NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Observational, Post-Authorization Safety Study (PASS) within the Consortium of Rheumatology Researchers of North America (CORRONA) Registry Comparing Rates of Malignancy, Cardiovascular and Serious Infection Outcomes among Patients Treated for Moderately to Severely Active Rheumatoid Arthritis
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Medicinal product	Xeljanz (tofacitinib)
Joint PASS	No
Country(-ies) of study	United States of America
Author	Jamie L. Geier, PhD Epidemiologist 235 East 42nd Street, 219/09/01 New York, NY 10017 USA

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CEO	Chief Executive Officer
CI	Confidence Interval
CORRONA	Consortium of Rheumatology Researchers of North America
CSO	Chief Statistical Officer
CV	Cardiovascular
DBA	Database Administrator
DMARD	Disease Modifying Anti-Rheumatic Drugs
DMOC	Data Monitoring and Oversight Committee
EMA	European Medicines Agency
EQ5D	EuroQol 5D
FDA	Food and Drug Administration
FTP/sFTP	File Transfer Protocol
HIPPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
ICF	Informed Consent Forms
ID	Identity
IEC	International Ethics Committee
IL	Interleukin
IP	Internet Protocol
IRB	Institutional Review Board
IS	Information Services
IT	Information Technology
JAK	Janus Kinase
NC	North Carolina
NDI	National Death Index
PASS	Post-Authorization Safety Study
PHI	Personal Health Information
PPV	Positive Predictive Value
PSUR	Periodic Safety Update Report
QHS	Quantitative Health Sciences
QMC	Quantitative Methods Core
RA	Rheumatoid Arthritis

SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIAC	Site Investigator Advisory Committee
SIE	Serious Infection Event
SOP	Standardized Operating Procedure
TBD	To Be Determined
TAE	Targeted Adverse Event
TBN	To Be Named
TNF	Tumor Necrosis Factor
TyK2	Tyrosine Kinase 2
UMMS	University of Massachusetts Medical School
URL	Universal Resource Locators
US	United States
VPN	Virtual Private Network

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Jamie L. Geier, PhD	Epidemiologist	Pfizer, Inc.	235 East 42nd Street, 219/09/01 New York, NY 10017 USA
Jeffrey Greenberg, MD, MPH	Chief Science Officer	CORRONA, Inc.	PO Box 786, Southborough, MA 01772
George W. Reed, PhD	Biostatistician	CORRONA, Inc.	PO Box 786, Southborough, MA 01772
Katherine C, Saunders, MS	Director of Epidemiology and Outcomes Research	CORRONA, Inc.	PO Box 786, Southborough, MA 01772
Christine J. Barr, BSN, MPH	Director of Pharmacovigilance	CORRONA, Inc.	PO Box 786, Southborough, MA 01772

4. ABSTRACT

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. To enable assessment of rare events and endpoints with long latency periods, Pfizer will implement a post-approval, population-based active surveillance study of tofacitinib-exposed patients using the Consortium of Rheumatology Researchers of North America (CORRONA) registry to actively collect safety data in a prospective manner. The CORRONA databases will be queried to identify patients treated with tofacitinib and capture the occurrence of safety endpoints of interest. The study population will comprise all patients who receive tofacitinib within the CORRONA registry, following United States (US) approval and marketing, through the end of the study period (estimated to be 5 years from the launch date). Two age and gender-matched comparator populations will be assembled consisting of patients with moderate-to-severe rheumatoid arthritis (RA). The primary comparator population will include patients exposed to biologic disease modifying antirheumatic drugs (DMARD) therapy for the treatment of RA; the secondary comparator population will include patients exposed to non-biologic DMARD therapies only (eg, methotrexate). The study will evaluate a range of safety outcomes associated with therapies used to treat RA including malignancies, cardiovascular events, and serious infections. Updates will be provided quarterly and reported to the Food and Drug Administration (FDA) every six months. A final study report will be submitted to the FDA approximately 5 years post study initiation.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Protocol Finalization	31 December 2013
Start of National Death Index Re-Consenting Procedures	06 January 2014
Data Extraction for Adverse Event Assessments	28 February 2014
Quarterly report 1 Note: Summary reports will be delivered quarterly throughout the study period. Data extraction will be 60 days post quarter end; reports will be delivered 90 days post quarter end.	31 March 2014
Final study report	01 April 2018

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease characterized by erosive destruction of the joints. While there is considerable variation in the estimates of those affected by RA, the majority of studies from Northern European areas and North America estimate a prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05%.[1] Presentation of RA typically occurs between the ages of 20 to 40 years with a female predominance on the order of 3:1.[8,12]

Because RA is currently incurable, the goals of treatment are to reduce disease activity, improve physical function and health-related quality of life, and inhibit progression of structural damage throughout the course of the patients' disease. Treatment is primarily focused on disease modifying anti-rheumatic drugs (DMARDs), which are either orally administered small molecules (eg, methotrexate or leflunomide) or newer, intravenously-administered biologics. Although multiple DMARDs are available to treat RA and combination therapy is frequently employed, many patients remain inadequately treated and continue to suffer pain, disability and progressive joint damage. Specifically, up to 1/3 of patients do not adequately respond and about half stop responding to any particular DMARD within 5 years.[9,4] Due to the duration and chronic nature of this disease, patients can expect to require treatment for up to 40 years over their lifetime. The likelihood that a patient will stop responding to any particular therapy means that many will exhaust available treatment options during the course of their disease. Thus, there remains an unmet medical need for additional therapeutic options with unique mechanisms of action, proven efficacy and acceptable safety profiles in patients with moderately to severely active rheumatoid arthritis.

By the end of 2012, over 5600 patients were treated with tofacitinib for RA in clinical trials. To enable further assessment of rare events and endpoints with long latency periods, Pfizer will implement a post-approval, population-based active surveillance study of

tofacitinib-exposed patients. Data collected will supplement the safety information obtained within the clinical program.

The Consortium of Rheumatology Researchers of North America, Inc. (CORRONA) registry will be the data source for this study. With over 30,000 patients enrolled to date, the registry is equipped to evaluate safety endpoints immediately post-launch of tofacitinib as well as over an extended period of time (ie, 5 years). The CORRONA databases will be queried to identify patients treated with tofacitinib and capture the occurrence of safety endpoints of interest (ie, cardiovascular events, serious infections and malignancies) relative to patients treated with biologic and non-biologic DMARDs. The study protocol is considered a living document, as coding algorithms and variable definitions may be refined per feasibility assessments performed during course of the study.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to characterize the safety of tofacitinib in the post-approval setting via:

1. The evaluation of incidence rates of selected adverse events of interest as identified within the tofacitinib risk management plan.

2. Comparison with two age and gender-matched comparator populations:

    a. Patients initiating a biologic DMARD therapy, alone or in combination with non-biologic DMARD therapies with no prior exposure to tofacitinib (primary comparator), and

    b. Patients initiating non-biologic DMARD therapies with no concurrent or prior exposure to biologics or small molecule therapies (secondary). Only exposure time while not on a biologic or small molecule therapy will be used.

9. RESEARCH METHODS

9.1. Study Design

This is a population-based study in a cohort of tofacitinib-exposed patients which uses the CORRONA registry to actively collect safety data in a prospective manner. In this study, all drugs are prescribed and follow-up visits captured as a part of normal medical practice; patient therapeutic strategies are not determined by this protocol.

9.2. Study Population

All patients exposed to tofacitinib within the CORRONA registry, following US approval and launch of the product, will be included in the study. Patients will be identified as incident (ie, those who start tofacitinib within the study setting and have no prior use of tofacitinib) and prevalent users.

