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ORIGINAL RESEARCH

# Clinical trials: their contribution to the efficiency of the clinical management of rheumatoid arthritis

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## Abstract

**Background:** This article presents a descriptive analysis of our Clinical Research Unit (CRU) at the Rheumatology Department in the University and Polytechnic Hospital La Fe (RD-UPH La Fe), Valencia (Spain), as well as an estimation of the economic impact of conducting clinical trials for the Spanish Health System in terms of avoided costs.

**Methods:** During the period 2011–2015, a retrospective observational study was conducted based on the trials performed in our CRU, along with a cost analysis from the health authority perspective.

**Results:** Most of the trials conducted during this period were phase III studies in patients with rheumatic disorders, particularly rheumatoid arthritis. An economic evaluation study showed that the implementation of these studies in our CRU resulted in an annual saving of €13,935.30 per patient.

**Conclusion:** Our CRU is an efficacy and efficiency tool for cost saving in the healthcare system.

**Keywords:** Clinical research, cost analysis, impact on healthcare, rheumatic disease, rheumatoid arthritis.

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## Introduction

Clinical research includes all carefully and ethically designed studies of investigational medicinal products (IMPs) aimed at evaluating their efficacy, safety, and tolerability in human subjects. Despite their limitations (strict selection of study subjects, short follow-up periods, and being conducted in non-clinical practice settings), clinical trials (CTs) provide the best scientific evidence for the approval and further commercialization of new medicines or the development of new administration forms and indications of those already on the market. In addition, CTs contribute to healthcare savings as an added value.

Healthcare technologies (especially those concerning medicinal products) account for the most significant proportion of health expenditure.[1] The inability to finance all the required interventions with our available resources has led us to choose a more efficient way of using our resources in a scenario of unlimited needs.[2]

Rheumatic diseases are highly prevalent. According to the EPISER study (Spanish Society of Rheumatology, 1998–1999),[3] up to 23% of persons older than 20 years report being affected by a rheumatic disorder, often accompanied by some degree of disability, and associated with high consumption of healthcare resources.[4]

Over the last years, rheumatology has experienced significant developments, attained a high level of both basic and clinical research, and witnessed the emergence of novel therapies.[5] Several biological compounds are being successfully used in rheumatoid arthritis (RA) and other rheumatic diseases. However, clinical response to these biological agents is not always achieved.

Our responsibility as healthcare professionals is to promote biomedical research as the best way to achieve therapeutic advances capable of improving our patients' quality of life. For this reason, a Clinical Research Unit (CRU) was created in our Rheumatology Department at the University and Polytechnic Hospital La Fe (RD-UPH La Fe), Valencia, in 2011. When performing CTs, the sponsor pays the direct healthcare costs of the patients, which leads to savings to the National Health System (NHS). Our study hypothesis is that the setting up of a CRU constitutes an effective and

efficient tool for the management of our Rheumatology Service. The aim is to estimate the economic impact of conducting CTs for the NHS in terms of avoided costs and to demonstrate that clinical research is an efficiency tool in healthcare settings. For this purpose, we performed a descriptive analysis of how clinical trial recruitment can reduce costs to healthcare systems.

# Methods

## Study design

This is a descriptive, observational, retrospective, single-centre study performed at the RD-UPH La Fe, comprising CTs conducted in our CRU between January 2011 and December 2015. Institutional review board approval was not required since it was a retrospective, observational study. Signed patient consent was not required since we used de-identified patient data.

