

Quantify RA Clinical Outcomes Database

1. 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), psoriatic RA, and psoriasis. 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
Indications	Rheumatoid arthritis (RA), psoriatic RA, and psoriasis
#Trials/References	94/129
# Patients	38,460
# Rows of Data	13,871
Last Updated	28-Apr-09
Compounds	MTX, adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, anakinra, ocrelizumab, ofatumumab, rituximab, tocilizumab, ustekinumab
Key efficacy end points	ACR response and components, Radiographic Progress of Disease, EULAR response, PASI, PsArc (37 endpoints in total)
Key safety end points	Tolerability percentages (40 endpoints in total)

2. Features and benefits

Key Features:

- **Comprehensiveness:** includes information for marketed drugs as well as drugs in development; data source includes journal publications, conference posters, regulatory reviews, etc.
- **Ease of tracking:** all clinical trial publications are listed in a separated 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

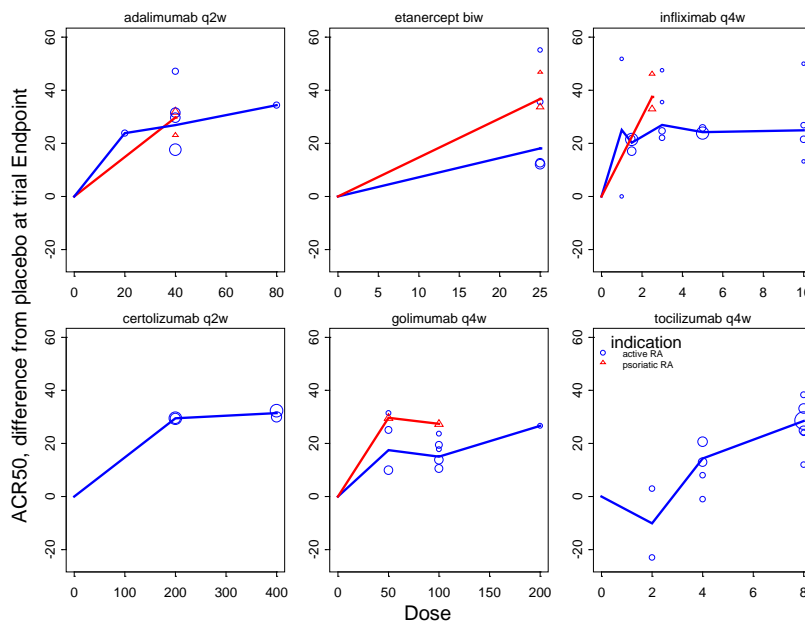
This type of analysis is important and frequently done, especially for compounds in crowded markets. However, large trial-to-trial variations make direct numbers comparison less compelling and sometimes even meaningless. Clinical outcomes databases capture a broad range of trial-specific information, 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

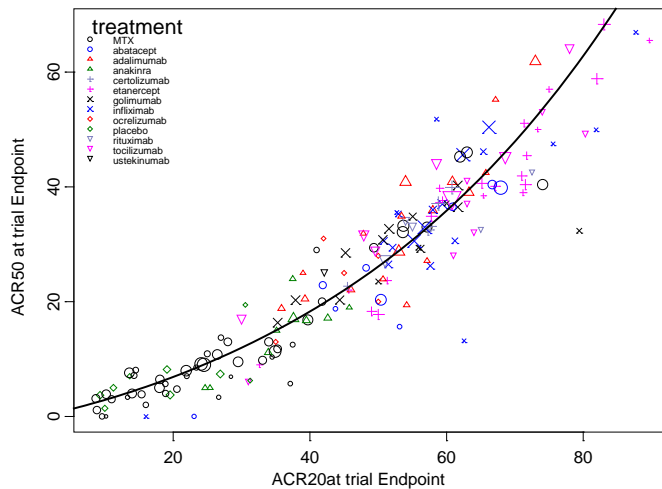
Examples:

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?



