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Complete List of Authors:	Kostuj, Tanja; Katholisches Klinikum Bochum Sankt Josef-Hospital, Klinik für Orthopädie und Unfallchirurgie Rehart, Stefan; Agaplesion Markus Hospital, Teaching Hospital of Johann Wolfgang-Goethe University, Clinic for orthopedics and traumatology Matta-Hurtado, Ronald; Catholic Hospital Dortmund-West, Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic Biehl, Christoph; Universitätsklinikum Giessen und Marburg , Klinik für Hand- Wiederherstellungs- und Unfallchirurgie Willburger, Roland; Katholisches Klinikum Bochum Sankt Elisabeth-Hospital, Department of Rheumatic-Orthopedics Schmidt, Klaus; Catholic Hospital Dortmund-West, Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic
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Pilot study for the Registry of Complications of the German Society for Surgery in Rheumatic-Diseases (DGORh) – Evaluation of methods and data from the first 1000 patients

Dr. med. Tanja Kostuj[1,2], - **Corresponding author**
[1]Catholic Hospital Bochum, St. Josefs-Hospital, University hospital of Ruhr-University-Bochum, Department of Orthopedics and traumatology, Gudrunstraße 56, 44791 Bochum, Germany
[2] Institute for Medical Biometry and Epidemiology, University of Witten / Herdecke, Alfred-Herrhausen-Straße 50, 58448 Witten, Germany
E-mail: tanja.kostuj@t-online.de; Phone: +49 170 3835773

Prof Dr. med. Stefan Rehart
Agaplesion Markus Hospital, Teaching Hospital of Johann Wolfgang-Goethe University, Clinic for orthopedics and traumatology, Wilhelm-Epstein-Str. 4, 60431 Frankfurt am Main , Germany

Mr. Ronald Matta-Hurtado,
Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic, Catholic Hospital Dortmund-West, Zollernstraße 40, 44379 Dortmund, Germany

Dr. med. Christoph Biehl,
Orthopedic and Rheumaorthopedic Clinic - Diakonie hospital, Ringstraße 64, 55543 Bad Kreuznach, Germany

Prof. Dr. med. Roland E. Willburger
Catholic Hospital Bochum, St. Elisabeth-Hospital, University hospital of Ruhr-University-Bochum, Department of Rheumatic-Orthopedics, Bleichstraße 15, 44787 Bochum, Germany

PD Dr. med. Klaus Schmidt
Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic, Catholic Hospital Dortmund-West, Zollernstraße 40, 44379 Dortmund, Germany

On behalf of the study-group "complication-register of the DGORh"

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The authors declare the following potential conflicts of interests:

TK: Shares of pharmaceutical industry or medical devices manufacturers might be included in a fond – but details are not known to the author.

SR: Has received speaker fees from the companies Abbvie / Grünenthal / MSD / implantcast / medac

CB: Has received speaker fees from the companies Link and Abbot

The remaining authors declare no potential conflict of interest.

The authors declare the following contribution of authorship:

TK: writing of manuscript, data analysis, modification of questionnaires for real time registry

SR: design of pilot questionnaires, review of questionnaires for real time registry, review of manuscript

RMH: data-collection and data analysis

CB: providing of references, review of manuscript
REW: providing of references, approval ethics committee
KS: design of pilot questionnaires, data-collection, review of manuscript

Further members from the pilot-study group are (listed alphabetically):

Dr. med. Ingo Arnold, Red Cross hospital, Bremen, Department of Rheumatology and Orthopedics
Dr. med. Ludwig Bause, St. Josef-Stift Sendenhorst, Department of Orthopedic Rheumatology
Dr. med Harald Dinges, Westpfalzklinikum Kusel, Clinic of Orthopedics, Traumatology and Rheumatic Orthopedics
PD Dr. med. Thomas Pauly, Rheinisches Rheumazentrum St. Elisabeth-Hospital, Department of Orthopedic Surgery/Rheumatology, Meerbusch-Lank
Dr. med. Stefan Schill, Joint-center, Rosenheim GmbH and Harthausen Bad Aibling Clinic
Dr. med. Roger Scholz, Department of Orthopedics, Collm-Clinic Oschatz

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No additionally data are available.

Abstract:

Objective:

Most of the patients with rheumatic diseases, undergoing surgical treatments, are receiving immune-modulating therapy. Based on the confusion if those medications affect their outcomes a national registry is established. Data from the first 1000 patients were used as a pilot study to identify relevant co-risk factors and to analyze, if a registry is suitable to develop accurate and relevant recommendations.

Design and participants:

Patient's data were collected in a consent form all patients undergoing surgical treatments. A second consent form was used, if a complication occurred. During the pilot study the risk-factors were considered only in patients where complications occur in order to obtain a quicker overview.

In this pilot study only descriptive statistical analysis were appropriate due to the inhomogeneous type of surgery and the medications used, as well as the limited number of observed complications. Analytic statistics of the confirmatory questions in midterm-outcome can be expected later on.

Results:

Complications occurred in 26 patients and were nearly equally contributed in the different types of surgeries. 21 of these patients received immune-modulating therapy, 5 did not. Infections were observed in 2.3% of patients receiving and in 5.1% with no immune-modulating therapy.

Conclusions:

Due to the inhomogeneity in the diseases and the treatments received by those patients it is difficult to develop standardized best-practice recommendations to optimize their care. Therefore, such a national registry has to include the most important and relevant variables that impact the care and outcomes of these patients to be suitable to develop accurate and relevant recommendations.

Article summary

Article focus:

- Do we find indicators that administration of immune-modulating medications appears to impact wound complications in different types of elective orthopedic surgery?

- Due to the inhomogeneity in the different types of rheumatic diseases itself as well as the treatments received by patients it is difficult to develop standardized best-practice recommendations. Is a registry suited to collect and analyze data from these inhomogeneous groups of patients?

Key message:

- The administration of immune-modulating medications appears to impact wound complications.
- The creation of a large, comprehensive national registry that includes the most important and relevant variables that impact the care and outcomes of these patients is essential.

Strengths and limitations of the study:

- The number of 1000 datasets from twelve centers with different structures were available to test, if a register is suited to analyze a possible impact of immune-modulating medications on wound complications to adapt the questionnaires for the use in the “real time” register.
- Due to the small number of patients with complications, the inhomogeneity in the different types of rheumatic diseases itself as well as the treatments received by patients so far extended statistical analyzes cannot be done with these first 1000 datasets and only tendencies can be derived.