## Economic evaluation

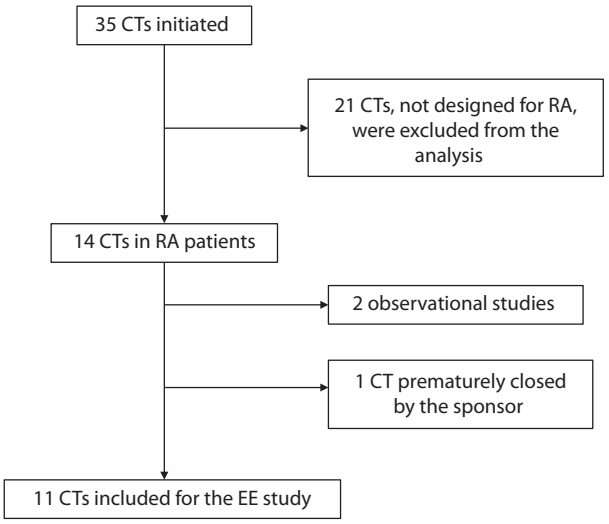
A cost analysis of CTs based on a Spanish Health System perspective was performed in patients with RA because this is the most prevalent inflammatory disease in which the greatest number of trials have been conducted. This analysis is based on data collected from CTs in patients with RA and from the clinical records of patients with RA treated in our Rheumatology Department. All CTs performed in patients with RA over the study period were analysed, although two observational studies in which the medication used had been funded by the health authority were excluded, as was a multinational study prematurely closed by the sponsor in which no patients were entered (Figure 1). We calculated the length of stay in the CT in weeks for each patient included with RA diagnosis. Afterwards, we also calculated the total number of weeks of treatment for the total of patients. Finally, a cost analysis model was developed to evaluate cost savings resulting from the inclusion of RA patients in CTs as a therapeutic option rather than treating them with a marketed biological agent according to the standard clinical practice.

## Estimation of resources

### Identification

To estimate the costs included in the analysis, a previous identification and selection of resources of interest was carried out based on the perspective used in our study. As our study is performed from a health authority perspective, only health direct costs were considered.[6] The following costs were identified and quantified during the study period: number of successive medical visits per specialist physician; number of visits to the nurse's office; diagnostic and/or laboratory tests; and pharmacological treatment (in our CRU, staffing costs are entirely funded by trial-related income, whilst direct healthcare of the patients during the conduct of a CT is paid by the sponsor).

**Figure 1. Study design.**




CT, clinical trial; EE, economic evaluation; RA, rheumatoid arthritis.

Resources also used with other therapeutic options (background pharmacological treatment of RA, pharmacological treatment of comorbidities, consumption of healthcare resources for the management of adverse events (AE), and resources associated with the administration of the medicinal product) were not included, because it is assumed that their costs are common to all alternatives being compared (i.e. for patients either included in a CT or treated with a marketed medicinal product). Non-healthcare direct costs were excluded from the analysis because they are irrelevant from the healthcare perspective.

### Quantification

The amount of resources (in physical units) consumed during the analysis period was determined by assigning an average value per patient. An average patient is one that requires a 3-month follow-up in the case of patients with RA.

### Assigning unit costs

The unit cost assigned to each healthcare resource corresponds to the price stipulated by the UPH La Fe according to the Law of Fees of the Generalitat Valenciana,[7] except the cost of the pharmacological treatment (etanercept) quantified in accordance with the Laboratory Selling Price (LSP) published by the General Pharmaceutical Council of Spain[8] at the time the analysis was undertaken (Table 1). Etanercept was considered the best commercial alternative treatment for the study as it is the marketed biological agent that was most widely used in routine clinical practice during our study period, and whose efficacy and tolerability have been shown to be similar to those of the other biologicals available at that moment, although it was less costly.

**Table 1. Unit costs assigned to each resource used (€ of 2016).**

| Concept | | Cost (€ + VAT) |
|---|---|---|
| Visit to the Specialist Physician (Successive) | | 40.2 |
| Extractions, injectable or sample collection at the health centre | | 20.90 |
| Rheumatoid factor | | 6.56 |
| Anti-CCP | | 6.56 |
| CRP | | 6.50 |
| ESR | | 3.26 |
| Automated blood cell count | | 3.26 |
| lucose | | 0.56 |
| BUN | | 0.71 |
| Creatinine | | 0.34 |
| Creatinine clearance | | 0.17 |
| GPT | | 0.62 |
| GOT | | 0.62 |
| GGT | | 0.79 |
| Alkaline phosphatase | | 0.56 |
| Total, direct and indirect bilirubin | | 0.60 |
| Ions | | 2.79 |
| Total proteins | | 0.50 |
| Albumin | | 0.38 |
| Calcium | | 0.63 |
| Phosphate | | 0.62 |
| Cholesterol (HDL, LDL, VLDL) | | 3.30 |
| Triglycerides | | 1.02 |
| Urinalysis (sediment and abnormal elements) | | 3.83 |
| **Etanercept (SPC)** | **LSP (€ + VAT)** | **LSP** |
| 50 mg/week | | |
| Etanercept (50 mg, four 1-mL preloaded syringes) | 1.043,30 | 947.22 |

Source: BOTPLUS 2.0[14]

Anti-CCP, anticyclic citrullinated peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; HDL, high-density lipoproteins; LDL, low-density lipoproteins; LSP, laboratory selling price; SPC, summary of product characteristics; VAT, value-added tax; VLDL, very low-density lipoproteins.