The comparator populations will be comprised of:

1. Patients exposed to biologic DMARDs for the treatment of RA (ie, TNF inhibitors). (Note: The patient population will be stratified by incident and prevalent users. Formal statistical comparisons (ie, rate ratios) will be conducted once an appropriate sample size (based on power calculations) is achieved. Additionally, a subcohort of patients exposed to tocilizumab only will be identified. Rates will be calculated separately for tocilizumab-exposed patients. Formal comparisons (ie, rate ratios) will be completed when statistical power is achieved.

2. Patients exposed to non-biological DMARDS (eg, methotrexate). (Note: The patient population will be stratified by incidence and prevalent users. Formal statistical comparisons (ie, rate ratios) will be conducted once an appropriate sample size (based on power calculations) is achieved).

Demographic data collected includes age, gender, race and ethnicity (Appendix A). In addition, baseline characteristics as show in Table 1 will be captured for the cohorts under study (ie, incident tofacitinib exposures, prevalent tofacitinib exposures, TNF inhibitor comparator, tocilizumab comparator, and non-biological DMARD comparator) to evaluate disease characteristics.

Table 1. Example of a Baseline Characteristics Table of Patients with at Least One Follow-up Visit after Use of tofacitinib Documented within the CORRONA Registry

		Tofacitinib patients			Comparator Population		
		N	Mean	SD	N	Mean	SD
Years since diagnosis	Male						
	Female						
	Total						
HAQ(mHAQ)	Male						
	Female						
	Total						
DAS28	Male						
	Female						
	Total						
Tender Joint Count	Male						
	Female						
	Total						
Swollen Joint Count	Male						
	Female						
	Total						
ESR (where available)	Male						
	Female						
	Total						
CRP(where available)	Male						
	Female						
	Total						
MD Global	Male						
	Female						
	Total						
Abbrev: CRP= C-Reactive Protein, DAS= Disease Activity Score, ESR= Erythrocyte sedimentation rate, HAQ=Health Assessment Questionnaire, MD=Medical Doctor, mHAQ=Modified Health Assessment Questionnaire.							

9.3. Setting

The Consortium of Rheumatology Researchers of North America, Inc. (CORRONA) was founded in 2000. CORRONA is an independent registry run by a group of experienced academic and clinical rheumatologists throughout the United States (US). Data on Rheumatoid Arthritis, Psoriatic Arthritis, Osteoarthritis, Osteoporosis, and Osteoporosis Risk derived from rheumatologists and patients are entered at the clinical point of care.

The CORRONA RA registry includes a network of 482 participating academic and community rheumatologists at 135 sites in more than 40 states within the US. CORRONA RA is a disease-based registry. Access to and use of biological disease modifying anti-rheumatic drugs (DMARDs) in the US varies depending on patient insurance and study period. In the CORRONA database, a cross-sectional analysis of patients using the patient's last visit in 2012 found approximately 37.9% of the CORRONA RA population was prescribed tumor necrosis factor (TNF) antagonists and 12.6% were prescribed a non-TNF

biologic. All patients with RA treated by participating rheumatologists are eligible for CORRONA. At enrollment, patient reported past drug use is obtained; current drug utilization is captured by both patient and physician report, and new drug start data are gathered by physician report during follow-up. Both patient and physician reported disease activity measures obtained at each visit are captured in CORRONA; this includes tender and swollen joint counts (28 joint counts), patient and physician global disease assessment, patient pain assessment and HAQ scores. CORRONA RA visits follow standard of care which is approximately every 4 months (CORRONA median time between visits for RA patients is 4.08 months).

9.3.1. Inclusion Criteria

The study population will comprise all patients, 18 years of age and older, who receive tofacitinib for the treatment of RA following US approval and marketing through the end of the study period (estimated to be 5 years from the launch date). Incident and prevalent users of tofacitinib will be included.

Two age and gender-matched comparator populations will be assembled consisting of adult patients with RA. The primary comparator population will include patients initiating a biologic DMARD therapy for treatment of RA as monotherapy or combination therapy and with no prior exposure to tofacitinib; the secondary comparator population will include patients initiating a non-biologic DMARD therapy with no concurrent or prior exposure to biologics or small molecule therapies. Only exposure time while not on a biologic or small molecule therapy will be used (eg, methotrexate).

9.4. Endpoints

The CORRONA registry is an efficient data collection system for evaluating a range of safety outcomes associated with therapies used to treat RA including cancers, cardiovascular events, and serious infections.[2,3,6,7,5,11] The endpoints chosen for study are events associated with RA itself and therapies used to treat moderate-to-severe disease. Serious infections and lymphomas are listed under the warning and precautions section of the tofacitinib US label. Additionally, treatment with tofacitinib is associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined to date.

Endpoints of interest will be captured within the quarterly targeted adverse event (TAE) report (see Table 2 below).

Table 2. Example of Targeted Adverse Event Table among Patients Exposed to tofacitinib Overall and Stratified by Sex (Incidence Rates per 100 Person Years)

	Male				Female				Total			
Events	**N**	**Rate**	**95% CI**		**N**	**Rate**	**95% CI**		**N**	**Rate**	**(95% CI)**	
Total serious infections[a]												
Pneumonia												
Septicemia												
Bone/Joint infection												
Cellulitis												
Diverticulitis												
Bronchitis												
Gastroenteritis												
UTI												
URI												
Other serious infection												
Opportunistic infection												
TB												
TB Testing[b]												
Total cardiac disorders												
MACE[c]												
CHF (new or worsening)												
Acute coronary syndrome[d]												
Other cardiac events[e]												
Hypertension												
CNS Disorders												
Demyelination Yes												
TIA/Stroke												
PML/Other												
Total Liver Disorders												
GI perforation												
Hemorrhage (hospitalization)												
Total malignant events												
Malignancies excluding NMSC												
Lymphoma												
Lung cancer												
Breast cancer												
Skin cancers NMSC Melanoma												
other cancer												
Fracture												

Death												
Pregnancy												

a. Serious defined as infections requiring hospitalization or use of parenteral antibiotics.

b. Item for patients starting their first biologic or small molecule therapy: CORRONA questionnairequeries the physicians on whether a patient starting a first biologic or small molecule has been tested for TB within the prior 6 months.

c. Major Adverse Cardiovascular Event including:Nonfatal events from the physician follow-up form of myocardial infarction (MI), Stroke and Transient Ischemic Attack (TIA) in addition to Cardiovascular-related deaths from the Exit form of MI, Congestive Heart Failure, arrhythmia, sudden cardiac death, Pulmonary Embolism , stroke/cerebrovascular accident, and other CV-related deaths.

d. Acute Coronary Syndrome included MI and unstable angina.

e. other cardiac events: CAD procedure, revascularization procedure, ventricular arrhythmia, cardiac arrest.

Abbrev: CAD=coronary artery disease, CHF=congestive heart failure, CNS=central nervous system, CV=cardiovascular, MACE=major adverse cardiovascular event, MI= myocardial infarction, NMSC=non-melanoma skin cancer, TIA=transient ischemic attack.

9.4.1. Endpoint Reporting Procedures

CORRONA has an established system used in other post-approval studies[7,6,10] to identify and capture endpoint data. The system uses TAE forms that correspond to the outcomes identified in Table 3. For events that are confirmed by the rheumatologist, source documentation appropriate to the type of event (eg, pathology reports when the TAE is a cancer) is requested by CORRONA. Events confirmed against source documents (ie, medical records) are adjudicated by specialists blinded to therapy (eg, cardiologists adjudicate CV events) to confirm the event occurred, the date of the event, and the specific type of event (See Figure 1).

