Supplemental Appendix

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Section 1. Title Page

Dose and duration-dependent corticosteroid risk for cardiovascular events in corticosteroid-naive patients with rheumatoid arthritis

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Section 2. Table of Contents

Section 3. Methods of calculating cumulative prednisone dose/duration of use

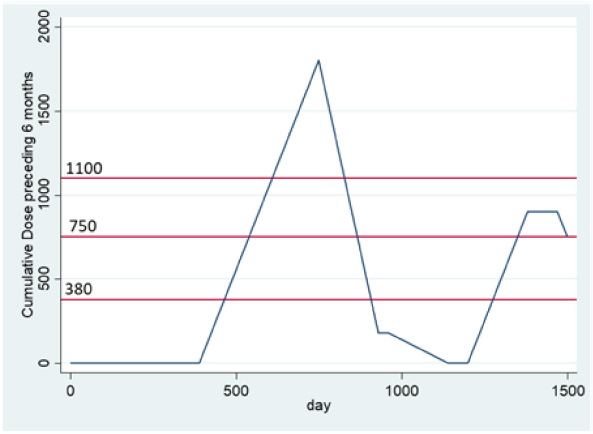
Time was divided into days to cover all events and changes of dose or duration of use across all patients. Prednisone dose and usage were updated at each visit for a patient. The assumption was made that a patient was on the prior dose with continuous use until the next visit unless the patient or physician reported a specific date of dose change or cessation of use.

As a time-varying analysis, for each time point after the index date (enrollment), we computed cumulative dose or duration of use over the preceding 6-months or 1-year. This is illustrated in eFigure1A with an example patient and shows how the preceding 6-month cumulative dose is updated in a time-varying manner. Cumulative dose and duration of use were divided into equivalent quartiles for analysis.

For any given series of days, eFigure 1B illustrated the computation of cumulative total dose or duration of use. The cumulative total dose (or duration of use) was calculated as the area under the dose curve for the preceding 6-months or 1-year interval.

Appendix eFigure 1. Computational model for total prednisone dose and duration.

A

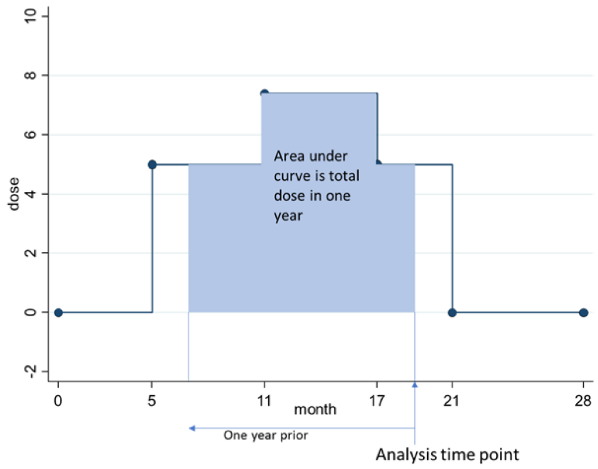


Legend:

A. Each point of the curve represents the preceding 6-month cumulative dose of prednisone use in a time-varying manner.

B. Prednisone dose and duration of use was then calculated over the preceding 6-months or 1-year at all time points, updated daily, based on the area under the curve.