## Statistical analysis

Data were collected from the CTs performed in our CRU from January 2011 to December 2015, as well as from the CT reports on file in this unit.

A descriptive analysis was conducted of our CRU along with an analysis of the type of CTs conducted by reviewing the rheumatic disease treated and the development phase of the trial. Statistical analyses were conducted using the IBM SPSS Statistics®.

Distribution tables of absolute and relative frequencies, as well as histograms, are used to describe study results. Discrete quantitative variables included investigator-controlled independent, grouping, and demographic variables. Dependent variables were outcome or response variables which could be either discrete or continuous quantitative. Confounding variables were not analysed. The simultaneous relationship of several variables in the statistical analysis was determined and classified using a multivariate analysis.

The descriptive statistics applied to the data collected was summarized to avoid managing the whole data set and provide an overview of variable distribution. To this end, frequency tables and their graphic representations were used. Measures of central tendency included mean, median, and mode, as well as minimum and maximum values. No measures of dispersion (e.g. range, standard deviation), position (e.g. quartiles, centiles), or form (bias, skewness, kurtosis) were used.

As for the general description of patients throughout the study follow-up, the following parameters were recorded for analysis: total number of active CTs per year during the study period; total number and percentage of CTs by phase of clinical development; total number and percentage of CTs by pathology; total number and percentage of screenings, screening failures, and randomized patients by pathology throughout the study.

# Results

The CRU team members include the principal investigator (and Head of the Rheumatology Department), three co-investigators (one of whom also coordinates the whole unit), and one dedicated nurse. All personnel members, both specialist physicians and specialized nurse, are skilled and well trained in Good Clinical Practice. Our CRU has budgetary autonomy because the studies performed are funded by pharmaceutical companies.

## Clinical research activities performed in the CRU

A total of 35 trials were conducted in our unit between January 2011 and December 2015. The number of active CTs increased

over the first 2 years from 8 in 2011 to 15 in 2012, with a plateau being reached during the three following years (20 trials per year). Most CTs were phase III trials (20; 57.1%), followed by observational studies (8; 22.8%), phase I/II (4; 11.4%) and IV trials (3; 8.6%). The trials were mainly performed in patients with RA (n=14).

## Analysis of the economic evaluation

Our economic evaluation (EE) analysis only included CTs conducted in patients with RA, whose average consumption value differs from that of patients with other conditions (as described in the Methods section). Two observational studies and one CT (premature closure by the sponsor) were discarded. Therefore, 11 CTs were considered for analysis, which included a total of 76 patients with RA.

For each patient, the duration of treatment with the IMP was recorded Afterwards, the total number of weeks with IMP treatment for all the patients was calculated, along with their completion status (completed or withdrawn from the trial), which totalled 2609 weeks of treatment. This represents a saving in expenses for the healthcare system in terms of biological therapy, health professional care (physicians and nurses) and laboratory testing for 1 patient over a 50-year period or, similarly, for 50 patients over 1 year (Table 2).

After assigning the unit costs to the resources considered in the EE analysis, the total cost was calculated by multiplying the consumption of each resource by its unit cost, per year and month (Table 3). We use the expression 'consumption of minimum resources' because, as discussed in the Methods section, our aim was to compare the healthcare saving translated into avoided costs with regard to the value of the biological agent that patients would have received if they had not been included in a clinical trial.