Table 3. Outcomes within the CORRONA Registry Identified ("Flagged") on Physician Follow Up Forms for Targeted Adverse Event Form Completion

Flagged Event	Targeted Adverse Event Report Type
Hypertension requiring hospitalization Cardiac revascularization procedure (CABG, stent, angioplasty) Ventricular arrhythmia Cardiac arrest Myocardial Infarction Acute Coronary Syndrome Unstable angina CHF requiring hospitalization Stroke Transient ischemic attack Other cardiovascular event ***(specify)*** Deep vein thrombosis Peripheral arterial thromboembolic event Urgent peripheral arterial revascularization Peripheral ischemia or gangrene (necrosis) Pulmonary embolism	Cardiovascular
Hemorrhage requiring hospitalization	Spontaneous Serious Bleeding
Lymphoma Lung cancer Breast cancer Skin cancer (melanoma) Skin cancer (basal/squamous cell) Other cancer ***(specify)*** Other hematologic malignancy Solid tumor ***(specify type of tumor)***	Cancer, Malignancy
Infection requiring hospitalization or IV antibiotic	Infection
GI perforation	GI Perforation
Hepatic event requiring biopsy or hospitalization	Hepatic
PML Other neurological requiring hospitalization/ other demyelinating disease	Neurologic
Biologic Infusion/Injection reaction (severe reaction/anaphylaxis)	Anaphylaxis or Severe Reaction
Accident ***(specify)*** Other serious medical diagnosis or event ***(specify)***	Generic Serious Event*

* Events not meeting case definition for a more specific TAE type, resulting in any of the following: hospitalization, prolonged hospitalization, death, significant disability or incapacity, congenital anomaly/birth defect or otherwise medically important in the opinion of the investigator.)

Specified safety endpoints will be reported as follows:

For the quarterly reports:

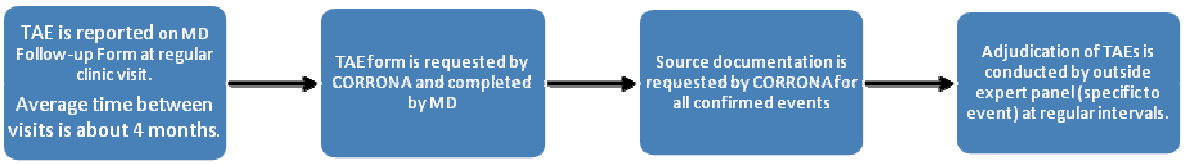
- The following events will be included:
  - MD reported events confirmed by TAE forms.
  - MD reported events for which TAE forms have yet been completed.
  - TAE events reported on the TAE form independent of any report on the MD questionnaire.

Safety endpoints will be reported for analysis (see Section 9.8).

- Primary analysis
  - MD reported events confirmed by TAE forms excluding events adjudicated as non-events.
  - TAE events reported on the TAE form independent of any report on the MD questionnaire excluding events adjudicated as non-events.
- Secondary analyses including
  - All study endpoints noted by physician report only.
  - Fully adjudicated endpoints using available source documentation.

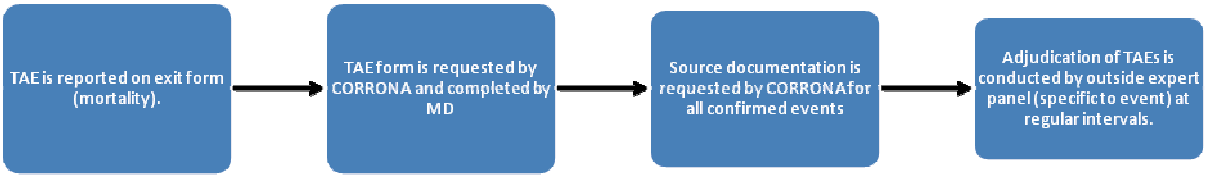
Figure 1. CORRONA Safety Endpoint Reporting Procedure

Targeted Adverse Events (TAEs) are most commonly reporting during a regular clinic visit.



TAEs may also be reported in between regular clinic visits.

Less commonly, a TAE may be reported on an exit form when the reason for exit is death and the cause of death is a TAE.



9.4.2. Endpoint Validation

CORRONA has examined the level of validity of malignancies, cardiovascular events and hospitalized infections within the registry. For this purpose, CORRONA has requested and successfully obtained hospital and outpatient medical records on the majority of patients. Medical records served as the gold standard for validation, with at least two physician adjudicators for each safety event.

- Malignancies

  Fisher and colleagues examined the accuracy of physician reported malignancies as compared with medical record review within the CORRONA registry.[5] For all incident malignancies reported from October 2001 to December 2007, the authors requested the completion of a TAE form to gather additional information as well as primary source documents for adjudication. (Note: CORRONA established a prospective request for source documentation for malignancies since 2008.) Each malignancy was classified as definite, probable, possible, or not a malignancy.

  A total of 461 incident malignancies from 20,837 patients with RA were reported on physician questionnaires. After adjudication, 234 were defined as definite, 69 probable, 101 possible, and 57 as not an incident malignancy. The positive predictive value (PPV) of physician report versus "definite or probable" malignancy was 0.66 (95% CI: 0.61-0.70). The PPV was 0.68 (95% CI: 0.63-0.72) when the TAE form confirmed the presence of malignancy. When "possible" malignancies were included, the PPV increased to 0.86 (95% CI: 0.83-0.89) and 0.89 (95% CI: 0.85-0.91) with the inclusion of the TAE form.

- Cardiovascular Events

  The validity of rheumatologist-confirmed CV events within the CORRONA registry (including MI, stroke or TIA) was assessed by Solomon and colleagues.[11] An adjudication committee reviewed cases reported by participating rheumatologists for which hospitalization records were available (56%, n=42). Events were classified into categories of definite, probable, possible and unlikely CV events. The PPV for confirmed cases (eg, definite or probable) where hospitalization records were available was 96%.

- Hospitalized Infections

  Curtis and colleagues evaluated rheumatologist reports of hospitalized infections within the CORRONA registry to establish their validity.[3] Using registry data collected between March 2002 and December 2007, the authors extracted 562 physician-reported events; 9% were classified as unlikely, leaving 509 hospitalized infectious episodes for evaluation.

  Of the 509 infectious episodes assessed, 53% of the episodes were classified as confirmed, 15% empirically treated (eg, there was evidence that the physician was treating an infection but definitive data including positive cultures were not identified) and 32% possible. A total of 606 unique infections were identified during the 509 hospitalized episodes; approximately 71% of the unique infections were classified as confirmed or empirically treated.

9.5. Risk Windows for Endpoints of Interest

Incidence rates will be based on two different definitions of the risk window, depending on the outcome of interest:

1. For all targeted adverse events except malignancy and death, the risk window will begin with the start of the index therapy and continue until the visit closest to 90 days after the end of therapy or end of data collection, whichever comes first. TAEs which occur beyond this risk window will not be counted for purposes of incidence rate estimation. However, in instances when a patient starts a second agent (ie, bDMARD) within the visit closest to 90 days after discontinuing a first one, the risk windows will overlap and the TAE will be attributed to both agents.

2. For analyses of risk for malignancies and death, the risk window for any therapy will include all person-time in the designated time period (since starting therapy) and extend until the end of data collection, even in the case of subsequent switching to another agent. When a malignancy is diagnosed after a second agent has been begun, both agents will receive credit in the incidence rate estimations.

Note: At the conclusion of the study period, incidence rates will be recalculated with complete data, and will reflect appropriate risk windows for the TAEs of interest. Cancer

incidence rates will also be calculated to reflect the experience of patients who have and have not switched therapies.

9.6. Study Size

Power calculations were conducted to estimate the expected sample sizes needed to detect pre-specified rate ratios using the following assumptions:

- An incidence rate of all malignancies, including lymphoma, among RA patients with moderate-to-severe disease of 0.0146 (CORRONA, data on file),
- 80% power, and
- Rate ratios of 1.5, 2.0 and 2.5 comparing incidence rates in tofacitinib versus non-tofacitinib patients with moderate-to-severe disease overall.