B

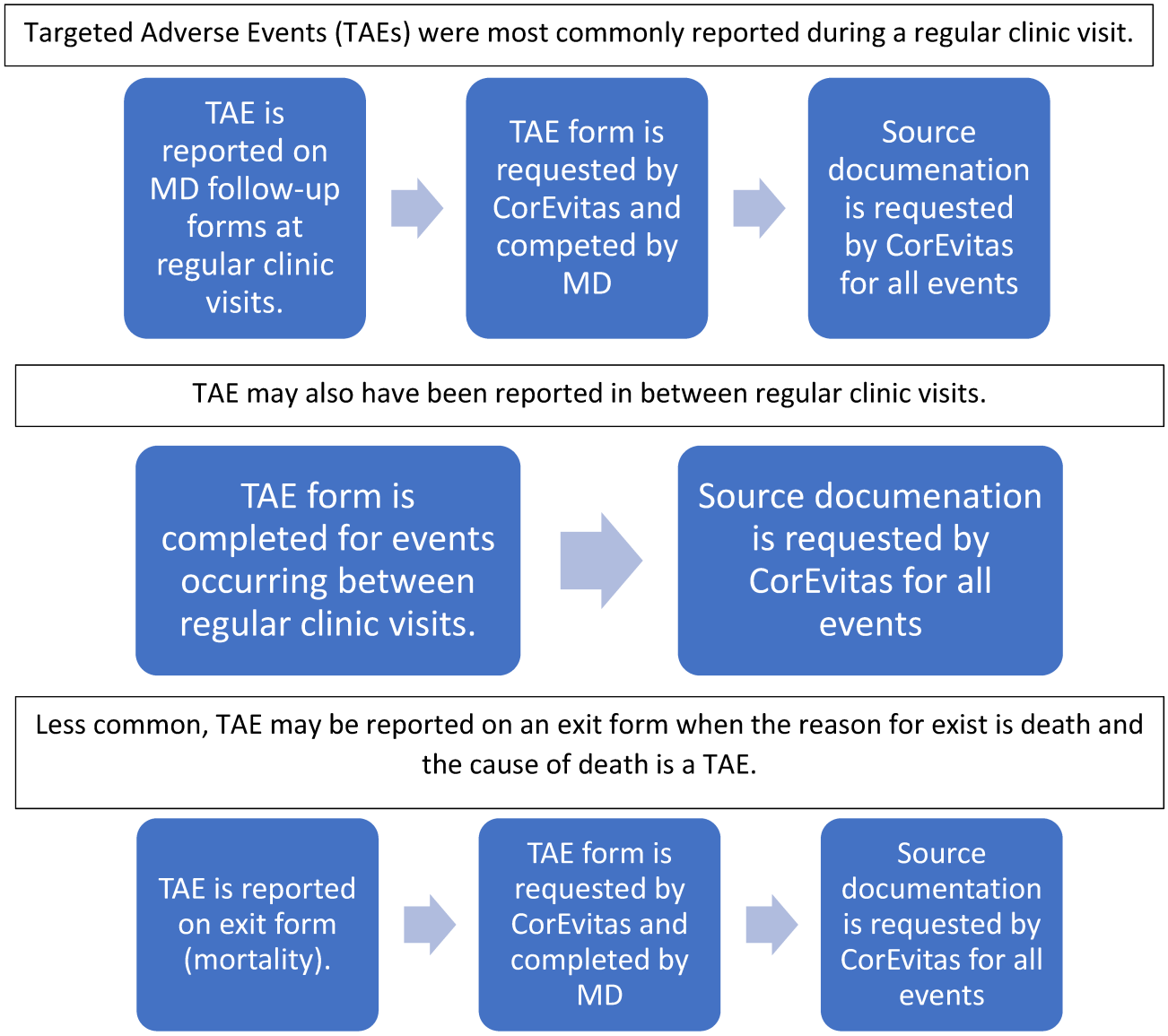


Section 4. Event collection protocol for CorEvitas (formerly Corrona) registry

The supplemental eFigure 2 below illustrates the collection of targeted adverse events (TAEs) in the CorEvitas (formerly Corrona) registry. All outcomes of interest are TAEs within CorEvitas.

Primary analysis of events was operationalized as follows. The registry used all events reported on physician forms except for events that were 'not confirmed' by the TAE form. Approximately 90% of reported events are validated with a TAE. Of the remaining 10%, approximately 4% were later ruled out and converted to "not an event"; 5-6% were incomplete in the system pending additional site follow-up/TAE completion.

Appendix eFigure 2. Targeted Adverse Events



Section 5. Absolute Number of Patients For Each Risk Assessment

Note that patients may contribute to more than one category over time due to the time varying analysis. Thus, the total number of patients will be greater than the number included in the study.