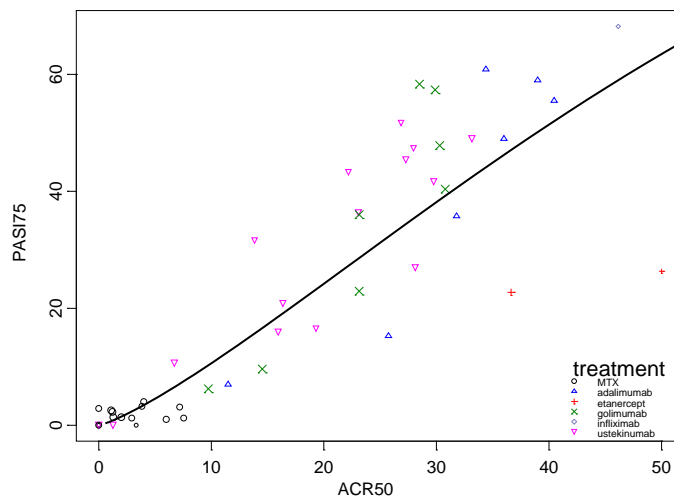
Approach: Use the ACR time course or Endpoint data to derive dose response relationships, accounting for regimen differences, indication and magnitude of placebo response

- 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 Emax by drug and drug class

- Question: Is there a similar difference in the dose relationship for ACR50 and PASI75 across drugs or drug classes in patients with psoriatic RA?



Approach: Use the ACR and PASI time course or Endpoint data to jointly analyze the dose response relationships for PASI75 and ACR50 and quantify the difference in placebo response, ED50 and Emax by drug and drug class

4. What is the difference in ACR dose response relationship in patients with early RA, chronic RA, Psoriatic RA, and Juvenile RA ?
5. Is there a difference in relative effect on the components that make up the ACR effect across drugs and mechanisms of action?
6. Is there a difference in speed of onset of ACR changes across drugs?
7. 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 naïve patients?
8. Is there a difference in Therapeutic Index between the TNF compounds?

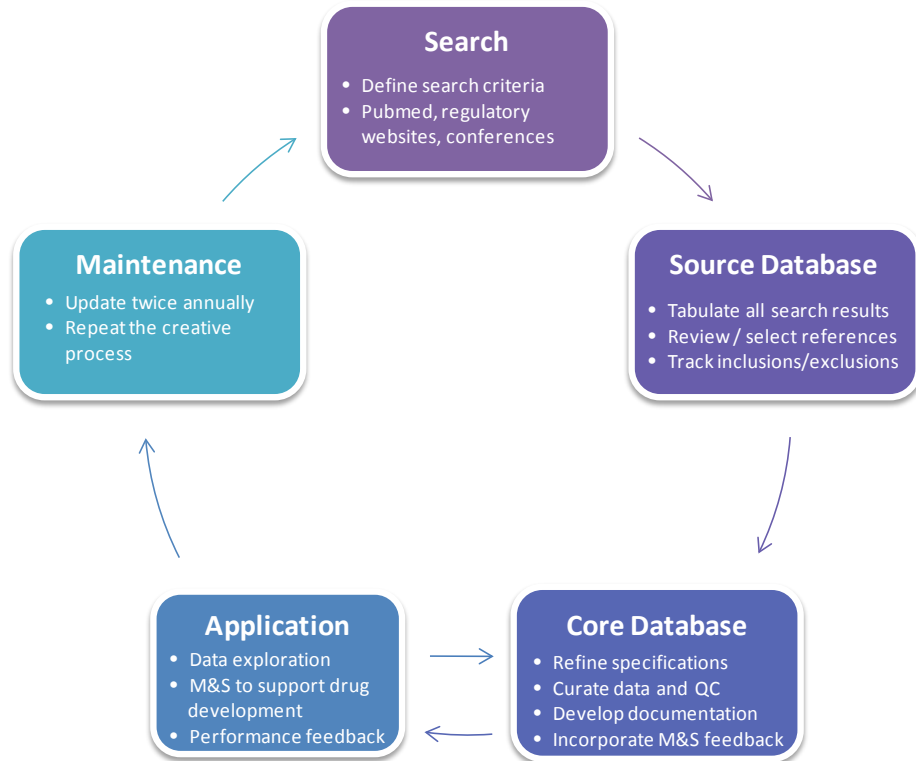
Why use our databases:

- Designed and managed by experienced modelers
- Provide most relevant data to support clients' needs for quantitative decision making
- Contain 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)

3. 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.



3. 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.

281 references were identified and documented in the source database, of which a total of 129 references were selected for inclusion in the database after careful review of the abstracts. The detailed reference information as well as reasons for exclusion is recorded to facilitate potential future expansion of the database. The 129 references selected for inclusion in the database provide information on 94 unique trials.

4. Overview of the RA Clinical Outcomes Database

The following randomized controlled trials provided information on safety and efficacy that was used for the registration with the FDA and EMEA as primary or supportive evidence. No published reference was found for 3 of the trials mentioned in the FDA or EMEA reviews. All 3 trials were listed as providing supportive information. The primary references for the other 32 trials are listed in the table.

