Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is a form of arthritis that causes pain, swelling, stiffness and loss of function in your joints. It can affect any joint, but is common in the wrist and fingers. More women than men get rheumatoid arthritis. It often starts between the ages of 25 and 55. You might have the disease for only a short time, or symptoms might come and go. The severe form can last a lifetime.

Rheumatoid arthritis is different from osteoarthritis, the common arthritis that often comes with older age. RA can affect body parts besides joints, such as your eyes, mouth and lungs. A multitude of related and ever-changing classifications exist. The overall term Rheumatism is of little importance in clinical trials. Other distinctions and terms relevant to clinical trials are:

Axial Spondyloarthritis:
- Ankylosing Spondylitis (usually diagnosis allows/ requires imaging proof) [aka morbus bechterew]
- (non-radiographic) axial spondyloarthritis (requires specific objective signs of inflammation)

Peripheral Spondyloarthritis:
- Psoriatic Arthritis (40% incidence of Arthritis in patients with Psoriasis)
- Arthritis in inflammatory bowel disease (IBD)
- Refractory Arthritis (old: non responding to DMARD, new: non responding to anti-TNF)

RA is an autoimmune disease, which means the arthritis results from your immune system attacking your body's own tissues.

No one knows what causes rheumatoid arthritis. Genes, environment and hormones might contribute. Treatments include medicine, lifestyle changes and surgery. These can slow or stop joint damage and reduce pain and swelling.

Disease Description

From NIAMS

Rheumatoid arthritis is a disease that affects the joints. It causes pain, swelling, and stiffness. If one knee or hand has rheumatoid arthritis, usually the other does too. This disease often occurs in more than one joint and can affect any joint in the body. People with this disease may feel sick and tired, and they sometimes get fevers.

Some people have this disease for only a few months or a year or two. Then it goes away without causing damage. Other people have times when the symptoms get worse (flares), and times when they get better (remissions). Others have a severe form of the disease that

can last for many years or a lifetime. This form of the disease can cause serious joint damage.

Anyone can get this disease, though it occurs more often in women. Rheumatoid arthritis often starts in middle age and is most common in older people. But children and young adults can also get it.

Doctors don't know the exact cause of rheumatoid arthritis. They know that with this arthritis, a person's immune system attacks his or her own body tissues. Researchers are learning many things about why and how this happens. Things that may cause rheumatoid arthritis are:

- Genes (passed from parent to child)
- Environment
- Hormones.
- Cigarette smoking may increase the risk of developing rheumatoid arthritis. There is also some evidence that cigarette smoking increases the likelihood that rheumatoid arthritis will be severe when it occurs.

Because of an increased risk of coronary atherosclerosis and associated morbidity and mortality in patients with RA, efforts to modify risk factors such as cigarette smoking, hyperlipidemia, hypertension, and sedentary lifestyle should accompany treatment directed at RA."

Rheumatoid arthritis can be hard to diagnose because:

- There is no single test for the disease
- The symptoms can be the same as those of other kinds of joint disease
- The full symptoms can take time to develop.

To diagnose rheumatoid arthritis, doctors use medical history, physical exam, X-rays, and lab tests.

More details on Wikipedia: RA on Wikipedia

Risk Factors for Rheumatoid Arthritis

Agency Guidelines

FDA

In 1999, the FDA published a guidance for industry for clinical development programs for drugs, devices, and biological products for the treatment of RA. See FDA RA Guidance for Industry (1999). The guideline names new claims evaluated in clinical trials during drug development, like reduction in the Signs and Symptoms of RA, as measured, for example, by the ACR 20**.**

The current guideline was issued in 1999. Due to scientific progress, some of the examples in the guideline, especially with regard to biological activity, may not be state-of-the-art anymore. However, besides other sources, this guideline is a good point to start digging deeper into RA trial methodology, especially for non-medics. Several new claims (A-F) for indications are described in detail, some of which include explicit recommendations for study designs, duration and outcome measures to support each claim. The following table summarises the main points from section II of the guideline (**II. New Claims For The Treatment Of RA**).