Keywords:

Inflammatory-arthritis, immune-modulating therapy, disease modifying anti-rheumatic drugs, biologicals, wound complications, registry

Main text:

Introduction:

Rheumatoid arthritis (RA) has a prevalence of approximately 1% in Western Europe and the United States, with a cumulative prevalence for all types of rheumatic diseases being 2%, while the incidence of inflammatory-arthritis diseases in Germany is 3% (about 2.5 billion patients). About 25 years ago approximately 25% of these patients underwent total joint replacement, yet recently the number of these procedures as well and the number of surgical treatments in general in RA patients has decreased in Europe, the United States and Japan [1-8]. This trend could be the result of the recently introduced, very early “treat-to-target“-treatment and/or the use of modern anti-inflammatory medications [9], which have increased during the same time period. Actually, about 70% of the patients with RA are receiving, so called, disease modifying anti-rheumatic drugs (DMARDs), while about 20% are treated with biologicals such as immune-modulating therapy [10]. This means that most of these patients, undergoing surgical treatments, are receiving immune-modulating therapy, for their inflammatory arthritic diseases. This raises the questions “do immune-modulating medications affect the outcomes of these surgical treatments?”, or “do they contribute to an increase in the number of wound complications?” Interestingly, for most of the 20 DMARDs or biologicals, being routinely administered, there are surprisingly few evidence-based recommendations for their perioperative use when complications occur [2, 9]. For example, in the case of methotrexate, when wound complications occur, the recommendation, based on the “expert opinion of a broad international panel of rheumatologists” is to continue administration [11]. National medical societies in France, the Netherlands, the US, UK and Japan, recommend that - concerning tumor-necrosis-factor alpha (TMF-α)- therapy should be substituted until wounds are healed

[12-15]. Based on this confusion the German Society for Orthopedics in Rheumatic-Diseases (DGORh) is conducting a pilot study, using data from its national registry, to answer the following questions:

- Can data in the DGORh national registry be suitable to develop accurate and relevant recommendations?
- What other risk factors, beside RA and medications, should be considered as it relates to wound disorders?

This report presents the methods used in this pilot-study and the preliminary results, from the first 1000 patients.

Methods and Material:

Risk adjustment

Based on rheumatology textbooks, published studies [2,15-19], and clinical experience of study group members, the following risk-factors were identified as being possible confounders as it relates to wound-disorders or non-unions in arthrodesis: diabetes mellitus, atherosclerosis, malignant tumors, cachexia due to HIV or other consuming diseases, corticoid therapy with more than 5 mg prednisolone-equivalent and/or administration for more than one year, current or history of bacterial infection in the wound or alio loco. In addition, other risk factors that were included were; sex, age, body mass-index (BMI), ASA's-classification, alcohol and smoking history.

In order to obtain a quicker overview of these possible risk-factors/possible confounders they were only considered in those patients who had wound disorders during the pilot-study.

Number and structure of centers involved in the pilot-study

A total number of twelve centers were included in the pilot-study (table 1).

Each center had an orthopedic surgeon with experience treating patients with inflammatory arthritic diseases. In order to have a representative cross section of the different types of provider's in Germany, different types of departments, which treat patients with rheumatic diseases, were asked to participate: hospitals specialized in rheumatology, university-based hospitals, departments whose focus was elective orthopedic surgery and departments that focus on treating trauma-patients.

Ethical approval:

Approval to conduct the study was obtained from the ethics-committee at Ruhr-University in Bochum (No.: 4138-11). The study was carried out in accordance with the Helsinki Declaration. All patients included in the study were asked and gave their written informed consent in an initial consent form. This form included, information about different types of rheumatic diseases, their onset, types of

medications administered to patients with rheumatic disease, details about medication regimens (continued or interrupted, estimated time for re-starting medication, etc.), and surgical treatments (date and type of surgery).

If a complication occurred, a second consent form was used, that included information about risk-factors, date and type of observed complication as well as indicated treatments.

Patients

Each patient suffering from an inflammatory-arthritis disease and getting surgical treatment in one of the centers was asked to participate in this study and included after written informed consent was given. No drop-outs / withdraws of consent occurred during this pilot study. The majority of the patients included in this pilot study (871 cases, 87%) suffered from RA, while 7.5% had a psoriatic arthritis, 2.8% suffered from a collagenosis and 1.8% from Bechterew's disease. Other rare diagnoses included not differentiated inflammatory-arthritis (four cases, 0.4%), Morbus Still (three cases, 0.3%) and Morbus Crohn (one case, 0.1%) (Figure1).

The median period of time from onset to the procedure leading to their inclusion in the study was 16 years, with an interquartile range (IQR) of 10-25 years, with a maximum of 64 years and a minimum of one year.

Statistical Methods

This article focuses on the methods and the adaption of the questionnaires for use in the registry and reports on the initial results from the first 1000 subjects included in the database.

Due to the inhomogeneous type of the surgical treatments and the medications used, as well as the limited number of observed complications, only descriptive statistical analysis were appropriate in this pilot study, however, analytic statistics of the confirmatory questions in midterm-outcome can be expected from the registry, which has started in the summer of 2014.

Medians, interquartile ranges, confidence intervals and significance (at 5%-level) for the incidence of wound complications in patients treated with immune-modulating medication, compared to those not treated, were computed using SPSS 22.0 for Windows™ (IBM Corporation, NY, USA).

Results:

Anti-inflammatory-drugs

More than 90% of patients (902) received pharmacological therapy, with 6% (60 patients) treated with corticosteroids as a monotherapy and 20% (197 patients) receiving a combination of DMARDS or biologicals and steroids. The majority 84% (840 patients) were treated with immune-modulating therapy based on DMARDS or biologicals, with 45% (453 patients) receiving methotrexate, either as a monotherapy (19%, 191 patients) or in combination with corticosteroids (11%, 109 patients) or

adalimumab (11%, 106 patients). Other common drugs were leflunomide in (18%, 179 patients) of which 7% (67 patients) received monotherapy, and etanercept (12%, 121 patients) of which 5% (47 patients) received monotherapy.

Over all more than half of all patients received monotherapy (51%, 507 patients), while 32% were treated with two different types of medication. Combinations of three (68 patients) or four different types of immune-modulating medications (2 patients) were rare and were reported in 7% and 0.2% respectively. The reported combinations are given in table 2.

Types of surgery

Nearly one third of all procedures can be categorized as bone and joint procedures: total joint replacements, arthrodeses and resection arthroplasty. Different types of synovectomies were performed in 18% of patients. Surgeries in the lower extremity were represented far more often (67%, 674 cases) than those in the upper extremities (26%, 262 cases). Only two patients with surgical treatment of the vertebral column were included (0.2%). The different types of surgical treatments are listed in table 3.

Complications occurred

Complications, summarized as “wound-disorders”, and infections occurred in 26 patients (2.6%) and were nearly equally contributed in the upper limbs, total hip- or knee-replacement, and foot and ankle surgeries. Twenty-one of these patients received pharmacological immune-modulating therapy, (interrupted perioperatively in 11 cases), while five of the patients did not receive a specific medication. 2.3% of patients with an immuno-modulating therapy had wound complaints, while 5.1% with no pharmacotherapy, due to their rheumatoid disease, experienced wound complications in the form of infections.

Deep infections, requiring revision surgery, occurred in nine patients; eight (0.9%) of which were patients treated with immune-modulating drugs, and one (0.1%) was not receiving medication.

Of the 26 patients with wound complications: 14 (54%) were being treated with corticosteroids for more than one year and nine patients (35%) were receiving doses greater than 5mg prednisolone-equivalent. Four patients (15%) had diabetes mellitus, two patients (8%) had vascular disease in the treated limb, two patients (8%) had carcinoma (none with cachexia) and one patient (4%) had a history of infection at the time of surgery. The average age of the patients with wound disorders/infections, at the time of surgery was 65 (IQR 49-72 minimum 14 maximum 78) years. The duration of the inflammatory-arthritic disease was 18 (IQR 10-29 minimum five maximum 46) years (95%-CI 11-27 years). Details for these 26 patients with wound complications/infections are given in table 4.

