CERTARA

Quantify RA
Clinical Outcomes Database

Summary Information

The current version of the database includes clinical safety and efficacy information on all biologics as well as newer synthetic DMARDs currently approved or in development for rheumatoid arthritis (RA). Information on older treatment options (MTX and other DMARDs) was included if they are used as active controls.

Table 1. Summary information

Parameter	Description
format	Excel or KEEP format
references	385
trials	229
trial.arms	756
patients	83,137
data.rows	50,129
compounds	abatacept, adalimumab, ALX0061, anakinra, anbainuo, atacicept, AZD9056, baricitinib, brodalumab, canakinumab, CCX354-C, certolizumab, clazakizumab, CT-P10, CT-P13, decernotinib, etanercept, filgotinib, fostamatinib, GLPGO259, golimumab, INCB39110, infliximab, itolizumab, ixekizumab, JNJ-40346527, LX3305, mavrilimumab, MTX, NNC114-0005, ocrelizumab, ofatumumab, olokizumab, ozoralizumab, peficitinib, rhIL-11, rituximab, ruxolitinib, sarilumab, secukinumab, sirukumab, sulfasalazine, sulfasalazine, hydroxychloroquine, sulfasalazine+hydroxychloroquine, tabalumab, tocilizumab, tofacitinib
mechanism.of.action	anti-BAFF, anti-BAFF/APRIL, anti-CD20, anti-CD28, anti-CD6, anti-GM-CSFRa, anti-IL-1, anti-IL-17, anti-IL-21, anti-IL-6, anti-TNF, CCR1 inhibitor, CSF-1R inhibitor, DMARD, interleukins, JAK kinase inhibitor, MAP kinase inhibitor, P2X7 antagonist, S1P lyase inhibitor, SYK kinase inhibitor
key.efficacy.endpoints	ACR/EULAR remission, ACR20, ACR50, ACR70, ACR90, ACRN, CDAI, CDAI low disease activity, CDAI remission, CRP, DAS low disease activity, DAS moderate disease activity, DAS remission, DAS responder, DAS score, EQ5D index, EQ5D VAS, erosion score, ESR, EULAR good, EULAR moderate/good, EULAR no response, FACIT-F, FACIT-F responder, fatigue, HAQ, HAQ mild disability, HAQ responder, joint space narrowing, lack of radiographic progression, major clinical response, morning stiffness, MOS sleep: adequacy, MOS sleep: awaken short of breath, MOS sleep: overall sleep problem, MOS sleep: sleep disturbance, MOS sleep: snoring, MOS sleep: somnolence, pain, pain responder, patient global assessment, physician global assessment, radiographic progression, SDAI, SDAI low disease activity, SDAI remission, SF36 bodily pain, SF36 general health, SF36 mental component summary, SF36 mental component summary responder, SF36 mental health, SF36 physical component summary, SF36 physical component summary responder, SF36 physical function, SF36 role emotional, SF36 role physical, SF36 social function, SF36 vitality, swollen joint count, tender joint count, total score
key.safety.endpoints	tolerability percentages, dropout rates

Features and Benefits

Key Features

- **Comprehensive:** includes information for marketed drugs; data sources include journal publications, conference posters, regulatory reviews, etc
- **Ease of tracking:** all clinical trial publications are listed in a separate source database and linked to unique clinical trial names
- **Flexibility:** the database design allows for quick updates as well as expansions to include additional indications/drugs/endpoints/trials
- **Model-friendliness:** designed and reviewed by experienced modelers to ensure highest quality and usability for modeling and simulation to support drug development strategies
- **Customizability:** can be augmented with clinical trial data proprietary to the client (this information goes into a separate proprietary database and will be owned by the client)