Power will depend on the uptake of tofacitinib initiations within the CORRONA Registry, corresponding comparator initiations, and expected follow-up time. Table 4 shows the preliminary 5-year uptake projections under different statistical assumptions for tofacitinib. The projected patient-years of time used a projection model that assumed peak enrollment at 50 and dropped to a steady state of 32/month for the remainder of the time. Projected person-time was estimated based on exposure time while on tofacitinib and all exposure time after tofacitinib regardless of discontinuation. Based on these assumptions the estimated tofacitinib person-years ranges from 2634 to 4610. A conservative power estimate assuming equal number of initiators (1500) with a mean of 1.6 years of follow-up or about 2400 person years of follow-up was used.

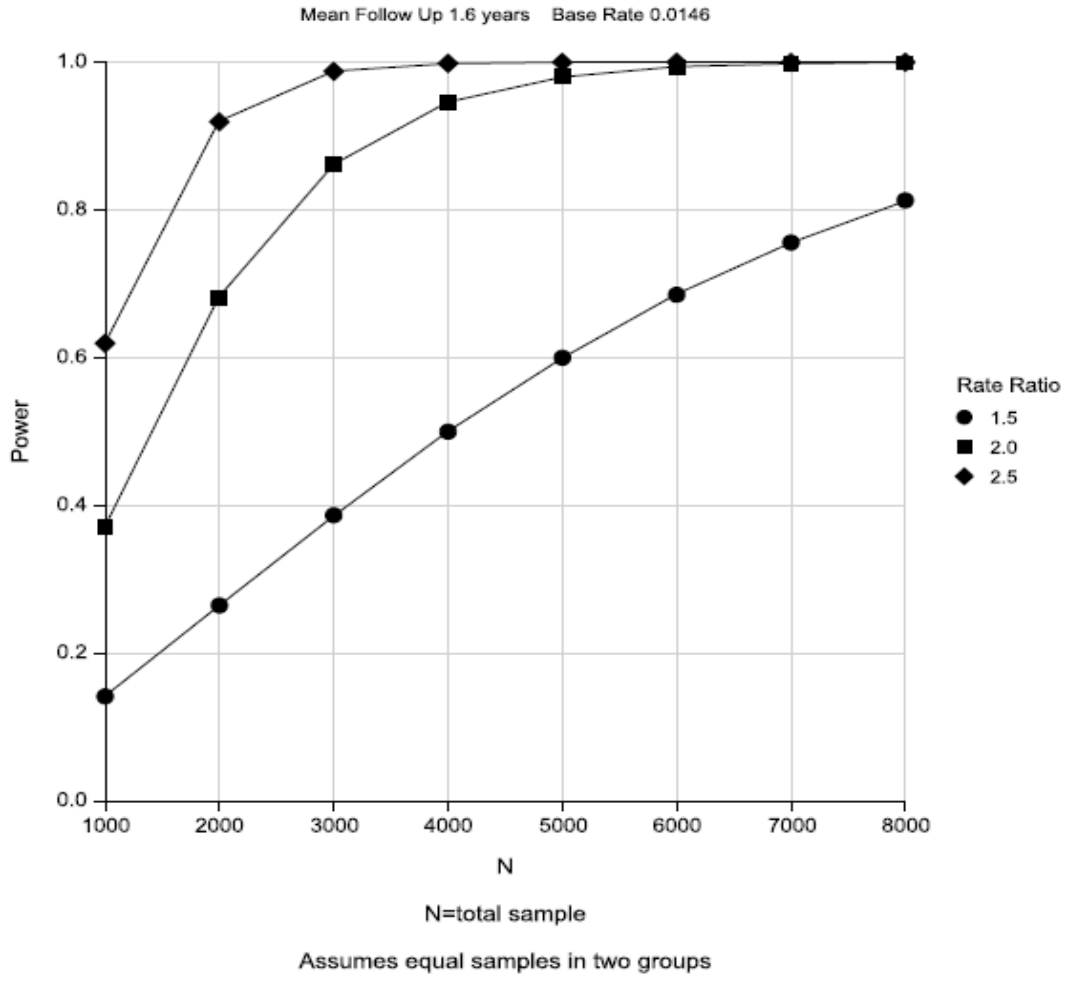
Figure 2 below shows that the study would have greater than 80% power to detect a rate ratio of 2.0 for malignancies if 3,000 patients (1,500 tofacitinib and 1,500 comparator) were included.

Table 4. Projected Patient Years of Exposure to Tofacitinib within the CORRONA Registry under Two Statistical Assumptions

End of Year	Patient-Years of Exposure	
	CORRONA[a]	CORRONA[b]
2014	251	440
2015	617	1080
2016	1136	1988
2017	1808	3165
2018	2634	4610

[a] Based on 4 Nov 2013 projections following linear peak assumptions- lower estimate, 40%
[b] Based on 4 Nov 2013 projections following linear peak assumptions- higher estimate, 70%

Figure 2. Curves Depicting the expected Power for Rate Ratios of 1.5, 2.0 and 2.5 under Different Sample Sizes (1:1 Enrollment of tofacitinib versus Comparator)



9.7. Data Sources

9.7.1. CORRONA Data Collection Program Questionnaires

Physicians and subjects complete CORRONA Data Collection Program Questionnaires approximately every four months. During the course of a regularly-scheduled office visit, the physician performs assessments as mandated on the CORRONA Data Collection Program Physician Questionnaires with recording of pertinent data. Results from certain laboratory tests are included, but not mandated, on these Questionnaires. Subjects are asked to complete Data Collection Program Questionnaires designed to capture information ranging from their general demographics and experience with prescription drug use to an overall global assessment of their disease. During their regularly-scheduled physician office visits, it is anticipated that subjects will spend approximately five to ten minutes completing the Questionnaires. Neither the Questionnaires completed by physicians nor the Questionnaires completed by subjects contain subject's names, addresses, telephone numbers, email addresses, or social security numbers.

Patients are enrolled in the CORRONA Data Collection Program during regularly-scheduled office visits. Upon enrollment, physicians complete a set of Enrollment Questionnaires, including a 28 joint count on RA subjects. Subjects also complete a CORRONA Data Collection Program Enrollment Questionnaire along with Health Assessment and EQ5D Questionnaires.

After the enrollment visit, patients with RA then complete CORRONA Data Collection Program Follow-up Questionnaires during regularly scheduled clinical encounters approximately every four months. Follow-up questionnaires are also completed at the time of a new therapy start or therapy switch. The next regularly scheduled visit continues to be scheduled off the baseline visit for subjects enrolled on or after June 1, 2008.

Data are collected on subjects for as long as they consent to remain in the study.

9.7.2. Subject Study Exit

In the event of a subject death, withdrawal from the study, loss to follow-up (defined as no study visits have occurred in the previous 15 months), or any other reason for non-participation, the Participant Final Exit Questionnaire is to be completed and submitted according to the submission procedures provided to the site by the CORRONA Organization. In the event the subject wishes to contribute additional data at some future date, the subject must sign a new informed consent form (ICF).

9.7.3. Targeted Adverse Event (TAE) Questionnaires

Adverse events which occur during participation in the Data Collection program are reported on the Targeted Adverse Event (TAE) Questionnaires. TAE Questionnaires are completed and submitted when a flagged event on a CORRONA Data Collection Program Provider Follow-up Questionnaire has been selected. Submission of de-identified source documents (ie, hospital records, laboratory results, etc.) in support of the reported TAE is required in order to be valid, unless otherwise determined by the CORRONA Organization. The TAE should be simultaneously reported on both the TAE Questionnaire and on the CORRONA Data Collection Program Provider Follow-up Questionnaire visit date that most closely follows the event (unless the TAE occurs on the date of the Follow-up Visit).