Discussion:

These initial results in this pilot study show, that wound complications occurred two times as often in patients not receiving immune-modulating medication, while deep infections were nearly equally distributed in patients receiving and not receiving drug therapy. This finding seems to be clinically relevant – even if there is no statistically significant difference by performing the fisher's exact test (p= 0.168) (figure 2). But due to the inhomogeneous group of surgical procedures, considerable variance of pharmacotherapy and the surprisingly low number of complications within the pilot-data it has to be interpreted with care.

With respect to the limited number of patients, the inhomogeneity in the types of surgeries and the pharmacotherapy received by the patients, analytic statistics cannot yet be performed on this initial set of data. These initial observations support the need to collect additional data that include risk factors, types of surgeries and pharmacotherapy in order to be able to formulate evidence-based recommendations for these patients.

This pilot study has helped to identify possible confounders, such as risk-factors and loss to follow-up due to missing patient identification, both important factors that must be taken into consideration as data collection moved forward.

The postulated risk-factors were found in patients with wound disorders, indicating, that these risk-factors will have to be considered as possible confounders in order to evaluate the influence of pharmacotherapy on wound complications. Based on this observation going forward these risk-factors have been included in the initial patient inclusion recording forms ("basic questionnaire"), This will

make it possible to perform risk-adjusted analyses combined with age, sex, BMI, ASA's classification, alcohol and smoking history, type and onset of rheumatic disease, in the real-time-registry (Figure 3). Taking these confounders into account, will help formulate more accurate and relevant preoperative recommendations related to the influence of pharmacotherapy in these patients.

The unexpected low number of patients with postoperative wound disorders and infection – compared to the considerably higher figure published in literature [10, 20, 21] – can be explained by the loss to follow-up for those patients with minor wound complications, treated with local therapy outside the hospital. These patients were not included in this pilot study because their patient ID was lost in the system as they received care both as ambulant and hospital-based patients. To remedy this a patient's pseudonym was generated based on non-changing patient data consisting of; date and location they were attended, place of birth - city and state -, Christian name and maiden name. This so called "salt-protected hash-code" ensures that, even the most complicated forms and between different institutions, patients can be linked to their individual data set helping to avoid a loss to follow-up in the real-time registry.

Finally, based on this pilot study additional data will be collected documenting in more detail the type of treatment wound disorders received and the final status of the wound complication, thus being able to distinguish between minor and major wound complications in the registry.

Limitations:

Due to the small number of patients with observed complications as well as due to the inhomogeneity in the different types of rheumatic diseases itself as well as the elective surgical treatments received by patients so far extended analytical statistics cannot be done. Thus so far no recommendations for the perioperative management of anti-inflammatory drugs but only tendencies can be derived from these first 1000 datasets.

Conclusion:

Besides age, sex, risk-factors, type and duration of the rheumatic disease, the administration of immune-modulating medications appears to impact wound complications. Due to the inhomogeneity in the disease itself and the treatments received by patients with rheumatic diseases it is difficult to develop standardized best-practice recommendations to optimize their care. Therefore, the creation of a large, comprehensive national registry that includes the most important and relevant variables that impact the care and outcomes of these patients is essential. This pilot study has helped to identify these variables and in doing so will contribute to improving the national registry so that its data can be used to formulate accurate and relevant recommendations for the care of this vulnerable patient population.

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References:

[1] Weiss R J, Stark A, Wick M C *et al.* Orthopaedic surgery of the lower limbs in 49, 802 rheumatoid arthritis patients: results from the Swedish National Inpatient Registry during 1987 to 2001. Ann Rheum Dis. 2006; 65: 335–341

[2] Weiss RJ, Ehlin A, Montgomery SM *et al.* Decrease of RA-related orthopaedic surgery of the upper limbs between 1998 and 2004: data from 54,579 Swedish RA inpatients.
Rheumatology (Oxford). 2008; 47:491-494

[3] da Silva E, Doran MF, Crowson CS *et al.* Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment.
Arthritis Rheum. 2003; 49: 216–220

[4] Shourt CA, Crowson CS, Gabriel SE *et al.*Orthopedic Surgery Among Patients with Rheumatoid Arthritis 1980–2007: a population-based study focused on surgery rates, sex, and mortality. J Rheumatol. 2012; 39: 481-485. doi: 10.3899/jrheum.111056.

[5] Grant HL, Ward M, Changes in the rates of joint surgery among patients with Rheumatoid Arthritis in California, 1983–2007. Ann Rheum Dis. 2010; 69: 868–871.

[6] Momohara S, Inoue E, Ikari K *et al.* Decrease in orthopaedic operations, including total joint replacements, in patients with rheumatoid arthritis between 2001 and 2007: data from Japanese outpatients in a single institute-based large observational cohort (IORRA). Ann Rheum Dis. 2010; 69:312-313.

[7] Krüger K, Albrecht K, Rehart S *et al.* [Recommendations of the German Society for Rheumatology on the perioperative approach under therapy with DMARDs and biologicals in inflammatory rheumatic diseases.] Z Rheumatol. 2014; 73: 77-84. doi: 10.1007/s00393-013-1301-z.

[8] Louie GH, Ward MM, Changes in the rates of joint surgery among patients with Rheumatoid Arthritis in California, 1983–2007. Ann Rheum Dis. 2010 May; 69(5):868-71. doi: 10.1136/ard.2009.112474.

[9] Gaubitz M. [Biologicals 2012.] Orthopäde. 2012; 41: 526-532; doi 10.1007/s00132-012-1931-x

[10] Welcker M, Sternad P, Krüger K. Aktuelle Empfehlungen der Deutschen Gesellschaft für Rheumatologie - Peroperatives Management klassischer und neuer Antirheumatika, Orthopädie & Rheuma. 2014; 17: 24-29

[11] Visser K, Katchamart W, Loza E *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E-Initiative. Ann Rheum Dis. 2009; 68: 1086-1093. doi: 10.1136/ard.2008.094474.

[12] Heldmann F, Dybowski F, Baraliakos X *et al.* Perioperativer Umgang mit Biologika bei rheumatoider Arthritis. Z Rheumatol. 2011; 70: 14-20. doi: 10.1007/s00393-010-0680-7.

[13] Goh L, Laversuch C, Samanta A. Should anti-TNF therapy be discontinued in rheumatoid arthritis patients undergoing elective orthopaedic surgery? A systematic review of the evidence. Rheumatol Int. 2012; 32:5-13. doi: 10.1007/s00296-011-2040-6.

[14] Pieringer H , Danninger K, Tzaribachev N *et al.* Patients with arthritis undergoing surgery: how should we manage tumour necrosis factor blocking agents perioperatively?-A systematic literature review 14 of 1249 -2011. Yonsei Med J. 2013; 54: 253–257. doi: 10.3349/ymj.2013.54.1.253.