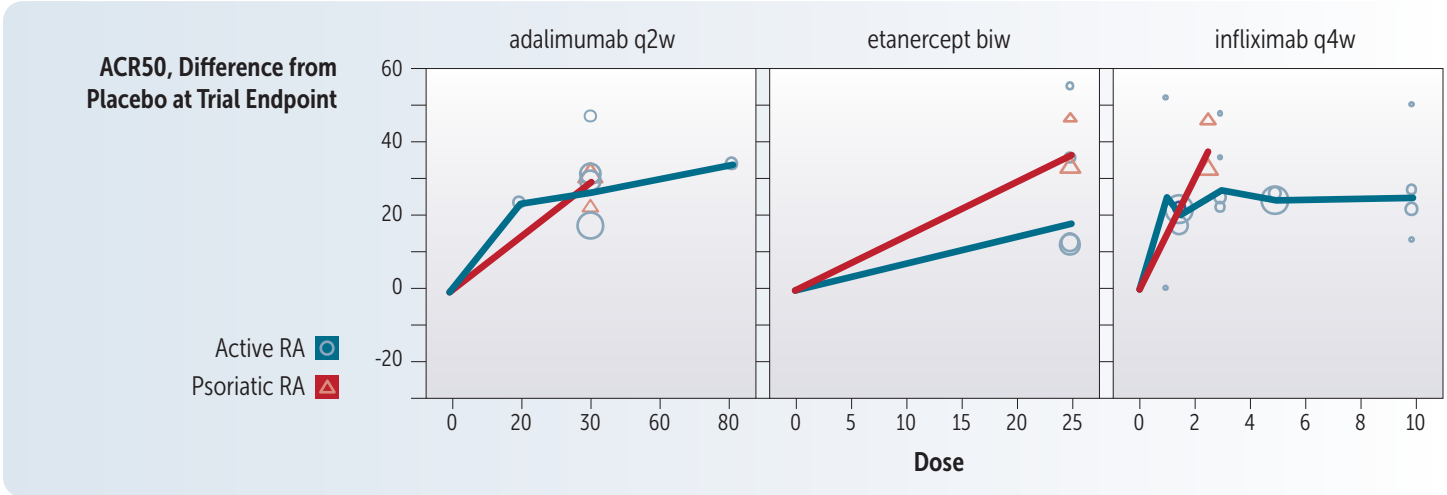
Potential Applications

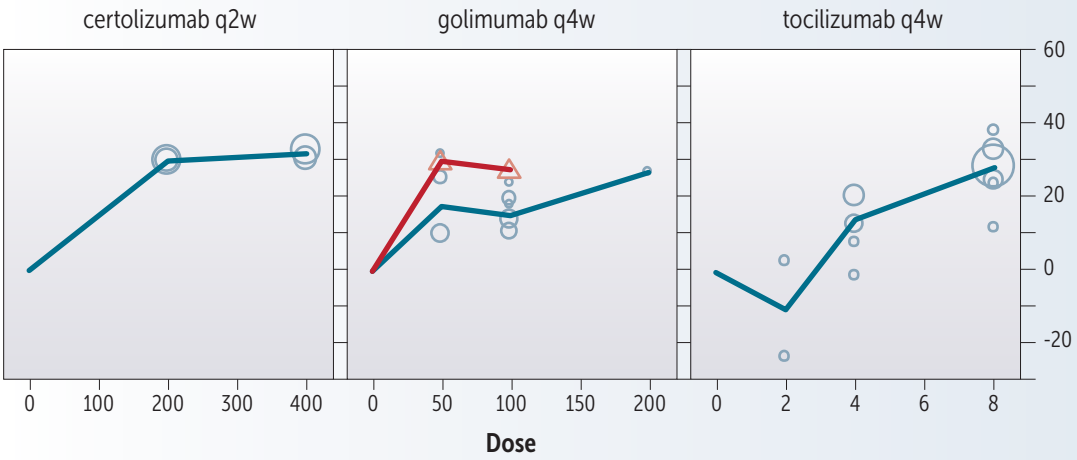
Understand relative efficacy and safety profiles: This type of analysis is important and frequently done, especially for compounds in crowded markets. However, large trial-to-trial variations make direct numbers comparison less compelling and sometimes even meaningless. Clinical outcomes databases capture a broad range of trial-specific information, which enables comparative efficacy and safety analysis NORMALIZED by variants such as existing therapy, placebo response, patient characteristics, etc.