Claim	Aim	Minimum Duration of Trial	Primary Outcome Measures	Primary Efficacy Evaluation	Explicit Study Design Recommendation from Description of Claim	Additional Consideration for Study Design
A. Reduction in the Signs and Symptoms of RA	demonstrate symptomatic benefits which are not only short-term	6 months, 3 months if "well-characterised pharmacologic class"	Composite endpoints: e.g. Paulus criteria, ACR20; Signs/Symptoms: e.g. 66- or 28-joint count, Physician/Patient Global Assessment	response over time preferred over baseline to final observation	--	products with potential to elicit antibody formation need to be assessed for durability
B. Major Clinical Response	demonstration of a continuous six-month period of success by the ACR 70	at least 7 months for drugs expected to have rapid onset of action otherwise longer	ACR70	statistically significant improvement in response rates by the continuous six-month ACR 70 definition	randomised, control group on background therapy	duration of 7 months should be confirmed upfront as this is the minimum duration
C. Complete Clinical Response	therapeutic benefit of greater magnitude than in B for a at least 6 months period.	depends on time to onset of drug effect, 1 year duration if rapid-onset	continuous six-month period of both remission by ACR criteria and radiographic arrest (no radiographic progression	categorical endpoint (patient complete response or treatment failure) as the	duration of at least 1 year	Showing a benefit requiring ongoing drug therapy should be considered

			or modified Sharp methods)	primary outcome measure		
D. Remission	remission by ACR criteria and radiographic arrest over 6 months while off all anti-rheumatic therapy	depends on time to onset of drug effect, 1 year duration if rapid-onset	continuous six-month period of both remission by ACR criteria and radiographic arrest (no radiographic progression or modified Sharp methods) while off all anti-rheumatic medication	categorical endpoint (patient complete response or treatment failure) as the primary outcome measure	--	Remission is not intended to imply cure, and a remission claim could be granted even if patients relapse after six months or more of remission
E. Prevention of Disability	encourage long-term trials in RA	2 - 5 years	HAQ, AIMS, general HR-QOL such as SF36	no explicit advice for primary outcome, however, subjects should not worsen on HR-QOL measures over the duration of the trial.	improvement in signs and symptoms should have been demonstrated previously or improvement in signs and symptoms should be demonstrated concomitantly, more general HR-QOL measures (e.g. SF-36) should be collected	improvement in signs and symptoms should be demonstrated concomitantly
F. Prevention of Structural Damage	demonstrate prevention of structural damage	at least 1 year	X-Ray: Slowing of progression, prevention of new erosions; MRI/Ultrasonography	X-Ray: Comparison of films taken at one year (and subsequently) with baseline; categorical	All randomised subjects should be evaluated, handling of dropouts needs to be specified. It is expected that the drug has been shown to be effective in one of A-E.	Pre-specification of handling of dropouts, logistics may be challenging. Sponsors who seek approval of a drug based on surrogate marker (21 CFR 314, subpart H and 21 CFR 601 subpart E)

				endpoint. Other techniques not well established.	However, slowing radiographic progression is seen as surrogate marker	should definitely consult FDA staff to discuss clinical trial setup and methodology.

While section II gives a general overview of what the aim of a study may be, section III (**III.. Considerations In RA Product Development**) summarises important points to take into account during product development in RA. Many of the following topics are also covered by more general guidelines (e.g. ICH E9, Guidance for Statistical Analysis Plans). However, the FDA Guideline gives specific advice and points out frequently encountered issues in RA product development:

Preclinical Considerations:

- Pharmacokinetics
- Biologic activity
- Toxicology

Pharmacokinetic/Pharmacodynamic Strategies:

- Considerations in Phase I trials
- Settings and Investigators
- Subjects
- Trial design
- Concomitant therapy
- Observations:
- SafetyEfficacy

Considerations in Phase II trials:

- Trial design
- Safety
- Concomitant therapy
- Gender effects

Efficacy Trial Considerations:

- Patient selection
- Concomitant anti-rheumatic therapy
- Other concomitant therapies
- Stratification
- Blinding
- Effect of dropouts and noncompliance
- Trial designs in RA:
- Superiority trials
- Equivalence trials
- Trial designs novel to the study of RA

Analysis Issues:

- Handling dropouts
- Comparison to baseline outcome measures

Statistical Considerations in Efficacy Trial Design:

- Randomisation/Stratification
- Identification of primary efficacy variables
- Prespecification of statistical analysis

- Multiple endpoints
- Dropouts
- Trials with several treatment groups/multiple comparisons
- Trials are simultaneously used to pursue more than one claim
- Interim analyses
- Sample size
- Trials to show clinical equivalence
- Appropriateness of the statistical methodology
- Site effects

Safety Analysis:

- Intrinsic trial design considerations
- Adequate numbers

Part **IV. Special Considerations for Biological Products** points out special characteristics and problems to consider for biologics. The information given in this chapter is far from being thorough, but it can give useful hints for those new to working with biologicals. The section lists common issues with biological systems, such as:

- Species Specificity
- Dose Response
- Toxicity Response
- Product Homogeneity
- The Role of Antibodies

Most of the content of the guideline also applies to the development of medical devices. However, section **V. Special Considerations for Medical Devices** gives more detail regarding Efficacy and Safety Considerations. The last chapter, **VI. Special Consideration for Juvenile Rheumatoid Arthritis** amends the previous sections with a definition of JRA, a detailed rationale for trials in this population, ethical considerations, and additional information to be considered if a sponsor seeks approval for JRA. Outcome variables and claims are adjusted to fit this population and trial design issues, concurrent anti-rheumatic agent administration, as well as multicenter trials and centre effects are discussed briefly.