[15] Krüger K. Perioperative medikamentöse Therapie rheumatischer Erkrankungen – Aktuelle Empfehlung der DGRh. Arthritis Rheum. 2014; 60: 158-162

[16] Ravi B, Escott B, Shah PS *et al.* A systematic review and meta-analysis comparing complications following total joint arthroplasty for rheumatoidarthritis versus for osteoarthritis. 40 Studies 1990-2011. Arthritis Rheum. 2012; 64: 3839-3849

[17] Den Broeder AA, Creemers MC, Fransen J *et al.* Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol. 2007; 34: 689-695

[18] Strangfeld A, Eveslage M, Schneider M *et al.* Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011; 70: 1914-1920

[19] Combe B, Landewe R, Lukas C *et al.* EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for international Clinical Sudies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007; 66: 34-45

[20] Doran MF, Crowson CS, Pond GR *et al.* Frequency of infection in patients with rheumatoid arthritis compared with controls: a population based study. Arthritis Rheum. 2002; 46: 2287-2293

[21] Rehart S, Petak N. [Modern disease modifying drugs in rheumatoid arthritis in the perioperative period. Patients with rheumatic diseases under therapy with methotrexate, leflunomide or TNF-alpha blockers in the perioperative period.] Akt Rheumatol. 2007; 32: 74-77

Tables:

Orthopedic Hospital Harthausen; Bad Aibling
Department of Rheuma-Surgery, Kreuznacher Diakonie; Bad Kreuznach
Department of Rheuma-Surgery, Red Cross Hospital; Bremen
Department of Rheuma-Orthopedics, St. Elisabeth-Hospital, University hospital (Ruhr University-Bochum); Bochum
Orthopedics, Traumatology and Rheuma-Orthopedics Clinic, Katholic Hospital Dortmund-West; Dortmund
Orthopedics and Traumatology Clinic, Agaplesion Markus hospital; Frankfurt / Main
Orthopedics, Traumatology and Rheuma-Orthopedics Clinic, Westpfalzclinic Kusel; Kusel
Orthopedic and Policlinic, University hospital Leipzig; Leipzig
Rheuma-ortphopedics, Rheinisches Center for Rheumatology Meerbusch; Meerbusch
Orthopedic Department, Collm-Clinic Oschatz; Oschatz
Rheuma-Orthopedics, North-western Center for Rheumatology St. Josef-Stift Sendenhorst; Sendenhorst

Table 1: Departments participating in the pilot-study.

	Aldalimumab	Ertanecept	Tocilizumab	Rituximab	Infliximab	Abatecept	Golimumab	MTX	Leflunomide	Azathioprine	Sulfasalazine	Hydroxy-cloroquine	Others	Corticoids	Total:
Aldalimumab	28	0	0	0	0	0	0	106	6	1	2	1	4	0	**68**
Ertanecept	0	47	0	0	0	0	0	41	17	1	4	3	1	24	**121**
Tocilizumab	0	0	12	0	0	0	0	4	1	0	2	0	0	3	**20**
Rituximab	0	0	0	16	0	0	0	11	2	0	2	2	0	6	**35**
Infliximab	0	0	0	0	3	0	0	5	0	0	1	0	0	2	**9**
Abatecept	0	0	0	0	0	3	0	6	2	0	0	1	0	2	**9**
Golimumab	0	0	0	0	0	0	3	7	0	0	0	0	0	6	**15**
MTX	106	41	4	11	5	6	7	191	43	2	31	24	10	109	**453**
Leflunomide	6	17	1	2	0	2	0	43	67	1	15	5	5	40	**179**
Azathioprine	1	1	0	0	0	0	0	2	1	10	0	1	0	5	**18**
Sulfasalazine	2	4	2	2	1	0	0	31	15	0	34	8	0	19	**99**
Hydroxy-cloroquine	1	3	0	2	0	1	0	24	5	1	8	11	1	22	**57**
Others	4	1	0	0	0	0	0	10	5	0	0	1	10	1	**32**
Corticoids	**6**	**24**	**3**	**6**	**2**	**2**	**6**	**109**	**40**	**5**	**19**	**22**	**1**	**60**	**253**

Table 2: Pharmacological therapy: steroids, DMARDs, Biologicals and their combinations as reported. MTX = Metothrexate.

	Teno-synovectomy	Synovectomy	Fusion or resections-arthroplasty	Total joint replacement	Others	Total:
Vertebra column			3	1	2	**6**
Shoulder	7	8	6	17		**38**
Elbow	1	14	7	6	5	**33**
Wrist		26	55	2	11	**94**
Flexor tendons (hand)	12					**12**
Extensor tendons (hand)	19					**19**
MCP-joints		5	9	17	1	**32**
DIP-/PIP-joints (hand)		4	19	4	7	**34**
Hip			3	148		**151**
Knee	1	56	4	175	4	**240**
Ankle joint	4	4	21	9	5	**43**
Subtalar joint	2	1	27		2	**32**
Toes	3	9	167	1	14	**194**
Tendons foot	6		3		5	**14**
Others					58	**58**
Total:	**55**	**127**	**324**	**380**	**114**	**1000**

Table 3: Addressed areas and kind of surgery performed in the 1000 pilot-patients, MCP-joints = metacarpo-phalangeal joints, DIP-/PIP-joints = distal interphalangeal / proximal interphalangeal joints.

Patient	Diagnosis	Immune modulating drugs	Medication interrupted preoperatively	Addressed area	Procedure	Age at surgical treatment / years	Duration of rheumatic disease / years	Used immune modulating drug	Medication combined with	Duration of immune modulating therapy / month
1		yes	yes	MCP II-III		64		Rituximab	Methotrexate	
2	R.A.	yes		MCP II-IV		65	9	Tocilizumab		18
3	R.A.	yes	yes	wrist	removal plate/screws	66	11	Leflunomide	Methotrexate	36
4	R.A.	no		forearm	osteosynthesis	74	28		Prednisolone - 5mg/d	
5	R.A.	yes	yes	elbow	bursectomy	54	30	Leflunomide	Diclofenac, Corticosteroid	24
6	R.A.	yes		elbow	synovectomy + arthroplasty	72	40	Methotrexate	Corticosteroid	168
7	R.A.	yes	yes	elbow	synovectomy	43	20	Methotrexate	Sulfasalazine + Corticosteroid	12
8	R.A.	yes	yes	hip	synovectomy	43	5	Eternacept	Prednisolone	
9	R.A.	yes		hip	total hip replacement	65	15	Sulfasalazine	Methotrexate	
10	R.A.	no		hip	total hip replacement	66	46		Corticosteroid	
11	R.A.	no		hip	total hip replacement	69	16		Corticosteroid, Phenprocoumone	
12	psoriatic arthritis	yes		hip	total hip replacement	58	5	Leflunomide		48
13	R.A.	no		knee	total hip replacement	43	27			
14	R.A.	no		knee	total hip replacement	75				
15	R.A.	yes		knee	total hip replacement	14		Methotrexate		
16	R.A.	yes		knee	bursectomy	52	7	Tocilizumab, Methotrexate	Acemetacine	13
17	R.A.	yes	yes	knee	open synovectomie	48	18	Leflunomide		12
18	M. Still	yes		ankle joint	ankle fusion	70	5	Ciclosporine A		60
19	R.A.	yes		ankle joint	removal plate/screws	73		Leflunomide		
20	R.A.	yes		foot	osteosynthesis			Leflunomide	Corticosteroid	5
21	R.A.	yes	yes	foot		73	27	Leflunomide		120

22	R.A.	yes	yes	MTP	fusion	45	34	Adalimumab		49
23	R.A.	yes	yes	MTP	fusion	51	11	Leflunomide		24
24	R.A.	yes	yes	Hallux	new total joint replacement after infection	65	25	Leflunomide		61
25	R.A.	yes	yes	Hallux	fusion	72	31	Adalimumab		60
26	R.A.	yes		Hallux	fusion	78	12	Methotrexate	Hydroxycloroquine + Corticosteroid	36