Link/Scale different endpoints or indications: Clinical outcomes databases aggregate endpoint data from tens of thousands of patients, making it possible to make reasonable predictions of clinical outcomes from existing data. For example, clinical teams find it valuable to predict a compound's performance in late phase development based on early development results.

Examples:

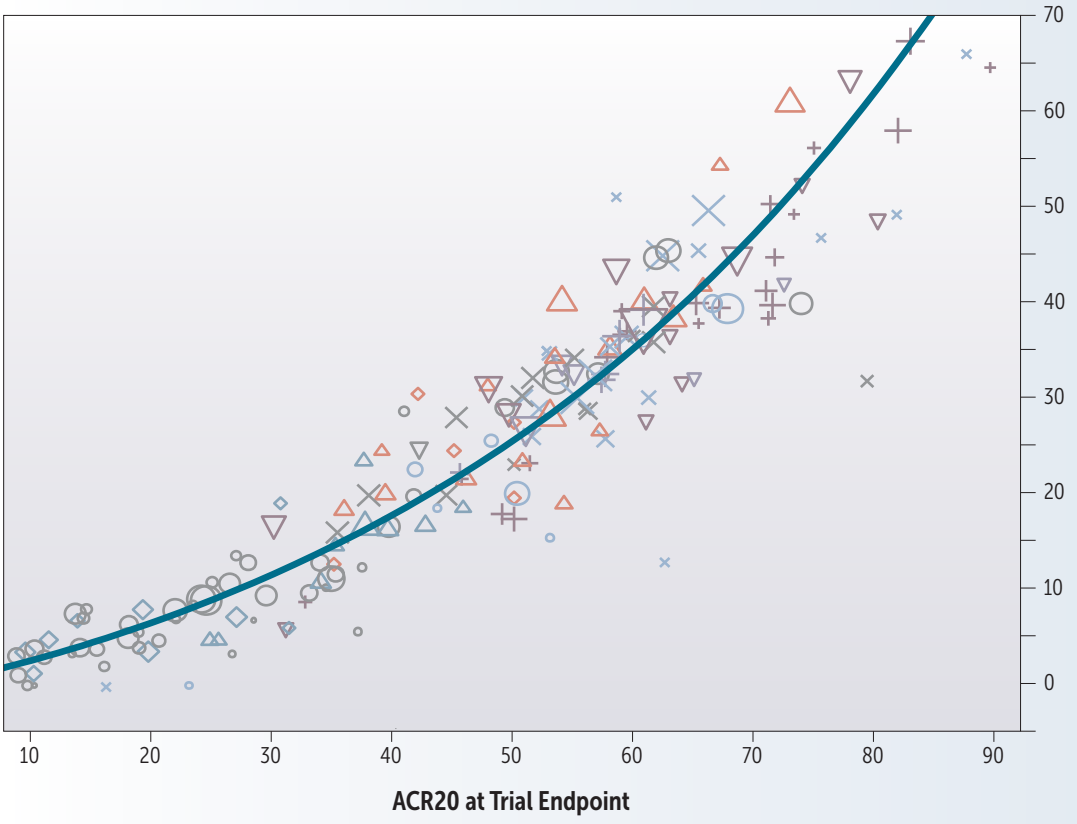
1. Question: How do the newer treatment options (certolizumab, golimumab, tocilizumab) compare to traditional biologics (adalimumab, etanercept, infliximab) when given to patients on stable MTX treatment?





Approach: Use the ACR time course or Endpoint data to derive dose response relationships, accounting for regimen differences, indication and magnitude of placebo response

2. Question: Is there a consistent difference in the dose relationship for ACR20 and ACR50 across drugs or drug classes?



Approach: Use the ACR time course or Endpoint data to jointly analyze the dose response relationships for ACR20 and ACR50 and quantify the difference in placebo response, ED50 and E_{max} by drug and drug class.

3. Is there a difference in relative effect on the components that make up the ACR effect across drugs and mechanisms of action?