Appendix eTable 1: Patient Counts

Daily Dose (mg) †	Patients contributing
none	19902
1-<5	722
≥5-9	1598
≥10	1077
Cumulative Dose (mg) †	
Over Preceding 6-Months	
none	19902
1-380	2500
381-750	2396
751-1100	2003
>1110	1001
Over Preceding 1-Year	
none	19902
1-500	2500
501-1100	2314
1101-2100	1710
>2100	919
Duration of Use (days)	
Over Preceding 6-Months	
none	19902
1-80	2500
81-160	2440
161-181	1864
>181	1705
Over Preceding 1-Year	
none	19902
1-100	2500
101-220	2274
221-360	1388
>360	858

Section 6. Sensitivity analysis: Exclusion of VTE as CVE

Appendix eTable 2. Unadjusted and adjusted Hazard Ratios after Exclusion of Deep Vein Thrombosis and Pulmonary Embolism as Cardiovascular Events

Risk for Cardiovascular Events Excluding DVT/PE				
Daily Dose (mg)†	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted* Hazard Ratio	95% Confidence Interval
none	1	ref	1	ref
1-<5	0.96	0.54-1.70	0.87	0.49-1.54
≥5-9	1.71	1.28-2.29	1.50	1.12-2.01
≥10	2.03	1.37-3.03	1.83	1.23-2.74
Cumulative Dose (mg)†	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted* Hazard Ratio	95% Confidence Interval
Over Preceding 6-Months				
none	1	ref	1	ref
1-380	0.83	0.49-1.41	0.78	0.46-1.32
381-750	1.14	0.73-1.78	1.05	0.67-1.64
751-1100	1.62	1.16-2.27	1.43	1.02-2.00
>1110	2.44	1.70-3.50	2.19	1.52-3.14
Over Preceding 1-Year				
none	1	ref	1	ref
1-500	0.97	0.61-1.55	0.92	0.58-1.47
501-1100	1.26	0.86-1.83	1.17	0.80-1.71
1101-2100	1.63	1.17-2.28	1.47	1.05-2.07
>2100	1.95	1.38-2.75	1.71	1.20-2.42
Duration of Use (days)	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted* Hazard Ratio	95% Confidence Interval
Over Preceding 6-Months				
none	1	ref	1	ref
1-80	0.56	0.30-1.05	0.53	0.28-0.99
81-160	1.69	1.18-2.44	1.58	1.10-2.28
160-181	2.18	1.04-4.59	1.98	0.94-4.18
>181	1.77	1.34-2.34	1.54	1.16-2.04
Over Preceding 1-Year				
none	1	ref	1	ref
1-100	1.13	0.75-1.72	1.08	0.71-1.63
101-220	1.48	1.07-2.05	1.39	1.00-1.93
221-360	0.94	0.55-1.59	0.83	0.49-1.42
>360	2.10	1.53-2.89	1.83	1.33-2.51

DVT, deep vein thrombosis; PE, pulmonary embolism.

†, prednisone-equivalents

*adjusted for age, sex, race, duration of RA, history of CV disease, diabetes mellitus, hyperlipidemia, hypertension, statin use, NSAID use, tobacco use, year of enrollment, baseline modified health assessment questionnaire score, CDAI, and cs, b, tsDMARDS use.

Section 7. Sensitivity analysis: Exclusion of patients with prior CV events

With exclusion of patients who had a history of prior CVE, 829 events occurred. The event rate was 1.34 events per 100 patient-years. The total number of patients was 18,168, with 2300 initiating prednisone.

Appendix eTable 3. Unadjusted and adjusted Hazard Ratios after exclusion of patients with a history of prior CVE