359

Patient	Wound disorder stitches in situ > 14 days	Wound disorder – secondary suture	Seroma	Revision due to seroma	Deep infection with revision	Risk factor Cortico-steroids >1 year	Risk factor Corticosteroid > 5 mg perdnisolone-equivalent	Risk factor diabetes mellitus	Risk factor chronical vascular disease	Carcinoma	HIV / cachexia	History of infection in addressed area	Infection alio loco
1					1				1				
2					1	1							
3					1	1	1						
4							1						
5		1				1	1	1		1			
6			1										
7		1				1	1						
8			1			1	1						
9	1												
10						1							
11	1												
12		1											
13		1											
14					1	1	1	1	1			1	1
15													
16				1		1	1						
17					1	1	1						
18	1					1							
19		1				1		1					
20	1					1							
21		1											
22					1					1			
23	1												
24					1			1					

25					1	1	1						
26					1	1							

Table 4: Patients with wound disorders/infections postoperatively. Median age at surgical treatment 64.9 years (IQR 48.8-72.0; min. 13.5; max. 78.0). Median duration of rheumatic disease, 20.0 years (IQR 11.5-29.0; min. 5.0; max. 46.0). Wound disorders were observed more often in patients not receiving immune modulating medication. The percentage of patients with infection was slightly higher in those not receiving immune modulating medications (0.9 vs. 1%). R.A. = rheumatoid arthritis.

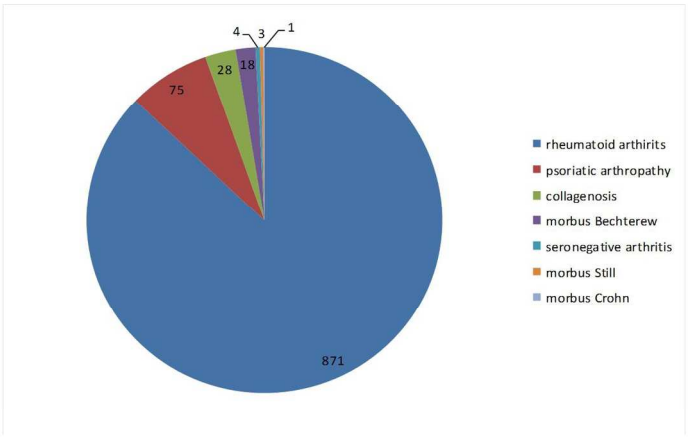

Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients

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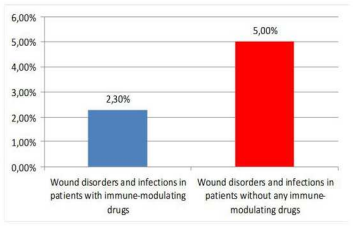

	No wound complications	Wound complications	
No immune-modulating drugs	n= 93 (94.9%)	n= 5 (5.1%)	n= 98
Immune-modulating drugs	n= 881 (97.7%)	n= 21 (2.3%)	n= 902
	n= 974	n= 26	n=1000

Figure 2: Wound disorders and infections occurred more than two times as often as in patients not receiving immune-modulating medication, compared to treated patients. There was no statistical significance (Fisher's exact test, p= 0.168, 5%-level) in the occurrence of wound complications between patients treated with immune-modulating drugs and those not treated.

Figure 2: Wound disorders and infections occurred more than two times as often as in patients not receiving immune-modulating medication, compared to treated patients. There was no statistical significance (Fisher's exact test, p= 0.168, 5%-level) in the occurrence of wound complications between patients treated with immune-modulating drugs and those not treated.

297x209mm (150 x 150 DPI)

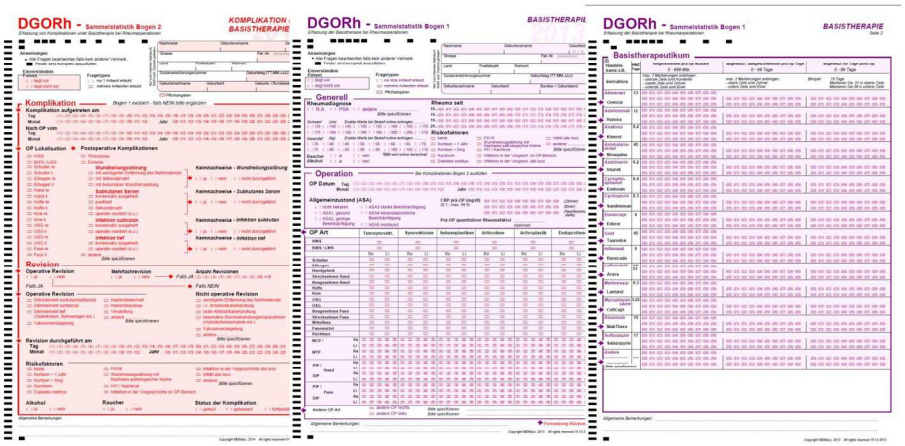

Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of the register.

297x209mm (150 x 150 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,4,9
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4/5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9/10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10/11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10/11*
Bias	9	Describe any efforts to address potential sources of bias	10/11
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	---
		(*c*) Explain how missing data were addressed	---
		(*d*) If applicable, explain how loss to follow-up was addressed	---
		(*e*) Describe any sensitivity analyses	---
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	---
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	---
		(c) Summarise follow-up time (eg, average and total amount)	---
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	---
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	---
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	---
Discussion			
Key results	18	Summarise key results with reference to study objectives	15/16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pilot study for the Registry of Complications in Rheumatic-Diseases (DGORh) from the German Society of Surgery– Evaluation of methods and data from the first 1000 patients

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Complete List of Authors:	Kostuj, Tanja; Katholisches Klinikum Bochum Sankt Josef-Hospital, Klinik für Orthopädie und Unfallchirurgie Rehart, Stefan; Agaplesion Markus Hospital, Teaching Hospital of Johann Wolfgang-Goethe University, Clinic for orthopedics and traumatology Matta-Hurtado, Ronald; Catholic Hospital Dortmund-West, Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic Biehl, Christoph; Universitätsklinikum Giessen und Marburg , Klinik für Hand- Wiederherstellungs- und Unfallchirurgie Willburger, Roland; Katholisches Klinikum Bochum Sankt Elisabeth-Hospital, Department of Rheumatic-Orthopedics Schmidt, Klaus; Catholic Hospital Dortmund-West, Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Public health, Patient-centred medicine, Rheumatology, Pharmacology and therapeutics
Keywords:	Inflammatory-arthritis, immune-modulating therapy, disease modifying anti-rheumatic drugs, biologicals, wound complications, registry

Pilot study for the Registry of Complications in Rheumatic-Diseases (DGORh) from the German Society of Surgery– Evaluation of methods and data from the first 1000 patients

Dr. med. Tanja Kostuj[1,2], - **Corresponding author**
[1]Catholic Hospital Bochum, St. Josefs-Hospital, University hospital of Ruhr-University-Bochum, Department of Orthopedics and traumatology, Gudrunstraße 56, 44791 Bochum, Germany
[2] Institute for Medical Biometry and Epidemiology, University of Witten / Herdecke, Alfred-Herrhausen-Straße 50, 58448 Witten, Germany
E-mail: tanja.kostuj@t-online.de; Phone: +49 170 3835773