**Table 2. Follow-up weeks in rheumatoid arthritis patients included in the clinical trials.**

| Clinical trial | Total patients included (n) | Total weeks (n) |
|---|---|---|
| ACT11575 | 1 | 12 |
| WA22762 (SUMMACTA) | 10 | 760 |
| ML28488(ACT Extension) | 4 | 384 |
| ML27828(JUST ACT) | 21 | 377 |
| M12-073(CONCERTO) | 7 | 130 |
| CX611-0101 | 5 | 72 |
| I4V-MC-JADW (BEACON) | 8 | 97 |
| I4V-MC-JADX(BUILD) | 4 | 72 |
| I4V-MC-JADV(BEAM) | 3 | 1 |
| I4V-MC-JADY (BEYOND) | 7 | 464 |
| ML28709(TO-SPACE) | 6 | 240 |
| **Patients (total n)** | 76 | |
| **Weeks (total n)** | | **2609** |
| **Years (total n)** | | **50.17** |

In summary, our results show that, after the creation and development of a CRU in our RD and specifically CTs in RA, the economic impact in terms of savings for our health system is high due to the avoided costs in biological therapy, human resources (specialists and specialized nursing), and laboratory tests. In 5 years, a total saving of €699,176 was achieved, which means an annual saving of €139,835 (Table 4).

# Discussion

Our CRU was created in January 2011. Despite its short lifetime, it has had an intense initial 2-year development program of active clinical trials, which has remained stable during the last 3 years. Over this period, the number of staff members has risen in concert with the unit's growing level of activity.

The primary scope of clinical research is to evaluate the safety and efficacy of IMPs to derive maximum therapeutic benefit for the patient. In this regard, our EE study also showed that CTs, in addition to being the best tool to confirm efficacy of medicinal products, represent *per se* an efficiency instrument because they translate into savings for our healthcare system in terms of pharmaceutical expenditures, human resources, and diagnostic testing. Furthermore, CTs are usually the only option for patients who want to gain access to drugs not yet on the market or marketed for a different indication, or for patients who fail to respond to other commercially available medicines.

## Study limitations

The main limitation of this EE study is that the analysis used to estimate the savings for the healthcare system was based exclusively on CTs performed in patients with RA, as compared to other published studies that have included all the trials related to the same specialty for calculating the economic impact or the avoided costs.[9-11] This decision, however, has allowed us to include some other types of avoided resources, such as visits by specialist physicians or visits by specialized nurses and laboratory tests, and not only the avoided costs from the biological treatment, because all the direct healthcare costs are relevant from the health authority perspective. To this end, a patient representative of RA was chosen, and an average consumption was assigned, which permitted us to analyse a homogeneous patient profile. However, for any particular disease, there may be a number of circumstances associated with different resource consumptions – such as a wide clinical heterogeneity, specific properties of the different therapeutic options and several aspects concerning the clinical follow-up – which are likely to influence the final outcomes.

**Table 3. Minimum annual resource consumption per average patient.**

| Identification | Quantification | Value assessment | Total cost |
|---|---|---|---|
| **Resources** | **Annual consumption** | **Unit cost (€)** | **Total cost per resource (€)** |
| Visit to the Specialist (Physician) (Successive) | 4 | 40.2 | 160.08 |
| Extractions, injectables, or sample collection at the health centre | 4 | 20.90 | 83.60 |
| Rheumatoid factor | 1 | 6.56 | 6.56 |
| Anti-CCP | 1 | 6.56 | 6.56 |
| CRP | 4 | 6.50 | 26 |
| ESR | 4 | 3.26 | 13.04 |
| Automated blood cell count | 4 | 3.26 | 13.04 |
| Glucose | 4 | 0.56 | 2.24 |
| BUN | 4 | 0.71 | 2.84 |
| Creatinine | 4 | 0.34 | 1.36 |
| Creatinine clearance | 4 | 0.17 | 0.68 |
| GPT | 4 | 0.62 | 2.48 |
| GOT | 4 | 0.62 | 2.48 |
| GGT | 4 | 0.79 | 3.16 |
| Alkaline phosphatase | 4 | 0.56 | 2.24 |
| Total, direct, and indirect bilirubin | 4 | 0.60 | 2.40 |
| Ions | 4 | 2.79 | 11.16 |
| Total proteins | 4 | 0.50 | 2.00 |
| Albumin | 4 | 0.38 | 1.52 |
| Calcium | 4 | 0.63 | 2.52 |
| Phosphate | 4 | 0.62 | 2.48 |
| Cholesterol (HDL, LDL, VLDL) | 2 | 3.30 | 6.60 |
| Triglycerides | 2 | 1.02 | 2.04 |
| Urinalysis (sediment and abnormal elements) | 4 | 3.83 | 15.32 |
| Hospital pharmacological products | 52 | 260.83 | 13,562.90 |
| **Minimum cost per patient/year** | | | **13,935.30** |
| **Minimum cost per patient/month** | | | **1161.28** |

Additionally, unit costs were obtained from the Law of Fees of the Generalitat Valenciana, in force at the time of analysis, as was the etanercept LSP.