Table 2. List of registration trials in the database

Drug	Study	Indication
<i>Adalimumab</i>	DE001/DE003	RA
	DE004	RA
	DE005	RA
	DE007	RA
	DE009/ARMADA	RA
	DE010	RA
	DE011	RA
	DE019	RA
	DE031/STAR	RA
	ADEPT	psoriatic RA
	PsA-II	psoriatic RA
	REVEAL	psoriasis
	M020-528	psoriasis
	<i>Etanercept</i>	16.0004
16.0009		RA
16.0012		early RA
16.0014		RA
300-EU		RA
16.0036		RA
308/TEMPO		RA
16.003		psoriatic RA
Study I		psoriasis
Study II		psoriasis
<i>Infliximab</i>	C0168T09	RA
	C0168T14	RA
	C0168T15/T17	RA
	C0168T22/ATTRACT	RA
	C0168T29/ASPIRE	early RA
	EXPRESS	psoriasis
	EXPRESSII	psoriasis
	SPIRIT	psoriasis
	IMPACTII	psoriatic RA
<i>Rituximab</i>	WA16291	RA
	WA17043/DANCER	RA
	WA17042/REFLEX	RA
<i>Abatacept</i>	IM101100	RA
	IM101101	RA

	IM101102/AIM	RA
	IM101029/ATTAIN	RA
	IM101031/ASSURE	RA
	IM103002	RA
Anakinra	S990145	RA
	S990757	RA
	S560	RA
	S960180	RA
	S96182	RA

The clinical outcomes database contains information from 94 trials, representing 301 unique treatment arms and about 38,460 patients. There are a total of 13,871 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 mono or combination therapy trials available for each drug, the number of treatment arms and the number of patients. Information on MTX/DMARD mono therapy that was already present as background therapy at time of randomization is available as control arm in 49 of the 94 trials (detail data not shown).

Table 3. Number of trials, treatment arms and patients for biological drugs

Name of Drug	# of trials	#of arms	# of patients
MTX	11	22	4255
adalimumab	14	49	5574
certolizumab	6	17	2273
etanercept	26	59	7450
golimumab	5	19	2000
infliximab	16	47	4984
abatacept	7	20	3422
anakinra	6	26	3196
ocrelizumab	1	6	237
ofatumumab	1	4	100
rituximab	3	9	1143
tocilizumab	7	18	3204
ustekinumab	5	19	3647
total	94	301	38460

Table 4. Overview of ACR-related endpoints

Endpoint	# of trials	# arms	# of	drugs
ACR20	67	211	24300	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/ocrelizumab/ofatumumab/rituximab/tocilizumab/ustekinumab
ACR50	63	198	23399	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/ocrelizumab/rituximab/tocilizumab/ustekinumab
ACR70	57	170	22404	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/ocrelizumab/rituximab/tocilizumab/ustekinumab
ACRN	5	20	2231	/MTX/adalimumab/etanercept/golimumab
PsACR	4	8	565	/adalimumab/etanercept/infliximab
CRP	49	161	16931	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/ocrelizumab/rituximab
ESR	27	86	8715	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/infliximab/rituximab/tocilizumab
HAQ	54	157	21003	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/rituximab/tocilizumab/
HAQ responder	18	48	8268	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/rituximab/tocilizumab/
Patient global assessment	44	135	15158	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/rituximab/tocilizumab
Physician global assessment	41	128	14173	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/rituximab/tocilizumab
pain	44	135	15125	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/rituximab/tocilizumab
swollen joint count	44	138	14805	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/rituximab/tocilizumab
tender joint count	44	138	14816	/MTX/abatacept/adalimumab/anakinra/certolizumab/etanercept/golimumab/infliximab/rituximab/tocilizumab

5. 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.

Psoriasis related outcomes

- Psoriasis Area and Severity Index (PASI):
 - % responders (PASI50, PASI75, PASI90, PASI100)
 - mean score (PASI)
- Physician's global assessment for psoriasis. Score is measured on a 0-5 scale ranging from clear, minimal, mild, moderate, marked to severe:
 - mean score (Physician global assessment)
 - % with certain improvement: score=0 (clear), score <=1 (clear and minimal)
- Dermatology life quality index (DLQI)
- affected percent of body surface area.
- Psoriatic Arthritis Response Criteria (PsArc)
- target lesion score
- patients with dactylitis digits
- patients with enthesopathy

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 or that did receive rescue therapy. In trials in which rescue treatment was provided also the dropout minus the patients that receive rescue is provided (dropout – rescue)
- Dropout AE: Dropout related to adverse events
- Dropout Efficacy: Dropout related to lack of Efficacy. Some trials provide rescue therapy 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 lack of efficacy

- 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
- cancer skin: skin cancer
- cancer 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