Prof Dr. med. Stefan Rehart
Agaplesion Markus Hospital, Teaching Hospital of Johann Wolfgang-Goethe University, Clinic for orthopedics and traumatology, Wilhelm-Epstein-Str. 4, 60431 Frankfurt am Main, Germany

Mr. Ronald Matta-Hurtado,
Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic, Catholic Hospital Dortmund-West, Zollernstraße 40, 44379 Dortmund, Germany

Dr. med. Christoph Biehl,
Orthopedic and Rheumaorthopedic Clinic - Diakonie hospital, Ringstraße 64, 55543 Bad Kreuznach, Germany

Prof. Dr. med. Roland E. Willburger
Catholic Hospital Bochum, St. Elisabeth-Hospital, University hospital of Ruhr-University-Bochum, Department of Rheumatic-Orthopedics, Bleichestraße 15, 44787 Bochum, Germany

PD Dr. med. Klaus Schmidt
Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic, Catholic Hospital Dortmund-West, Zollernstraße 40, 44379 Dortmund, Germany

On behalf of the study-group "complication-register of the DGORh"

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The authors declare the following potential conflicts of interests:

TK: Pharmaceutical or medical device companies may be involved in some of the included studies however the details are unknown to the author.

SR: Has received speaker fees from the companies Abbvie / Grünenthal / MSD / implantcast / medac

CB: Has received speaker fees from the companies Link and Abbot

The remaining authors declare no conflicts of interest.

The authors declare the following contribution of authorship:

TK: writing of manuscript, data analysis, modification of questionnaires for real time registry

SR: design of pilot questionnaires, review of questionnaires for real time registry, review of manuscript

RMH: data-collection and data analysis

CB: providing of references, review of manuscript

REW: providing of references, approval ethics committee

KS: design of pilot questionnaires, data-collection, review of manuscript

Further members from the pilot-study group are (listed alphabetically):

Dr. med. Ingo Arnold, Red Cross hospital, Bremen, Department of Rheumatology and Orthopedics

Dr. med. Ludwig Bause, St. Josef-Stift Sendenhorst, Department of Orthopedic Rheumatology

Dr. med Harald Dinges, Westpfalzklinikum Kusel, Clinic of Orthopedics, Traumatology and Rheumatic Orthopedics

PD Dr. med. Thomas Pauly, Rheinisches Rheumazentrum St. Elisabeth-Hospital, Department of Orthopedic Surgery/Rheumatology, Meerbusch-Lank

Dr. med. Stefan Schill, Joint-center, Rosenheim GmbH and Harthausen Bad Aibling Clinic

Dr. med. Roger Scholz, Department of Orthopedics, Collm-Clinic Oschatz

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Data sharing:

No additionally data are available.

Abstract:

Objective:

Most patients suffering with rheumatic diseases, that undergo surgical treatment, are receiving immune-modulating therapy. To determine if these medications affect their outcomes a national registry was established in Germany by the German Society of Surgery. Data from the first 1000 patients were used in a pilot study to identify relevant co-risk factors and to determine if such a registry is suitable for developing accurate and relevant recommendations.

Design and participants:

Data was collected from patients undergoing surgical treatments with their written consent. A second consent form was used, if a complication occurred. During this pilot study risk-factors were considered only in patients with complications in order to obtain a quicker overview.

In this pilot study only descriptive statistical analysis were employed due to inhomogeneous data regarding the surgery and the medications they received, as well as the limited number of observed complications. Analytic statistics will be performed to confirm the questions asked in a future outcome study.

Results:

Complications, distributed equally among the different types of surgeries, occurred in 26 patients. Twenty one of these patients were receiving immune-modulating therapy and 5 were not. Infections were observed in 2.3% of patients receiving, and in 5.1% not receiving immunosuppression.

Conclusions:

Due to the inhomogeneity in the diseases and the treatments received by the patients in this pilot study it is difficult to develop standardized best-practice recommendations to optimize their care. Therefore, such a national registry has to include the most important and relevant variables that impact the care and outcomes of these patients to be suitable to develop accurate and relevant recommendations.

Article summary

Strengths and limitations of the study:

- Data from 1000 patients, from twelve centers, with different structures were available to test, if a register is suited to analyze the possible impact of immune-modulating medications on wound complications to adapt the questionnaires for the use in the “real time” register.
- Due to the small number of patients with complications, the inhomogeneity in the different types of rheumatic diseases, and the treatments received by patients extended statistical analyses could not be performed on this first 1000 datasets and only tendencies could be derived.

Keywords:

Inflammatory-arthritis, immune-modulating therapy, disease modifying anti-rheumatic drugs, biologicals, wound complications, registry

Main text:

Introduction:

Rheumatoid arthritis (RA) has a prevalence of approximately 1% in Western Europe and the United States, with a cumulative prevalence for all types of rheumatic diseases being 2%, while the incidence of inflammatory-arthritis diseases in Germany is 3% (about 2.5 billion patients). About 25 years ago approximately 25% of these patients underwent total joint replacement, yet recently the number of these procedures as well as the number of surgical treatments in general in RA patients has decreased in Europe, the United States and Japan [1-8]. This trend could be the result of the recently introduced, very early “treat-to-target“-treatment and/or the use of modern anti-inflammatory medications [9], which have increased during the same time period. Actually, about 70% of the patients with RA are receiving, so called, disease modifying anti-rheumatic drugs (DMARDs), while about 20% are treated with biologicals such as immune-modulating therapy [10]. This means that most of these patients, undergoing surgical treatments, are receiving immune-modulating therapy, for their inflammatory arthritic diseases. However, it remains unclear if immune-modulating medications affect the outcomes of these surgical treatments or if they contribute to an increase in the number of wound complications.

Interestingly, for most of the 20 DMARDs or biologicals, being routinely administered, there are surprisingly few evidence-based recommendations for their perioperative use when complications occur [2, 9]. For example, in the case of methotrexate, the recommendation to continue administration was based on the expert opinion of a broad international panel of rheumatologists[11]. National medical societies in France, the Netherlands, the US, UK and Japan, recommend that - concerning tumor-necrosis-factor alpha (TMF-α)- therapy should be substituted until wounds are healed [12-15].

Based on this confusion the German Society for Orthopedics in Rheumatic-Diseases (DGORh) established a national registry that included surgical patients suffering with inflammatory-arthritis disease. The aim of this pilot study was to determine if data from this national registry could be used to identify risk factors to develop accurate and relevant treatment recommendations. For example in RA patients receiving medications who have subcutaneous or deep wound infections.

This report presents the methods used in this pilot-study and the preliminary results, from the first 1000 patients.

Methods and Material:

Risk adjustment

Based on rheumatology textbooks, published studies [2,15-19], and clinical experience of study group members, the following risk-factors were identified as being possible confounders as it relates to wound-disorders or non-unions in arthrodesis: diabetes mellitus, atherosclerosis, malignant tumors, cachexia due to HIV or other consuming diseases, corticoid therapy with more than 5 mg prednisolone-equivalent and/or administration for more than one year, current or history of bacterial infection in the wound or alio loco. In addition, other risk factors that were included were; sex, age, body mass-index (BMI), ASA's-classification, alcohol and smoking history.