## Proposals for potential research lines

The total impact on the healthcare system can be calculated from this study in terms of avoided costs for all the CTs conducted in the RD-UPH La Fe. For that purpose, we would use the health authority perspective; therefore, as with the CTs performed in RA, we would include the direct healthcare resources, excluding the non-healthcare direct costs and indirect costs.

We would also assign an average per-patient value based on the data collected from other patients experiencing the

**Table 4. Economic impact attributable to CTs in RA.**

| | |
|---|---|
| Patients included in the CTs analysed in the EE (n) | 76 |
| Total follow-up time of CTs | 2609 weeks (50.1 years) |
| Economic impact attributed per patient/year | € 13,935.30 |
| Economic impact attributed per year (average) | € 139,835.38 |
| Economic impact attributed to CTs for 5 years | € 699,176.88 |

CTs, clinical trials; EE, economic evaluation; RA, rheumatoid arthritis.

same rheumatic disease. We would not consider low-level and scarcely relevant resources, as well as those common to the other options because their measurement would be time-consuming, and their contribution to the global cost is usually very small.

The economic evaluation of healthcare technologies or, particularly, pharmacoeconomics studies (mainly focused on the evaluation of medicinal products) has gained momentum over the last few years due to the need to link intervention-related benefits with the cost of such interventions. Health professionals should become involved and play a more relevant role in the priority-decision process within a context where available resources are insufficient. The aim of economic evaluations in medicine is to assist in the adoption of efficient decisions without limiting clinical freedom. Decisions related to new medicines must be based not only on efficacy, safety, and quality criteria but also on the cost component.[12]

In this regard, a rapidly growing interest in the economic evaluation of CTs has emerged, with the inclusion of sections devoted to the use of healthcare resources.[13] A specific resource-utilization sheet for identification and quantification purposes should be included in the study case report form, and data on resource consumption should be entered in the patient's clinical record. The informed consent should include information on the type of costs to be recorded. Adequate training on the resources to be included in the studies is essential for both investigators and coordinators.

## Conclusion

Rheumatology is one of the medical specialties in which clinical research has experienced fast growth in recent years, as shown by the increasing activity in our CRU since its creation in 2011. The conduct of CTs represents a key component of scientific and therapeutic development where safety, welfare, and dignity of participating subjects are consistently preserved; the integrity, reliability, and quality of the data collected are guaranteed; and savings for our healthcare system are obtained.

Thus, healthcare managers should consider CRUs not only as a means of strengthening the scientific fabric and the industrial development in their country but also as efficiency tools within their health system. As health professionals, we should adopt efficiency criteria for clinical decision making in a publicly funded healthcare system, to achieve the highest benefits for our entire population in a context of limited resources.

In summary, after the creation and implementation of our CRU, we managed to save a total amount of €13,935.30 per patient in CT per year. CRUs should be considered as an efficient tool for healthcare systems.

**Contributions:** All authors contributed extensively to the work presented in this paper. All authors have contributed significantly to the conception, design, or acquisition of data, or analysis and interpretation of data. All authors have participated in drafting, reviewing, and/or revising the manuscript and have approved its submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

**Disclosure and potential conflicts of interest:** Dr Román Ivorra reports that he is on advisory boards for Pfizer, Sanofi, and Roche, outside the submitted work. No conflicts of interest exist concerning the conduct of this work. Etanercept was chosen as a therapeutic alternative based on cost efficacy/cost-effectiveness criteria, regardless of the pharmaceutical company marketing the drug. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at https://www.drugsincontext.com/wp-content/uploads/2019/11/dic.212612-COI.pdf

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