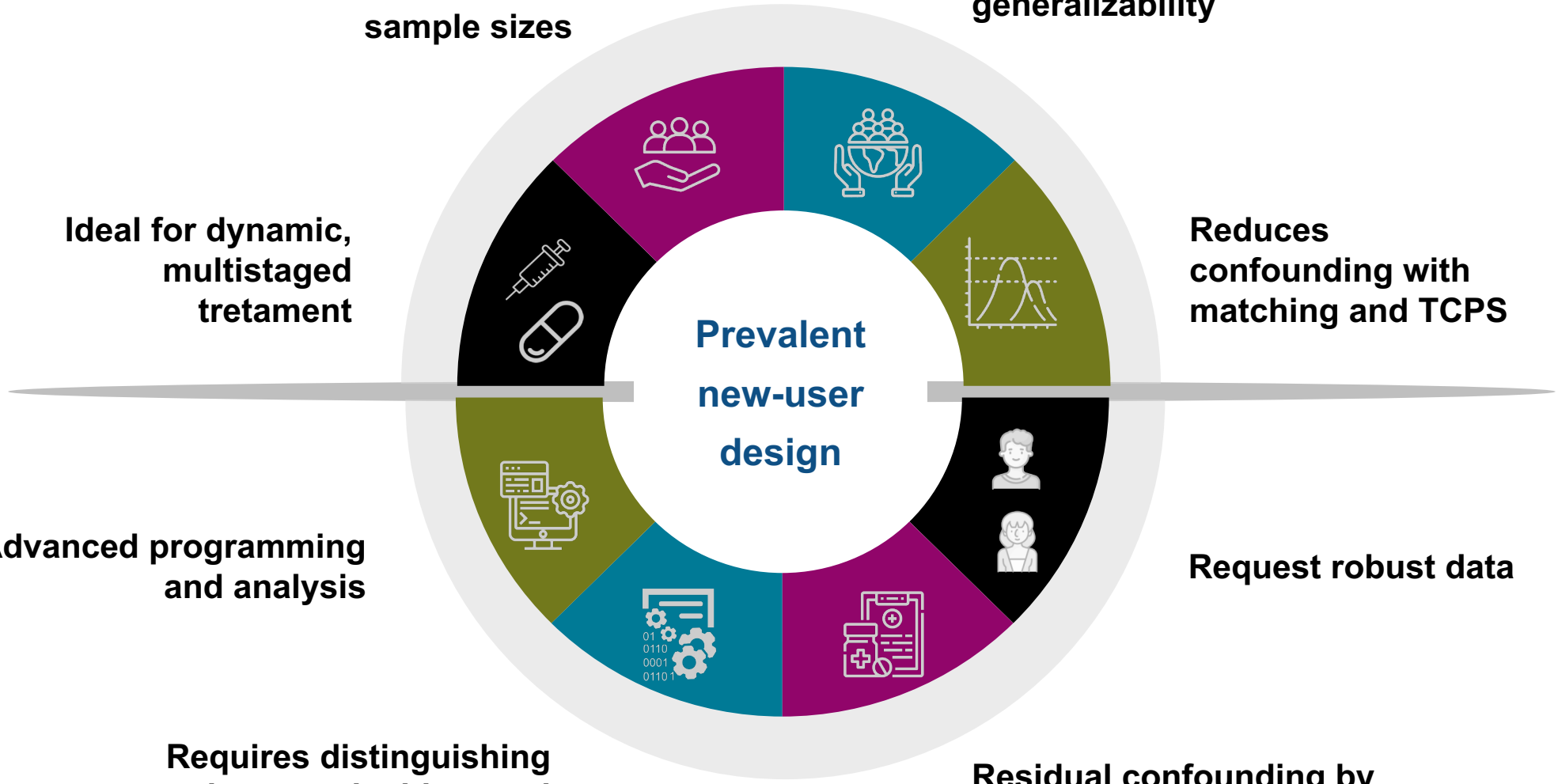
Challenges

In the statistical analyses:

- **Complexity** of implementation

- Accounting for **time-varying treatments and confounders in Cox-proportional hazard models** can be challenging, especially in long follow-up studies.

Take home message



Relevant publications on the prevalent new user design

1. Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiol Drug Saf*. 2017;26(4):459-468. doi:https://doi.org/10.1002/pds.4107
2. Young JC, Webster-Clark M, Shmuel S, et al. Clarifying the causal contrast: An empirical example applying the prevalent new user study design. *Pharmacoepidemiol Drug Saf*. 2024;33(4):e5790. doi:10.1002/pds.5790
3. Faquetti ML, Vallejo-Yagüe E, Cordtz R, Dreyer L, Burden AM. JAK-inhibitors and risk on serious viral infection, venous thromboembolism and cardiac events in patients with rheumatoid arthritis: A protocol for a prevalent new-user cohort study using the Danish nationwide DANBIO register. *PLOS ONE*. 2023;18(7):e0288757. doi:10.1371/journal.pone.0288757
4. Fisher A, Fralick M, Filion KB, et al. Sodium-glucose co-transporter-2 inhibitors and the risk of urosepsis: A multi-site, prevalent new-user cohort study. *Diabetes Obes Metab*. 2020;22(9):1648-1658. doi:10.1111/dom.14082
5. Tazare J, Gibbons DC, Bokern M, et al. Prevalent new user designs: A literature review of current implementation practice. *Pharmacoepidemiol Drug Saf*. Published online June 22, 2023:pds.5656. doi:10.1002/pds.5656
6. Suissa S, Dell'Aniello S, Renoux C. The Prevalent New-user Design for Studies With no Active Comparator: The Example of Statins and Cancer. *Epidemiol Camb Mass*. 2023;34(5):681-689. doi:10.1097/EDE.0000000000001628

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