In order to obtain a quicker overview of these possible risk-factors/possible confounders they were only considered in those patients who had wound disorders during the pilot-study. This might cause a bias in statistical analyses and interpretation of data concerning wound disorders, seroma, and infection however we accept this, since the

main focus of this pilot study was to see if risk factors are present, and did not expect to have enough data to perform statistical analyses. In the actual registry data this type of bias would not be possible since all risk factors and confounders must to be reported in the basic form, in order to obtain valid statistical data.

Number and structure of centers involved in the pilot-study

A total number of twelve centers were included in the pilot-study (table 1).

Each center had an orthopedic surgeon with experience treating patients with inflammatory arthritic diseases. In order to have a representative cross section of the different types of provider's in Germany, different types of departments, which treat patients with rheumatic diseases, were asked to participate: hospitals specialized in rheumatology, university-based hospitals, departments whose focus was elective orthopedic surgery and departments that focus on treating trauma-patients.

Ethical approval:

Approval to conduct the study was obtained from the ethics-committee at Ruhr-University in Bochum (No.: 4138-11). The study was carried out in accordance with the Helsinki Declaration. All patients included in the study were invited and gave their written informed consent in an initial consent form. This form, administered by the attending physician, included information about different types of rheumatic diseases, their onset, types of medications administered to patients with rheumatic disease, details about medication regimens (continued or interrupted, estimated time for re-starting medication, etc.), and surgical treatments (date and type of surgery)

If a complication occurred, a second consent form was used, that included information about risk factors, date, and type of observed complication, as well as indicated treatments. This pilot study focused on the following complications and treatments: wound disorders and skin necrosis (delayed removal of stiches, type local treatment, suture), seroma (evacuation, local suture, re-operation), subcutaneous infections (CDC A1) (with i.v. antibiotics treatment or re-operation), deep infections (CDC A2 + A3) (i.v. antibiotics and re-operation). Minor complications, that did not result in an appointment at the outpatient department or to readmission, but instead were treated in a doctor's office were not taken into account.

Patients

Each patient suffering from inflammatory-arthritis disease and receiving surgical treatment in one of the centers was asked to participate in this study and was included after written informed consent was given. Inflammatory-arthritis and elective surgical treatment in the musculoskeletal system was the only inclusion criteria. No exclusion criteria were defined. No drop-outs / withdraws of consent occurred during this pilot study. The majority of the patients included in this pilot study (871 cases, 87%) suffered from RA, while 7.5% had a psoriatic arthritis, 2.8% suffered from a collagenosis and 1.8% from ankylosing spondylosis. Other rare diagnoses included not differentiated inflammatory-arthritis (four cases, 0.4%), Still's disease (three cases, 0.3%) and Crohn's disease (one case, 0.1%) (Figure1).

The median period of time from onset to the procedure leading to their inclusion in the study was 16 years, with an interquartile range (IQR) of 10-25 years, with a maximum of 64 years and a minimum of one year.

Statistical Methods

This article focuses on the methods and the adaption of the questionnaires for use in the registry and reports on the initial results from the first 1000 subjects included in the database.

Due to the inhomogeneous type of the surgical treatments and the medications used, as well as the limited number of observed complications, only descriptive statistical analysis were appropriate in this pilot study, however, analytic statistics of the confirmatory questions in midterm-outcome can be expected from the registry, which has started in the summer of 2014.

Medians, interquartile ranges, confidence intervals and significance (at 5%-level) for the incidence of wound complications in patients treated with immune-modulating medication, compared to those not treated, were computed using SPSS 22.0 for Windows™ (IBM Corporation, NY, USA).

Results:

Anti-inflammatory-drugs

More than 90% of patients (902) received pharmacological therapy, with 6% (60 patients) treated with corticosteroids as a monotherapy and 20% (197 patients) receiving a combination of DMARDS or biologicals and steroids. The majority 84% (840 patients) were treated with immune-modulating therapy based on DMARDS or biologicals, with 45% (453 patients) receiving methotrexate, either as a monotherapy (19%, 191 patients) or in combination with corticosteroids (11%, 109 patients) or adalimumab (11%, 106 patients). Other common drugs were leflunomide in (18%, 179

patients) of which 7% (67 patients) received monotherapy, and etanercept (12%, 121 patients) of which 5% (47 patients) received monotherapy.

Overall more than half of all patients received monotherapy (51%, 507 patients), while 32% were treated with two different types of medication. Combinations of three (68 patients) or four different types of immune-modulating medications (2 patients) were rare and were reported in 7% and 0.2% respectively. The reported combinations are given in table 2.

Types of surgery

Nearly one third of all procedures can be categorized as bone and joint procedures: total joint replacements, arthrodeses and resection arthroplasty. Different types of synovectomies were performed in 18% of patients. Surgeries in the lower extremity were represented far more often (67%, 674 cases) than those in the upper extremities (26%, 262 cases). Only two patients with surgical treatment of the vertebral column were included (0.2%). The different types of surgical treatments are listed in table 3.

Complications occurred

Complications, summarized as “wound-disorders”, and infections occurred in 26 patients (2.6%) and were nearly equally contributed in the upper limbs, total hip- or knee-replacement, and foot and ankle surgeries. Twenty-one of these patients received pharmacological immune-modulating therapy, (interrupted perioperatively in 11 cases), while five of the patients did not receive a specific medication. 2.3% of patients with an immuno-modulating therapy had wound complaints, while 5.1% with no

pharmacotherapy, due to their rheumatoid disease, experienced wound complications in the form of infections.

Deep infections, requiring revision surgery, occurred in nine patients; eight (0.9%) of which were patients treated with immune-modulating drugs, and one (0.1%) was not receiving medication.

Of the 26 patients with wound complications: 14 (54%) were being treated with corticosteroids for more than one year and nine patients (35%) were receiving doses greater than 5mg prednisolone-equivalent. Four patients (15%) had diabetes mellitus, two patients (8%) had vascular disease in the treated limb, two patients (8%) had carcinoma (none with cachexia) and one patient (4%) had a history of infection at the time of surgery. The average age of the patients with wound disorders/infections, at the time of surgery was 65 (IQR 49-72 minimum 14 maximum 78) years. The duration of the inflammatory-arthritic disease was 18 (IQR 10-29 minimum five maximum 46) years (95%-CI 11-27 years). Details for these 26 patients with wound complications/infections are given in table 4.

Discussion:

These initial results in this pilot study show, that wound complications occurred two times as often in patients not receiving immune-modulating medication, while deep infections were nearly equally distributed in patients receiving and not receiving drug therapy. This finding seems to be clinically relevant – even if there is no statistically significant difference by performing the fisher's exact test (p= 0.168) (figure 2). But due to the inhomogeneous group of surgical procedures, considerable variance of

pharmacotherapy and the surprisingly low number of complications within the pilot-data it has to be interpreted with care.

With respect to the limited number of patients, the inhomogeneity in the types of surgeries and the pharmacotherapy received by the patients, analytic statistics cannot yet be performed on this initial set of data. These initial observations support the need to collect additional data that include risk factors, types of surgeries and pharmacotherapy in order to be able to formulate evidence-based recommendations for these patients.

This pilot study has helped to identify possible confounders, such as risk-factors and loss to follow-up due to missing patient identification, both important factors that must be taken into consideration as data collection moved forward.