9.7.4. National Death Index (NDI) Linkage

NDI linkage will be completed by a trusted 3rd party academic site at the University of Massachusetts Medical School (UMMS). The Quantitative Methods Core (QMC) of the Department of Quantitative Health Sciences (QHS) at UMMS, will perform the tasks as detailed in the attached Standard Operating Procedure (SOP). Briefly, QMC staff will set up and maintain a database in the UMMS Regulatory Environment (described in detail in Appendix A of the attached SOP) on a QMC server to hold cumulative PII/PHI data as forwarded directly by the CORRONA electronic data capture vendor. Approximately every 12 months, , the Chief Statistical Officer of CORRONA will forward a file of patients identified by their CORRONA Registry ID Number to QMC Staff to determine their vital status. QMC Staff will associate the CORRONA Registry ID number with patient PII and forward the patients' PII to the National Death Index (and other sources as requested) to

determine the vital status of the selected patients. Upon receipt of the vital status information from the National Death Index, QMC staff will strip the PII information from the vital status records and reestablish the link with the CORRONA Registry ID Number for return to the CORRONA Chief Statistical Officer. Complete details of this operation, including quality control checks, are contained in the attached SOP.

QMC will act as the honest broker with approval by NEIRB and UMass IRB. However, it should be noted that QMC staff are not associated with the CORRONA Registries in any other way except to provide this service. QMC Staff have no input into the conduct of the CORRONA Registry design, operations, or analysis.

9.8. Data Analysis

All patients will be described in terms of demographic characteristics (eg, age, gender), prior RA therapies received, comorbidities at time of tofacitinib therapy initiation, duration of tofacitinib therapy, and subsequent RA treatments received. For the safety endpoints of interest, summary statistics, frequencies, crude cumulative incidence proportions, and crude incidence rates (ie, number of events per person-years) and associated 95% confidence intervals will be calculated as appropriate. Depending on data availability, subgroup analyses may be performed.

The primary summary of rates of events will be time to first event based on an index date defined for each population (for tofacitinib initiators this will be date of initiation). Time to first event or survival analysis allows an analytic framework for estimation, adjustment for possible confounders and comparison between treatment groups. This approach also allows for variable amount of follow-up and does not assume a constant risk over time. Within this framework, the total number of years of patient follow-up will be computed by total time up to an event or up to last follow-up as well as the total number of events (or in survival terminology, failures). The number of events (failures) divided by total person-years of follow-up will result in the event rate. Rates will be expressed as events/100 person-years of follow-up.

Quarterly reports will be produced beginning 1st quarter of 2014. Initially, reports will provide rates of the endpoints (Section 9.3) by selected drug groups covering time from first reported tofacitinib use to the present time. Each report will provide cumulative rates from to the data cut used for each report

As additional patient follow-up time accumulates so that sufficient person-time is available, additional subgroups will be defined and included in the report including:

- Age and gender standardized rates.
- Subgroups based on disease severity and prior comorbidity status.

A designated Data Monitoring and Oversight Committee (DMOC) will be created to determine the need for a full analytic comparison of rates using multivariable adjustment and/or propensity matching of patients. The DMOC will be comprised of 3 members: 1) a

Rheumatologist familiar with the CORRONA registry; 2) a Biostatistician familiar with the CORRONA registry; and 3) an Epidemiologist familiar with the CORRONA registry. No member of the DMOC will be an employee of either Pfizer or CORRONA. The DMOC will receive the periodic report for review of rates of events. The primary comparator group for tofacitinib initiators is patients initiating biologic DMARDs (Section 9.3).

Detailed analytic plans will depend, in part, on the sample size at the time of the requested comparison as well as patient characteristics in the populations and the specific events to be compared. For example, the number of events will influence the use of small sample size or large sample size methods and the event type will determine exposure time (current/recent exposure vs ever- exposed.) When the determination of an analytic comparison of rates is made the specific details of the analytic plan can be documented. But the plans will include the following steps:

- Patient demographic and clinical factors at the time of initiation, and prior treatment patterns will be compared. Standardized differences and p-values generated from statistical tests comparing the two groups will be generated.

- Standardized differences will inform the key covariates used to estimate a propensity score model (propensity for initiating tofacitinib vs biologic DMARDs). In addition to covariates with a standardized difference >0.1, covariates potentially associated with the event of interest will be chosen a priori based on clinical expertise and input. These covariates may differ by the event being analyzed.

- At the time of the requested analysis, if the sample size allows adjustment for the number of covariates indicated by the prior step, the primary comparison will be in the full population of tofacitinib initiators and biologic DMARD initiators excluding only those patient initiations that fail to fall in the region of common support based on the estimated propensity score. This is sometimes called the propensity trimmed population (trimming patients with no similar propensity in each group).

- The alternative (a sensitivity analysis if the first method is chosen) is to use the propensity score to match tofacitinib initiations to biologic DMARD initiations. One-to-one matching is carried out with a low caliper (maximum difference allowed), generally set to 0.01. The biologic DMARD initiation sample at the time of the analysis will inform the caliper – larger sample sizes allow for stricter matching without loss of sample size.

- The use of the trimmed population provides a larger sample size for more precision and adjustment through multivariable modeling. The matched population will have a small sample size that minimizes bias with a trade-off of precision. If the sample allows, the primary analysis uses the trimmed population with a sensitivity analysis using the matched population.

- Under both analyses, a Cox regression model will be fit to analyze time to first event and compare rates of events between the two groups (tofacitinib and biologic

DMARDs). The trimmed population model would include covariates not in balance and the a priori chosen covariates for the specific event of interest. Proportional hazard assumptions will be tested and time varying covariates can be used. Parametric models can determine the importance of random effects through the use of frailty models (for example the physician as a random effect with patients clustered within physician). The matched population model would include only covariates unable to be balanced with the matching. Hazard ratios comparing risk in tofacitinib vs biologic DMARDs and 95% confidence intervals will be estimated to provide evidence of any association of drug group and risk of the event of interest.

As patient follow-up time increases for sufficient patient-years of follow-up per year (or even quarter) – contemporary rates of events will be added to the reports in addition to the total cumulative rates of events.

Statistical analyses will be performed using STATA 12.1 (StataCorp, LP, College Station, TX). All analyses will be carried out under the direction of Dr. George Reed, PhD, who is Chief Statistical Officer for CORRONA, and Professor of Medicine at University of Massachusetts Medical School.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.9. Quality Control

The CORRONA registry has standard operating procedures in place to monitor, perform edit and logic checks, and make corrections to the data, as necessary. Specifically, the data for each site is reviewed by the Quality Department or other delegated CORRONA representative for completeness and internal consistency at regular intervals. The Quality Department generates a list of queries for each site, sends to the clinical site coordinator, and requests verification or correction for each query within 14 days. The Quality Department or other designated CORRONA representative enters corrected data onto the CORRONA database. An audit trail of all corrections to the data, and the personnel making and date of corrections, is stored with the data in the CORRONA database.

9.9.1. CORRONA Governance and Oversight

The Consortium of Rheumatology Researchers of North America, Inc. is a New York State S Corporation. CORRONA is in compliance with State of New York regulations and maintains a formal Board of Directors and Executive Committee that oversee the operations of the company.

Formal Executive Roles of President/Chief Executive Officer, Chief Operating Officer and Chief Scientific Officer are augmented by an omnibus Sr. Vice President role and a Chief Site Quality Officer. The Board of Directors and Executive Committee must report any financial conflicts to the CORRONA Ethics Subcommittee of the Board.

Science and publication matters are reviewed by the Scientific Advisory Committee (SAC) and site issues are addressed by the Site Investigator Advisory Committee (SIAC).

Executive Leadership is as follows:

Joel Kremer, MD	President and Founder
James Cavan, MS	VP, Chief Operating Officer, Secretary and Treasurer
Jeff Greenberg, MD, MPH	VP, Chief Scientific Officer
Alan Gibofsky, MD, JD	Sr. Vice President

Corporate Council:

Jay Barker, JD	Drinker, Biddle and Reath, LLP
Robyn Shapiro, JD	Drinker, Biddle and Reath, LLP (Bioethics)

9.10. Limitations of the Research Methods

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing the CORRONA registry, a well-established US-based rheumatology registry. Despite the strengths of the registry, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint misclassification, and generalizability are of concern when evaluating event rates.