4. Is there a difference in speed of onset of ACR changes across drugs?

5. What is the difference in response to a biologic if given as mono therapy compared to combination therapy with MTX in patients that are receiving and have an inadequate response to MTX or naive patients?

6. Is there a difference in Therapeutic Index between the TNF compounds?

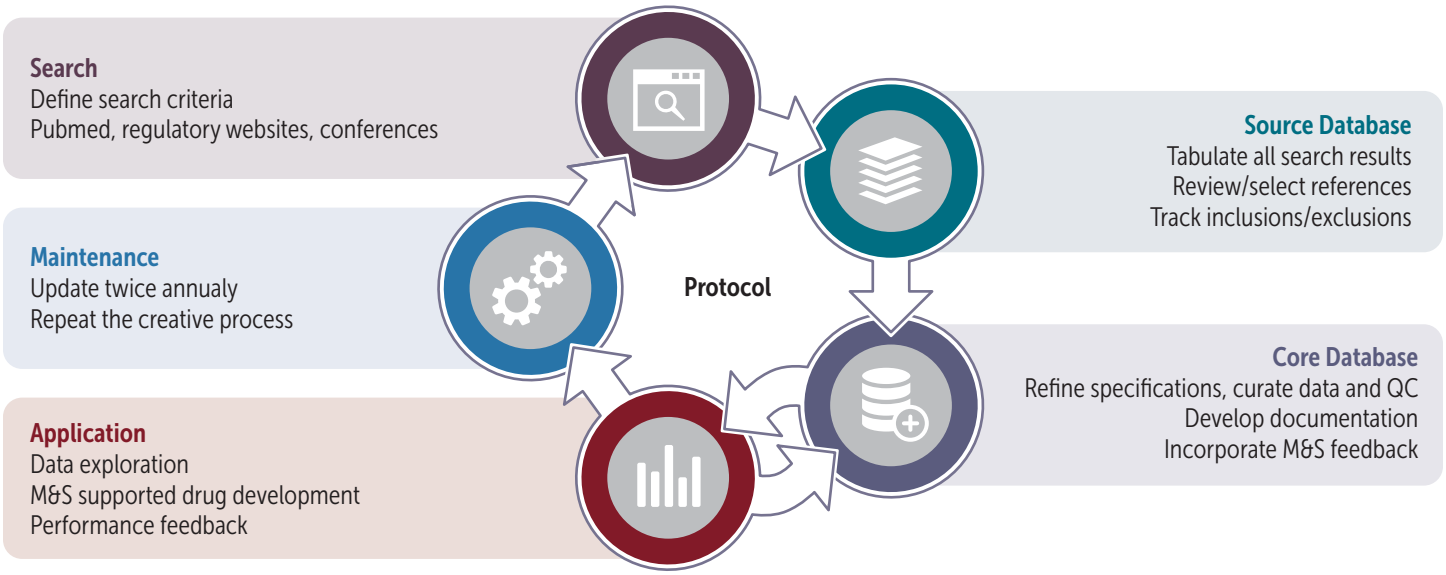
Why Use Our Databases

- Designed and managed by experienced modelers
- Provides most relevant data to support clients' needs for quantitative decision making
- Contains up-to-date and high quality data so that it is always readily available to provide timely analysis required to support critical clinical trial decisions
- Supported by additional services such as modeling and simulation consulting services and custom curation services (by our partner, GVK Bio)

Organization and Structure

This product consists of two databases, the source database and the clinical outcomes database (core database), developed for RA. The source database is a database that maintains the sources of information identified by searches and reviewed for inclusion or exclusion from the database. The clinical outcomes database contains the information on trial, treatment and patients characteristics and safety and efficacy results of the trials identified for inclusion in the database.

The following is a flowchart showing the process with which databases are created, optimized and updated.



Overview of the RA Source Database

The primary data sources were controlled clinical trials published in the medical literature or available through the FIA from the FDA. A secondary source of information was published abstracts or presentations of clinical trial data from conferences and corporate websites.