Risk for CVE Excluding Patients with Prior History of CVE				
Daily Dose (mg)†	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted* Hazard Ratio	95% Confidence Interval
none	1	ref	1	ref
1-<5	0.93	0.50-1.74	0.81	0.43-1.51
≥5-9	1.94	1.44-2.62	1.68	1.24-2.27
≥10	2.19	1.43-3.36	2.04	1.33-3.14
Cumulative Dose (mg)†	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted* Hazard Ratio	95% Confidence Interval
Over Preceding 6-Months				
none	1	ref	1	ref
1-380	0.86	0.49-1.53	0.81	0.46-1.43
381-750	1.34	0.86-2.09	1.20	0.77-1.87
751-1100	1.79	1.27-2.54	1.57	1.11-2.22
>1110	2.38	1.60-3.55	2.19	1.46-3.28
Over Preceding 1-Year				
none	1	ref	1	ref
1-500	0.98	0.59-1.64	0.92	0.51-1.53
501-1100	1.44	0.98-2.12	1.35	0.91-1.98
1101-2100	1.60	1.11-2.31	1.44	0.99-2.07
>2100	2.23	1.57-3.18	1.98	1.38-2.82
Duration of Use (days)	Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted* Hazard Ratio	95% Confidence Interval
Over Preceding 6-Months				
none	1	ref	1	ref
1-80	0.75	0.42-1.36	0.71	0.39-1.29
81-160	1.76	1.19-2.60	1.64	1.11-2.43
160-181	1.47	0.55-3.92	1.34	0.50-3.61
>181	1.92	1.44-2.57	1.65	1.23-2.21
Over Preceding 1-Year				
none	1	ref	1	ref
1-100	1.14	0.73-1.81	1.09	0.69-1.72
101-220	1.63	1.16-2.30	1.54	1.09-2.17
221-360	1.03	0.60-1.79	0.91	0.54-1.58
>360	2.26	1.62-3.15	1.94	1.39-2.71

†, prednisone-equivalents

*adjusted for age, sex, race, duration of RA, history of CV disease, diabetes mellitus, hyperlipidemia, hypertension, statin use, NSAID use, tobacco use, year of enrollment, baseline modified health assessment questionnaire score, CDAI, and cs, b, tsDMARDS use.

Section 8: Sensitivity analysis: Exclusion of "Other" CVE

This sensitivity analysis excluded "Other" CVE to assess for impact on results. With exclusion of "Other" events, a total of 817 events occurred.

Appendix eTable 4. Unadjusted and adjusted Hazard Ratios after Exclusion of Other CVE

Daily Dose (mg) †	**Unadjusted Hazard Ratio [95% CI]**	**Adjusted* Hazard Ratio [95% CI]**
none	1 [ref]	1 [ref]
1-<5	1.14 [0.63-2.06]	1.01 [0.56-1.84]
≥5-9	1.86 [1.36-2.55]	1.65 [1.20-2.27]
≥10	2.03 [1.40-3.17]	1.91 [1.22-2.99]
Cumulative Dose (mg) †	**Unadjusted Hazard Ratio [95% CI]**	**Adjusted* Hazard Ratio [95% CI]**
Over Preceding 6-Months		
none	1 [ref]	1 [ref]
1-380	0.90 [0.51-1.59]	0.84 [0.47-1.49]
381-750	1.23 [0.76-2.00]	1.13 [0.70-1.83]
751-1100	1.90 [1.34-2.71]	1.69 [1.19-2.41]
>1110	2.30 [1.51-3.48]	2.16 [1.42-3.29]
Over Preceding 1-Year		
none	1 [ref]	1 [ref]
1-500	1.02 [0.61-1.70]	0.96 [0.58-1.61]
501-1100	1.42 [0.95-2.12]	1.32 [0.88-1.97]
1101-2100	1.73 [1.20-2.50]	1.58 [1.09-2.29]
>2100	2.09 [1.43-3.07]	1.90 [1.29-2.79]
Duration of Use (days)	**Unadjusted Hazard Ratio [95% CI]**	**Adjusted* Hazard Ratio [95% CI]**
Over Preceding 6-Months		
none	1 [ref]	1 [ref]
1-80	0.77 [0.43-1.40]	0.73 [0.40-1.33]
81-160	1.63 [1.07-2.47]	1.52 [1.00-2.31]
161-181	1.17 [0.38-3.63]	1.10 [0.35-3.42]
>181	2.04 [1.52-2.74]	1.80 [1.33-2.43]
Over Preceding 1-Year		
none	1 [ref]	1 [ref]
1-100	1.17 [0.74-1.85]	1.12 [0.70-1.75]
101-220	1.42 [0.98-2.07]	1.36 [0.93-1.98]
221-360	1.29 [0.77-2.15]	1.16 [0.69-1.94]
>360	2.38 [1.69-3.37]	2.08 [1.47-2.95]

†, prednisone-equivalents

*adjusted for age, sex, race, duration of RA, history of CV disease, diabetes mellitus, hyperlipidemia, hypertension, statin use, NSAID use, tobacco use, year of enrollment, baseline modified health assessment questionnaire score, CDAI, and cs, b, tsDMARDS use.