As a new therapy in the RA treatment armamentarium, it is possible that patients treated with tofacitinib will represent those with the most severe cases of disease, longer disease duration, history of multiple failed RA therapies and physical comorbidities that place patients at risk for adverse events. Biases resulting from channeling may present as increased rates of adverse events in the early phases of the study. Comparison to internal comparators may illuminate such channeling. Stratification on key indicators of disease severity, patient characteristics and past therapies can be done for contextualization. Trend analyses may be conducted to evaluate rates over time.

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While CORRONA has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation. Instead, a hybrid reporting system has been adopted to utilize the fullest extent of data available. As highlighted previously, primary analyses will include all confirmed endpoints via a combination of physician report and follow-up TAE forms. Secondary analyses will include reports by physician report only as well as fully adjudicated endpoints using available source documentation. Doing so will provide a range by which to estimate event rates in the study population. Pfizer has also committed to support the re-consenting of patients within the registry to enable linkages to the NDI to enhance validation efforts.

9.11. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

10.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

All protocols are approved by the New England IRB. At Academic sites with Academic IRB's, the approval of the Academic IRB's is also obtained.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the FDA Guidance for Industry, Good Pharmacovigilance and Pharmacoepidemiologic Assessment. Per Pfizer's subscription to the CORRONA database,

analyses will be conducted by authorized third parties and in accordance with CORRONA scientific review policies. This database does not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses patient-level electronic health related databases (e-HRD), in which it is generally not possible to link (ie, identify a potential association between) a particular product and medical event for any individual.

This study protocol may require review of the patient medical chart and/or narrative/verbatim fields in the dataset. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the defined dataset (defined per the patient population and study period specified in the protocol).

The data collection process involves collecting drug-related effects in individuals. The reviewer may identify a serious adverse event (SAE) with explicit attribution to a Pfizer drug via patient chart and/or narrative /verbatim field review (and with an identifiable reporter). Such SAEs must be reported to Pfizer or its representative for submission to regulatory authorities. Explicit attribution is not inferred by a temporal relationship between drug administration and an SAE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the SAE.

DEFINITION OF AN ADVERSE EVENT

An AE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including infant and toddler formulas [hereinafter "pediatric formulas"]) or medical device. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

SERIOUS ADVERSE EVENTS

For the purpose of safety regulatory reporting, a serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event many not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If there is a written notation in the medical chart/narrative field indicating that a physician attributed a serious adverse event to a Pfizer drug, Pfizer will complete a Non-Interventional Study Adverse Event Report Form within 24 hours of identification of the event and submit it to Pfizer Safety.

Reports of overdose, misuse, extravasation associated with the use of a Pfizer product will be recorded on the adverse event page(s) of the case report form, irrespective of the presence of an associated AE/SAE. The investigator must submit reports of overdose, misuse, extravasation to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE.

Reports of occupational exposure to a Pfizer product are to be submitted to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Progress reports will be submitted to the US FDA at 6 month intervals. A final report, anticipated 5 years post-study start, will be submitted to FDA communicating the full study experience.

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14. LIST OF TABLES

Table 1. Example of a Baseline Characteristics Table of Patients with at Least One Follow-up Visit after Use of tofacitinib Documented within the CORRONA Registry

Table 2. Example of Targeted Adverse Event Table among Patients Exposed to tofacitinib Overall and Stratified by Sex (Incidence Rates per 100 Person Years)

Table 3. Outcomes within the CORRONA Registry Identified ("Flagged") on Physician Follow Up Forms for Targeted Adverse Event Form Completion

Table 4. Projected Patient Years of Exposure to Tofacitinib within the CORRONA Registry under Two Statistical Assumptions

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Figure 1. CORRONA Safety Endpoint Reporting Procedure

Figure 2. Curves Depicting the expected Power for Rate Ratios of 1.5, 2.0 and 2.5 under Different Sample Sizes (1:1 Enrollment of tofacitinib versus Comparator)

ANNEX 1 ADDITIONAL INFORMATION

University of Massachusetts Medical School Standard Operating Procedure

1.0. Purpose

1.1. The purpose of this Standard Operating Procedure (SOP) is to describe the protection of PHI (Personal Health Information) data for the CORRONA Registries, both current and future. This protection will include: procedures of accepting PHI data from CORRONA's database vendor and clinical sites, storage and protection of the PHI data, processing of requests for updated mortality data, and production of data in response to those requests. The process described here will ensure the complete separation of the PHI data from the clinical data in CORRONA and preserve the identity of the patients in the CORRONA Registries. This SOP relates to the updating of mortality data for the CORRONA Registries. If other types of updates, such as adverse events, are requested in the future, an additional SOP will be generated for that process.

2.0. Scope and Applicability

2.1. This SOP applies to all QMC personnel, faculty, and staff.

2.2. This SOP applies to the PHI for the current CORRONA Registries and any future CORRONA Registries. It is expected that there will be no deviations from these procedures, as deviations would jeopardize patient privacy.

2.3. These procedures are organized into four categories:

2.3.1. Procedures for accepting PHI data from CORRONA's database vendor, verification of the source of the data, and safeguards to assure confidentiality during the transfer process;

2.3.2. Procedures for the storage of the PHI data for the CORRONA Registries and protection of the data at rest;

2.3.3. Procedures for the processing of requests for data generated by the PHI data, the approval process, and the specification of the programming to generate the requested data; and

2.3.4. Procedures for the actual production of the requested data, including the quality control of the programming, the potential download of data from governmental sources, including (but not restricted to) the National Death Index (NDI) and the Social Security Administration Master Death File, the deidentification (and quality control of the deidentification process) of the resulting data, and the secure transfer to CORRONA.

3.0. References

None

4.0. Definitions

4.1. The term "CORRONA Registries" will be interpreted as applying to the current registry and any future registries.

4.2. Private Health Information (PHI) will be interpreted as meaning any information that can be used to identify an individual or to identify any health-related conditions of an individual. The list of federally-accepted PHI is included in Appendix B.

5.0. Responsibilities

5.1. SAS and database programmers, including QMC faculty, staff, and the QMC Database Administrator, are responsible for understanding and following these coding conventions without exception.

5.2. The QMC Director is responsible for training (and annual retraining) the QMC personnel (listed in 5.1 above) on this SOP and ensuring adherence to this SOP. This training will be documented and kept on file in the office of the QMC Director.

6.0. Background

6.1. The CORRONA Registries, both current and future, provides a mechanism for registering and tracking patients with specific conditions, such as rheumatoid arthritis. One of the functions of these registries is to gather and report follow-up information on mortality. CORRONA is blinded to patient PHI, including all identifying information, and requires a complete separation of CORRONA staff from patient PHI. The University of Massachusetts Medical School (UMMS) QMC, formed within the Division of Biostatistics and Health Services Research within the Department of Quantitative Health Sciences, is an entity with no relationship with CORRONA except through the agreements relevant to the functions detailed in this SOP.

7.0. Operational Procedures

7.1. Procedures for accepting PHI data from CORRONA's database vendor, verification of the source of the data, and safeguards to assure confidentiality during the transfer process.

7.1.1. PHI data will be accepted from two sources: CORRONA's database vendor and through paper-based case report forms.

7.1.1.1. To accept data from CORRONA's database vendor, a secure FTP (sFTP) site will be established within the UMMS Regulatory Environment.

7.1.1.2. Access to this site will be limited to a single database vendor account with a log-in and password combination.

7.1.1.3. Data will be uploaded to the sFTP site through a secure VPN (virtual private network), set up by the vendor and included in their SOPs. The uploaded files will have a date stamp included in the file name. The sFTP site will be checked daily for new uploaded files.