CMPM: Points To Consider On Clinical Investigation Of Medical Products Other Than NSAIDS For Treatment Of Rheumatoid Arthritis. In 1988, the CDER published a guideline for the Clinical Evaluation of Anti-Inflammatory and Anti-rheumatic Drugs. See CDER RA Guideline (1988).

EMA

In 2003, the EMA published points to consider on clinical investigation of medicinal products other than NSAIDs for the treatment of Rheumatoid Arthritis. See EMA RA guideline (2003)- Compared to the FDA Guideline, the respective EMA document is rather small (8 pages). It is a more recent document (2003), but as said before, examples and statements may be outdated meanwhile due to scientific progress. This possibility is clearly addressed in the

introduction of the document; however, it is made clear that any claim based on further development of techniques “must show convincing evidence, including validation and demonstration of clinical relevance”. The aim of the document “is to provide guidance with respect to the design of clinical studies related to therapeutic efficacy and clinical safety of anti-rheumatic therapy”. Therefore, it clearly provides information necessary to set up clinical trials of later stages.
The list of claims for indications is shorter and points to the improvement of disease symptoms:

To relieve pain, to decrease inflammatory synovitis improve or sustain
physical function prevent structural damage

This approach is different to the FDA guideline, which covers almost all aims of the EMA guideline with the claim “Reduction in Signs and Symptoms” already. The tools to measure efficacy for signs and symptoms, however, are the same (e.g. 28-joint count, Physician/Patient Global Assessment, pain score, ESR, CRP, HAQ, radiographs). Other measures may be acceptable but need to be validated. Validated composite endpoints are to be used to document efficacy (DAS, Paulus, ACR,…) as additional primary or secondary endpoints. These need to be consistent with the single efficacy endpoints. The FDA guideline clearly allows composite endpoints as primary efficacy measure (e.g. ACR20 for claim Reduction in the Signs and Symptoms of RA). Compared to the numerous claims listed in the FDA guideline, the EMA PtC does not give clear advice on long-term trials and the definition of more ambitious outcomes like clinical response or remission of RA symptoms.

Both guidelines mention the potential use of imaging techniques such as
MRI, ultrasound and radiographs to examine structural joint damage. Comparison of radiographs taken before and after introducing the study drug is the only method mentioned in more detail in both documents. The actual procedure to perform X-rays, their evaluation and methods of statistical analysis need to be part of the trial protocol and should be agreed with the respective Agency before the start of the study. Other techniques, such as MRI or ultrasound, were not seen as established methods at the time the documents were issued. The EMA guideline explicitly sees these methods as “supportive evidence for efficacy but only when the methods have been subjected to prior validation and their clinical relevance predefined”.
The FDA guideline sees “the technique's potential for identifying small, albeit statistically significant changes”, but “the magnitude of the difference that would reflect actual patient benefit is unclear and needs to be established”.

Clinical Trial Endpoints:

Several scales have been developed and validated to measure the improvement of RA in a clinical trial setting. These scales are used in research to determine eligibility
to participate in a research trial or to assess severity and disease progression. Scales may also be used in clinical practice to identify and monitor problems or gauge clinical function and degree of progression.

None of these single measures can serve as a “gold standard” for the assessment of patient status in RA. Therefore, in clinical trials, a combination of the following measurements is performed.

Dichotomous Measurement:

- **EULAR Response Criteria**
- **ACR Response Criteria** (ACR20, ACR50, ACR70) - Reported as % improvement, comparing disease activity at two discrete time points (ACR20 ≥ 20%improvement, ACR50 is ≥ 50%improvement, ACR70 is ≥ 70% improvement)
- **2010 ACR/EULAR** - the 2012 ACR/EULAR is a new classification criterion for RA, which was developed to address the lack of sensitivity in early disease.