385 references were selected for inclusion in the RA database after careful review of the abstracts and full papers when necessary. The detailed reference information as well as reasons for exclusion is recorded to facilitate potential future expansion of the database. The 385 references selected for inclusion in the database provide information on 229 unique trials.

Overview of the RA Clinical Outcomes Database

The clinical outcomes database contains information from 229 trials, representing 756 unique treatment arms and about 83,137 patients. There are a total of 50,129 rows in the database. The table below provides an overview of the available data for randomized treatments, i.e. treatments that were started at time of randomization and not present as background therapy. The table shows the number of treatment arms and the number of patients for each study drug.

Table 2. Number of trials, treatment arms and patients by drug

randomized.drug	trials	arms	patients
placebo	171	174	16949
abatacept	5	5	1269
abatacept iv	11	16	3166
abatacept iv+MTX	1	1	256
abatacept+MTX	1	1	119
adalimumab	18	29	3831
adalimumab iv	3	11	152
adalimumab+MTX	9	13	1972
ALX0061	2	7	48
anakinra	7	21	2335
anbainuo	1	1	132
anbainuo+MTX	1	1	132
atacicept	2	5	348
AZD9056	2	6	305
baricitinib	7	17	1845
baricitinib+MTX	1	1	215
brodalumab	2	6	207
brodalumab iv	1	2	12
canakinumab	1	3	206
canakinumab iv	1	4	38
CCX354-C	1	2	106
certolizumab	10	14	2926
certolizumab iv	1	3	24
certolizumab+MTX	1	1	159
clazakizumab	1	5	298
clazakizumab iv	1	3	98
CT-P10	1	1	103

CT-P13	1	1	302
decernotinib	2	8	450
etanercept	27	43	4917
etanercept+anakinra	1	2	162
etanercept+MTX	4	4	812
filgotinib	4	15	817
fostamatinib	7	16	2493
GLPGO259	1	1	20
golimumab	7	17	1672
golimumab iv	2	6	1106
golimumab+MTX	1	2	318
INCB39110	1	4	49
infliximab	14	29	2389
infliximab+MTX	5	6	924
itolizumab	1	3	60
ixekizumab	1	2	218
ixekizumab iv	1	3	59
JNJ-40346527	1	1	63
leflunomide, sulfasalazine, hydroxychloroquine	1	1	103
LX3305	1	3	159
mavrilimumab	2	7	437
mavrilimumab iv	1	7	27
MTX	31	35	5797
MTX+methylprednisolone	1	1	15
MTX+sulfasalazine	1	1	133
NNC114-0005	1	3	15
ocrelizumab	5	14	1815
ocrelizumab+MTX	1	2	403
ofatumumab	3	7	353
olokizumab	2	8	150
olokizumab iv	1	2	13
ozoralizumab	1	5	208
peficitinib	3	12	769
rhIL-11	1	4	72
rituximab	8	13	1532
rituximab+cyclophosphamide	1	1	41
rituximab+MTX	1	2	503
ruxolitinib	1	4	41
sarilumab	3	9	1476
secukinumab	2	6	364
secukinumab iv	2	2	90
sirukumab	3	9	309
sulfasalazine, hydroxychloroquine	1	1	145
sulfasalazine+hydroxychloroquine	1	1	130
sulfasalazine+hydroxychloroquine+MTX	1	1	132
tabalumab	4	12	1871

tabalumab iv	2	5	167
tocilizumab	4	5	1270
tocilizumab iv	20	32	6621
tocilizumab iv+MTX	1	2	581
tofacitinib	11	35	4491
TOTAL	**229**	**756**	**83137**

Outcome fields

The following efficacy measurements are recorded in the database. RA related outcomes:

- American college of rheumatology (ACR) response criteria
  - ACR 20% response criteria (ACR20)
  - ACR 50% response criteria (ACR50)
  - ACR 70% response criteria (ACR70)
  - ACR 90% response criteria (ACR90)
  - Hybrid ACR score (ACRhybrid)
  - Numeric ACR (ACRN) and area under the curve (AUC)
  - Major clinical response: sustained ACR response
- Components of ACR response
  - Tender joint counts
  - Swollen joint counts
  - Total (tender and swollen) joint count
  - Patient global assessments of disease activity (Patient global assessment)
  - Physician global assessments of disease activity (Physician global assessment)
  - Patient assessment of pain (Pain)
  - Subject assessment of physical function using health assessment questionnaire (HAQ). This includes responder assessment according to several criteria
  - C-reactive protein (CRP)
  - Erythrocyte sedimentation rate (ESR)
- Radiographic Progression of the Disease (Genant or Modified Sharp Scores)
  - Total sharp score
  - Erosion score
  - Joint narrowing score
  - Percent patients without radiographic progression
- European League Against Rheumatism Responses (EULAR)
  - Includes different responder definitions: good, moderate, etc
- Disease activity score (DAS)
  - Includes different responder definitions: improvement, low disease activity, remission
- Paulus responder criteria
- Duration of morning stiffness
- Short form health survey (SF-36)
  - Includes all domains (eight scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health, and the aggregate physical and mental component summary measures)
- Patients receiving rescue treatment (Rescue). Use the threshold field to define criteria for rescue.
- Fatigue: measured on FACIT or other scales

The following safety and tolerability information is recorded in the database. The number of patients, percent of patients or rate (events per patient year) is recorded. For each safety outcome the numeric values (mean, etc) is also extracted if available at baseline or during trial:

- Dropout: Total dropout/treatment discontinuation. This refers to all patients that did not complete the study. In trials in which rescue treatment was provided according to a-priori defined no response criteria, the dropout did not include the number of patients that received rescue.
- Dropout AE: Dropout related to adverse events
- Dropout Efficacy: Dropout related to lack of Efficacy. Some trials provide rescue thera py for patients with lack of efficacy. The number of patients that rescue is captured from those trials. This can be compared to dropout due to lack of efficacy.
- Rescue: Patients receiving rescue treatment due to a predefined lack of efficacy criterion
- Death
- AE total: any adverse events
- AE clinical: clinical adverse events
- AE lab: laboratory adverse events

- AE serious: serious or severe adverse event
- Dose increase, interruption, reduction or modification: AE resulting in changes in dose
- Injection site reaction
- Infusion reaction: AE occurring during or within a short time period of the infusion
- Infections: all infections
- Infections serious: all serious infections
- Infection upper respiratory: upper respiratory infection
- Infection urinary tract: urinary tract infection
- Cellulites
- Rhinitis
- Pharyngitis
- Nasopharyngitis
- Sinusitis
- Tuberculosis
- Immunologic reaction
- Malignancy
- Malignancy skin: skin cancer
- Malignancy not skin: all other malignancies not involving skin
- Lymphoma
- Actual leukocyte, neutrophil, lymphocyte, or platelet count or changes in cell counts
- Hemoglobin levels or changes in hemoglobin
- ALT (increase): alanine transaminase levels or changes in alanine transaminase
- ALT (increase): asparate transaminase levels or changes in asparate transaminase
- Headache
- Dizziness
- Diarrhea
- Nausea
- Fatigue
- Development of autoantibodies
  - Anti-nuclear antibody (ANA)
  - Anti-double standard DNA antibody (anti-dsDNA)
- Development of anti-drug antibodies

The outcomes are often measured at various points over time. Every observation of the outcome that is reported in the body of the text, graph or tables was recorded in the data base (ie, all available time points). Each clinical outcome was recorded on a separate line in the database. A different line (row) of the database was used for each time point at which an observation is made. The fields (columns) that were recorded for every efficacy and safety/tolerability outcomes are listed below. Textual data reported in the body text, graphs or tables was extracted. Graphical data was digitized. There is no duplication of exactly the same outcome information if it is provided in textual as well as graphical form. If the outcome for a specific endpoint at a specific point in time is provided for different patient groups (ITT vs Per Protocol), imputation techniques (LOCF vs observed cases), or statistical analysis (raw mean vs least squares mean), the information were extracted for each reported value.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.