7.1.1.4. The QMC database programmer will download the incoming data into a separate transaction database within the Regulatory Environment for review and editing prior to submission to the main CORRONA PHI database. This process will be automated, but will generate a log for review by the QMC database programmer for verification that all files were downloaded successfully.

7.1.1.5. The editing will consist of an SQL program that will check for missing values, values that are not in the right format (such as Social Security Numbers), verification that the record is not a duplicate for an existing record in the main CORRONA PHI database, and any other edits that the Chief Statistical Officer (CSO) for CORRONA pre-specifies. If the incoming record updates an existing record, the procedure in Section 7.1.1.7 will be followed.

7.1.1.6. Any incoming records that fail the edit process will be segregated from the records that passed the edit into a separate table in the transaction database. The edit process will generate a report for the CORRONA Project Manager for transmission back to the site for resolution. The report will not contain any PHI, using only the CORRONA Study ID number for patient identification and requesting review of specific fields (such as Social Security Number) for a specific reason (such as wrong format) without displaying the submitted information. Revised information will be submitted through the CORRONA Web-interface using standard CORRONA procedures and will be processed/transmitted normally.

7.1.1.7. After the completion of the edit process, the records that passed the edit procedure will be uploaded into the main CORRONA PHI database for storage. If an existing record needs to be modified

because of a change in the PHI (such as a change of address), a procedure will be implemented to update the existing data (for which the incoming data has the appropriate indicator) and the audit trail will document those changes.

7.1.1.8. For CORRONA sites that are not able to enter data into the CORRONA Web-interface, a paper-based case report form system will be provided, through which a site can complete the PHI case report form (designed by QMC staff) and fax the form to the secure sFax server dedicated to this project. The sFax windows service will then request the fax from sFax (the service will run every 20 minutes) and new faxes will be securely sent to the QMC secure server for processing.

7.1.1.9. The QMC server, using Teleform© data capture software, will read the data from the form and display it for a designated QMC data coordinator to verify with 100% verification of all fields. If a field (such as an address) is not interpretable, it will be indicated as such for the edit program (Section 7.1.1.10 below) to flag for resolution.

7.1.1.10. Once the incoming fax PHI forms are verified, they will be updated to the transaction database in the UMMS Regulatory Environment for usual editing and processing as above. Any form(s) that fail the edit process will be handled as in Section 7.1.1.6 above.

7.2. Procedures for the storage of the PHI data for the CORRONA Registries and protection of the data at rest.

7.2.1. The main CORRONA PHI database will be established and maintained in MS SQL/Server on a dedicated server in the UMMS Regulatory Environment. An audit trail will be instituted in the database to record all additions, changes, and deletions in the database. All processing of data will occur in that environment using SAS (SAS Institute, Inc., Cary, NC) to directly access data in the main CORRONA PHI database through SAS/Access. Access to the main CORRONA PHI database will be limited to the QMC Director, the QMC database administrator, and the designated QMC database applications programmer through log in identification and passwords.

7.2.2. The UMMS Regulatory Environment requires the UMMS Information Services to establish each account in that environment, after receipt of approvals from the UMMS IRB. Each individual requesting an account in the environment must be listed on the IRB form and must have current Human Subjects Training through the Collaborative Institutional Training Initiative (CITI) as required by UMMS. Three individuals will be listed on the form for the CORRONA PHI project: the QMC Director, the QMC Database

Administrator (DBA), and the QMC database applications programmer designated to this project. The QMC DBA is included as a backup to the applications programmer in case the applications programmer is not available (eg, sick or out of town) and would not normally be involved in the project. The QMC DBA will be familiar with the system design and procedures. Both the QMC DBA and the QMC database applications programmer will report to the QMC Director for this project.

7.2.3. All SAS programming will follow the QMC SOP on SAS Programming Conventions.

7.2.4. The description of the UMMS Regulatory Environment is contained in Appendix A of this SOP. A change in the Regulatory Environment, including any hardware and software changes, will not require a new revision of this SOP unless it impacts the processes of the CORRONA PHI system described herein.

7.3. Procedures for the processing of requests for data generated by the PHI data, the approval process, and the specification of the programming to generate the requested data.

7.3.1. Requests for data files generated by PHI data will be accepted only as original data request form with original signatures of the designated CORRONA officer as well as the Chief Statistical Officer of CORRONA delivered directly to the QMC Director.

7.3.2. Upon receipt of the fully completed data request form, the QMC Director will contact the CORRONA Chief Statistical Officer to verify the form and to discuss the details of the request.

7.3.2.1. The data request can only be to update mortality status of CORRONA patients using a prespecified governmental data source, such as the NDI;

7.3.2.2. Any other type of information requested will have to be authorized by written agreement between CORRONA officials and the QMC Director with review and consent of the respective IRBs. A separate SOP, or a revision of this SOP, will be required in that circumstance.

7.3.3. Upon discussion between the CORRONA CSO and the QMC Director, the QMC Director will sign the data request form, initiate a paper file as well as an electronic file for all documentation related to the data request, and forward the data request and any written clarifications based on the discussions between the CORRONA CSO and the QMC Director to the designated QMC database applications programmer for programming.

7.3.4. The designated QMC database applications programmer will review the data request and draft the programming specifications for the data request. The SAS programming specifications will be reviewed by the QMC Director to validate the specifications against the data request. The final specifications will become part of the permanent record of the data request.

7.4. Procedures for the actual production of the requested data, including the quality control of the programming, the potential download of data from Federal sources, including (but not restricted to) the National Death Index (NDI) and the Social Security Administration Master Death File, the deidentification (and quality control of the deidentification process) of the resulting data, and the secure transfer to CORRONA.

7.4.1. Once the programming specifications are approved by the QMC Director, the designated QMC database applications programmer will write the SAS program and run a test on a subset of the incoming CORRONA data set. The program and the test run will be verified by the QMC Director, in keeping with the QMC SOP on SAS Program Risk Assessment. Once verified, the QMC Director will sign the Data Request Form to signify the verification. The SAS program will become part of the permanent record of the data request. It is anticipated that, once written for a particular data source (such as the NDI), the SAS program will be modified only if the format of the incoming data needs to change or the required format of the file to be transferred to the data source changes or if a new exception is found in the data that can be programmed for future transmissions.

7.4.2. Requests for data will involve transfer of a SAS data set from the CSO of CORRONA to the QMC Director containing CORRONA Patient ID numbers and any other data relevant to the request. These data will be uploaded to the UMMS-CORRONA sFTP site with an independent e-mail sent by the CSO of CORRONA to the QMC Director notifying him/her of the upload.

7.4.3. The uploaded data will be downloaded to the Regulatory Environment where it will be merged with the appropriate PHI data to obtain information needed for matching with the relevant data sources as described above (Section 7.3.3) or other data sources that may exist in the future.

7.4.4. The validated SAS program will be run on the full data set, producing the final data file for transmission to the appropriate data source. The full listing will be reviewed and a systematic 10% sample of the generated records will be validated against the database records to verify successful and accurate merging throughout the file. This sample will be reviewed by the QMC Director and, when the successful merge is verified, the QMC Director will sign the Data Request Form signifying the successful merge. The SAS log of this merge will become part of the permanent record of the data request.

7.4.4.1. If the SAS program does not run to a successful completion or if the review of the sample or the log indicates a problem, the QMC database application programmer will have the responsibility to research the exception that caused the problem, modify the SAS program to handle the exception, and rerun the program as in 7.4.4. This modification will be documented, the QMC Director notified, and the written documentation included in the file of the data request.

7.4.4.2. If the SAS program does not run to a successful completion due to an invalid entry in a required field, the CORRONA CSO will be notified of the problem by the QMC Director and an resolution acceptable to both will be agreed upon and implemented. Any revised data file will be handled as in Section 7.4.4.

7.4.5. The designated QMC database applications programmer will submit this data to the relevant data sources using secure data transfer as provided by the data source. Matched data returned from the data source will be received through secure data transfer.