Continuous Measurement:

- **DAS** - the DAS (Disease Activity Score) includes tender and swollen joint counts, erythrocyte sedimentation rate and a subjective assessment
- **DAS 28** - the DAS28 is a modification of the DAS. It is based on a smaller number of joints.
- **DAS-CRP** - the DAS-CRP or DAS28-CRP is a modification of the DAS28. It includes the C-reactive protein instead of the erythrocyte sedimentation rate.
- **SDAI** - the SDAI (simplified disease activity index) includes tender and swollen joint counts, patient and investigator global assessments, as well as the C-reactive protein measurement
- **CDAI** - the CDAI (clinical disease activity index) is similar to the SDAI, but does not include the C-reactive protein measurement

Patient Recorded Outcomes

- **Health Assessment Questionnaire Disability Index (HAQ-DI)** - the HAQ-DI (Health Assessment Questionnaire - Disability Index) is part of the HAQ, which is focused on disability questions.
- **Modified Health Assessment Questionnaire (mHAQ)** - the mHAQ is a modified HAQ and reduces the number of questions from 20 (HAQ) to 8 (mHAQ)
- **Multidimensional HAQ (MDHAQ)**

Other:

- Imaging
  - **Plain radiographs**
  - Musculoskeletal ultrasound
  - **Magnetic Resonance Imaging (MRI)**

Data Challenges:

Concomitant Medication

Often, subjects need to take a combination of drugs from various classes to treat symptoms of RA, such as pain and swelling:

Analgesics
non-steroidal anti-inflammatory drugs (NSAIDs)
Corticosteroids
Disease-modifying anti-rheumatic drugs (DMARD)

These drugs need to be taken by patients to ensure day-to-day activity and functioning of joints. Therefore, they are often present at baseline in clinical trials, and trial protocols allow the ongoing intake during the trial period. However, most protocols require that these drugs be kept stable for a specific amount of time prior to enrolment and during the trial period. Many trial protocols define rules to exclude joints or complete subjects from the analysis if changes in dosing or use of rescue medications occur (e.g. intra-articular injection of corticosteroids or use of analgesics 48h prior to joint assessments). CRF completion instructions should outline how to document the use of RA-related drugs. E.g. a dosing frequency such as "as needed", "PRN", etc. should be avoided.
Use of prohibited drugs and rescue medication often needs to be checked to find protocol deviators. The actual identification of these medications sounds rather trivial, but it involves programmers and medical experts. In order to keep the effort as low as possible, a glossary of all medications used in the trial can be a big help to categorise medications according to their ATC codes into meaningful groups (e.g. DMARDS, NSAIDS, aTNF, vaccination, etc). Once set up, such a list can be used to find new concomitant medications to be reviewed by medics from those already classified. In a clinical development program, such a list can ensure a standardised approach to treat concomitant medications in all studies across the project in the same way.

Component Scores (ACR, DAS..)

Clinical trials in RA often have to use component scores due to the lack of a single outcome measure. These scores are calculated using total scores from patient questionnaires (e.g. HAQ-DI, Patient Global Assessment of Pain), investigator assessments (e.g. tender/swollen joint counts, Physicians' Assessment of Disease Activity) and lab results (e.g. CRP, ESR). In order to be able to calculate a component score, all components must be available. This can be challenging for a number of reasons:

- Were all assessments done on the same day
    - If not, what time window is allowed until a single assessment is no longer valid
    - Which date will be used for the component score
- questionnaires are not filled in at all by subjects, or are incomplete
    - Is there a chance to impute missing results
- Investigator assessments should be done by the same person across all visits

Plain Radiographs:

With regard to radiology, usually joints are read at least by two readers. Whereby longer terms are reasonable.

=> Complicated calculation rules, which have to handle this amount of data.

=>radiographs are often not done on the visit itself, i.e. the date for radiographs varies from other measurements.

MRI/Radiographs Interim Calculations:

The calculation of the one score, which is going into the analysis, is already complicated for these methods. Therefore, interim results might be reasonable.

=>What to do with these interim results - are they necessary to be kept - if yes, how?

Data Collection:

Is there a CDE project for data collection and sharing available? Check for more details.

SDTM Data:

State if there are special domains already available for this disease. Are there TA-specific working groups on the CDISC page stated? Check

If there is no standard given on the CDISC pages, state how the disease-specific information/primary measurements could be stored in the SDTM data. You might want to propose a naming convention.

ADaM Data:

State if there are special domains already available for this disease. Are there TA-specific working groups on the CDISC page that also address ADaM standards? Check

If there is no standard given on the CDISC pages, state how the disease-specific information/primary measurements could be stored in the ADaM data. You might want to propose a naming convention.