7.4.6. Federal data sources, such as the NDI, return information with probabilities of the accuracy of the match included. The match with the highest probability (for SSI) or marked with an "*" for NDI will be retained and that probability will be contained in the data record returned to CORRONA. If no record is marked with an "*" for an NDI retrieval, no match will be assumed and the patient will be assumed to still be alive. Upon prior agreement, this default can be changed through mutual agreement between the CORRONA CSO and the QMC Director and documented in this SOP.

7.4.7. Upon request of the CORRONA CSO, the QMC Director may initiate a subscription to the Social Security Administration Death Master File through the NIST, requiring at least monthly updates to maintain the file. While the NDI is estimated to record 99% of the deaths within the United States (including Puerto Rico), it does not record deaths outside of the country, such as immigrants who return to their home country after retirement. In this case, the matching would be performed within the UMMS Regulated Environment using the most up-to-date SSA Death Master File. As with the NDI, only matches that are certain (as prespecified by agreement with the CORRONA CSO) will be reported to CORRONA as a death.

7.4.8. The returned data transfer will be read into SAS and converted to a SAS data set for return transmission to the CORRONA CSO. All PHI information, as defined in Appendix B, will be deleted from the SAS dataset to be returned to the CORRONA CSO. Once created, the QMC Director will verify that no PHI is contained in the SAS dataset to be returned to the CORRONA CSO. Once verified, the designated QMC database applications programmer will

upload the returned SAS dataset to the sFTP site. Once uploaded, the QMC Director will notify the CORRONA CSO of successful upload. Once the upload is completed, the QMC Director will sign the Data Request Form to signify completion of the data request. A copy of the completed Data Request Form will be returned to the CORRONA CSO and to the initiating CORRONA corporate officer.

8.0. Actions following a breach of PHI

8.1. Pursuant to section 13402 of the Health Information Technology for Economic and Clinical Health (HITECH) Act, HIPAA covered entities and their business associates are required to provide notification following a breach of unsecured protected health information.

8.1.1. In the event of a breach (inadvertent release of PHI to non-covered entities), the QMC Director will notify the CORRONA CSO, the CORRONA CEO, and the UMMS IRB within 24 hours of discovery. The circumstances of the breach will be completely documented by staff involved and forwarded to the CORRONA CSO and to the UMMS IRB as soon as a full investigation is completed, but no later than 60 days.

8.1.2. The directions of the UMMS IRB will be followed without exception. These directions may include individual notification, media notification, and notification to the Secretary of HHS.

9.0. Deliverables

9.1. SAS data set with updated information as requested from CORRONA.

Revision History

Rev #	Issue Date	Summary of Changes
1		
0	1/19/2013	

Signatures

Title/Dept	Printed Name	Signature	Date (mm/dd/yy)
(1)			
(2)			
(3)			

(1) Author

(2) Supervisor/owner

(3) Quality Assurance

File: QMC CORRONA PHI Protection 2-15-2013.docx

Appendix A

Description of the University of Massachusetts Medical School Regulatory Environment

In 2010 Information Services (IS) completed construction of a "state of the art" data center to house the many hundred computer servers and mass storage devices used for administrative, research and educational computing at UMass Medical School. When the new data center was designed, Information Services included in the design plans a physically secure and electronically protected portion of the data center with its own insulated network space labeled "the Regulated Environment" to provide a secure environment for the storage and handling of sensitive electronic data including protected health information (PHI) and protected personal information (PPI). The Regulated Environment is securely housed within the new IS data center, meaning that physical access is limited to those IT professionals employed by IS with a job-related need and proper electronic identification.

1. Data Access for Researchers:

Electronic access to sensitive data resources within the regulated environment has been controlled using the highest standard of proven network architecture. For Investigational Review Board (IRB) approved investigations with PHI or PPI, IRB approved principal investigators (PIs) and their staff must all be CITI (The Collaborative Institutional Training Initiative) certified. Research data can be transferred into the regulated environment by one of three ways:

1. Through SFTP from the vendor,
2. Initiation of an sFax service request by the sFax Windows service within the regulated environment,
3. Through MOVEit DMZ file transfer. (MOVEit services create server logs of all file transfer activity as well as notifications of server events and completed transfers and provides non-repudiation and FIPS 140-2 validated cryptography).

Within the Regulated Environment, Research Computing provides a Dell PowerEdge R710 server running Windows Server 2008 R2 operating system. This server was configured in consultation with SAS Institute to maximize its capability for analyses of very large datasets using SAS, such as those encountered often in health services research. This server is dedicated to the CORRONA project and can ONLY be accessed using protocols designed to maintain the strictest security and to minimize disclosure of PHI and other sensitive data. Access to the CORRONA server is only provided to investigators and their staff who have current IRB approved studies and current CITI HIPAA/privacy training certification. It is protected by three-factor authentication. The three-factors consist of UMass Medical School username and password (factor #1), an RSA SecurID 700, (#2) and a pin number (#3). The SecurID 700 is used in conjunction with RSA® Authentication Manager. Together, these require users to identify themselves with two unique factors – something they know, a PIN,

and something they have, a unique one-time password (OTP) that changes every 60-seconds – before they are granted access to the Regulated Environment.

2. Server Configuration (as of the date of this SOP)

• Dell PowerEdge R710 Server • 2 1333MHz processors 12GB Memory (6x2GB) • 146GB 15K RPM Self-Encrypting SAS 6Gbps 2.5in Hot-plug Hard Drive (342-0552) • Windows Server 2008 R2 Operating System.

Data files cannot be transferred electronically outside of the regulated environment, except as indicated above through the MOVEit DMZ file transfer utility. Data within the regulated environment is stored on EMC CLARiiON data arrays with journaling and other features to insure HIPAA compliance. IS disks are configured in RAID 5 arrays to ensure robustness to failures and are backed up according to a rigorous schedule. Data backups are retained to comply with retention requirements of funding agencies as well as more demanding Massachusetts regulations[2] which requires retention for a minimum of 6 years or longer in some circumstances.

Support of Clinical Trials and Study Data:

Currently UMMS and UMMHC house nearly 900 open human studies, approximately 350 of which are clinical trials (*ie,* drug or device interventions). These studies are conducted at a variety of sites: the Medical School, in one or more member hospitals of the clinical system or in the community at affiliated specialty centers. The UMMS is registered with the Office for Human Research Protections (OHRP) and holds the federal-wide assurance (FWA) for both institutions, with the Institutional Review Board meeting twice per month. In accord with federal mandate, the UMass IRB also registered with the FDA.

UMASSMED's Biomedical Research Informatics Development Group (BRIDG) Core integrates current tools and develops adaptive, reusable tools to support research throughout the translational spectrum – including clinical trials, observational studies, and implementation science. Consistent with our theme of collaboration with national initiatives, UMMS is a member of the REDCap Consortium (http://project-redcap.org). The consortium currently has 372 members, including many CTSA-funded academic centers, and is supporting data for 35,330 studies. UMMS has implemented 2 secure web-based applications (REDCap and REDCap Survey) to support electronic data capture for research studies. BRIDG has expanded beyond REDCap to support clinical studies data management using other systems (eg, MS SQL Server) and integrates clinical study data into the data warehouse.

Appendix B

Protected Health Information as defined for Compliance with the Health Insurance Portability and Accountability Act (HIPAA)

The following information is deemed to be protected health information (PHI) in the HIPAA regulations:

1. Names;
2. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
    a. The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
    b. The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date,, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Telephone numbers;
5. Fax numbers;
6. Electronic mail addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web Universal Resource Locators (URLs);

15. Internet Protocol (IP) address numbers;

16. Biometric identifiers, including finger and voice prints;

17. Full face photographic images and any comparable images; and

18. Any other unique identifying number, characteristic, or code, except as assigned by an investigator to code data.

Source: www.hhs.gov/ocr/privacy

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