The postulated risk-factors were found in patients with wound disorders, indicating, that these risk-factors will have to be considered as possible confounders in order to evaluate the influence of pharmacotherapy on wound complications. Based on this observation going forward these risk-factors have been included in the initial patient inclusion recording forms (“basic questionnaire”), This will make it possible to perform risk-adjusted analyses combined with age, sex, BMI, ASA’s classification, alcohol and smoking history, type and onset of rheumatic disease, in the real-time-registry (Figure 3). Taking these confounders into account, will help formulate more accurate and relevant preoperative recommendations related to the influence of pharmacotherapy in these patients.

The unexpected low number of patients with postoperative wound disorders and infection – compared to the considerably higher figure published in literature [10, 20, 21] – can be explained by the loss to follow-up for those patients with minor wound

complications, treated with local therapy outside the hospital. These patients were not included in this study because the ID assigned to them their respective hospitals would not make follow up possible as they received care anywhere else. To remedy this a patient's pseudonym was generated based on non-changing patient data consisting of; date and location they were attended, place of birth -city and state -, Christian name and maiden name. This so called "salt-protected hash-code" ensures that, even the most complicated forms and between different institutions, patients can be linked to their individual data set helping to avoid a loss to follow-up in the real-time registry.

Finally, based on this pilot study additional data will be collected documenting in more detail the type of treatment wound disorders received and the final status of the wound complication, thus being able to distinguish between minor and major wound complications in the registry.

Limitations:

Due to the small number of patients with observed complications as well as due to the inhomogeneity in the different types of rheumatic diseases itself as well as the elective surgical treatments received by patients so far extended analytical statistics cannot be done. Thus so far no recommendations for the perioperative management of anti-inflammatory drugs but only tendencies can be derived from these first 1000 datasets.

In the actual registry, analysis of data reported in high volumes, like monotherapy and single surgeries will be considered first line, while those occurring in low-volumes like multiple surgeries or combinations of medication will be designated second line and will be analyzed taking the first line into consideration.

Conclusion:

Besides age, sex, risk-factors, type and duration of the rheumatic disease, the administration of immune-modulating medications appears to impact wound complications. Due to the inhomogeneity in the disease itself and the treatments received by patients with rheumatic diseases it is difficult to develop standardized best-practice recommendations to optimize their care. Therefore, the creation of a large, comprehensive national registry that includes the most important and relevant variables that impact the care and outcomes of these patients is essential. This pilot study has helped to identify these variables and in doing so will contribute to improving the national registry so that its data can be used to formulate accurate and relevant recommendations for the care of this vulnerable patient population.

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Results from 873 pilot study patients were presented as a poster at the GMDS (German Society for Medical computer science, Biometry and Epidemiology)-Congress 2014 in Göttingen / Germany

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References:

[1] Weiss R J, Stark A, Wick M C *et al.* Orthopaedic surgery of the lower limbs in 49, 802 rheumatoid arthritis patients: results from the Swedish National Inpatient Registry during 1987 to 2001. Ann Rheum Dis. 2006; 65: 335–341

[2] Weiss RJ, Ehlin A, Montgomery SM *et al.* Decrease of RA-related orthopaedic surgery of the upper limbs between 1998 and 2004: data from 54,579 Swedish RA inpatients.
Rheumatology (Oxford). 2008; 47:491-494

[3] da Silva E, Doran MF, Crowson CS *et al.* Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment.
Arthritis Rheum. 2003; 49: 216–220

[4] Shourt CA, Crowson CS, Gabriel SE *et al.*Orthopedic Surgery Among Patients with Rheumatoid Arthritis 1980–2007: a population-based study focused on surgery rates, sex, and mortality. J Rheumatol. 2012; 39: 481-485. doi: 10.3899/jrheum.111056.

[5] Grant HL, Ward M, Changes in the rates of joint surgery among patients with Rheumatoid Arthritis in California, 1983–2007.
Ann Rheum Dis. 2010; 69: 868–871.

[6] Momohara S, Inoue E, Ikari K *et al.* Decrease in orthopaedic operations, including total joint replacements, in patients with rheumatoid arthritis between 2001 and 2007: data from Japanese outpatients in a single institute-based large observational cohort (IORRA). Ann Rheum Dis. 2010; 69:312-313.

[7] Krüger K, Albrecht K, Rehart S *et al.* [Recommendations of the German Society for Rheumatology on the perioperative approach under therapy with DMARDs and biologicals in inflammatory rheumatic diseases.] Z Rheumatol. 2014; 73: 77-84. doi: 10.1007/s00393-013-1301-z.

[8] Louie GH, Ward MM, Changes in the rates of joint surgery among patients with Rheumatoid Arthritis in California, 1983–2007. Ann Rheum Dis. 2010 May; 69(5):868-71. doi: 10.1136/ard.2009.112474.

[9] Gaubitz M. [Biologicals 2012.] Orthopäde. 2012; 41: 526-532; doi 10.1007/s00132-012-1931-x

[10] Welcker M, Sternad P, Krüger K. Aktuelle Empfehlungen der Deutschen Gesellschaft für Rheumatologie - Peroperatives Management klassischer und neuer Antirheumatika, Orthopädie & Rheuma. 2014; 17: 24-29

[11] Visser K, Katchamart W, Loza E *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E-Initiative. Ann Rheum Dis. 2009; 68: 1086-1093. doi: 10.1136/ard.2008.094474.

[12] Heldmann F, Dybowski F, Baraliakos X *et al.* Perioperativer Umgang mit Biologika bei rheumatoider Arthritis. Z Rheumatol. 2011; 70: 14-20. doi: 10.1007/s00393-010-0680-7.

[13] Goh L, Laversuch C, Samanta A. Should anti-TNF therapy be discontinued in rheumatoid arthritis patients undergoing elective orthopaedic surgery? A systematic review of the evidence. Rheumatol Int. 2012; 32:5-13. doi: 10.1007/s00296-011-2040-6.

[14] Pieringer H , Danninger K, Tzaribachev N *et al.* Patients with arthritis undergoing surgery: how should we manage tumour necrosis factor blocking agents perioperatively?-A systematic literature review 14 of 1249 -2011. Yonsei Med J. 2013; 54: 253–257. doi: 10.3349/ymj.2013.54.1.253.

[15] Krüger K. Perioperative medikamentöse Therapie rheumatischer Erkrankungen – Aktuelle Empfehlung der DGRh. Arthritis Rheum. 2014; 60: 158-162

[16] Ravi B, Escott B, Shah PS *et al.* A systematic review and meta-analysis comparing complications following total joint arthroplasty for rheumatoidarthritis versus for osteoarthritis. 40 Studies 1990-2011. Arthritis Rheum. 2012; 64: 3839-3849

[17] Den Broeder AA, Creemers MC, Fransen J *et al.* Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol. 2007; 34: 689-695

[18] Strangfeld A, Eveslage M, Schneider M *et al.* Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011; 70: 1914-1920

[19] Combe B, Landewe R, Lukas C *et al.* EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for international Clinical Sudies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007; 66: 34-45

[20] Doran MF, Crowson CS, Pond GR *et al.* Frequency of infection in patients with rheumatoid arthritis compared with controls: a population based study. Arthritis Rheum. 2002; 46: 2287-2293

[21] Rehart S, Petak N. [Modern disease modifying drugs in rheumatoid arthritis in the perioperative period. Patients with rheumatic diseases under therapy with methotrexate, leflunomide or TNF-alpha blockers in the perioperative period.] Akt Rheumatol. 2007; 32: 74-77

Tables:

Orthopedic Hospital Harthausen; Bad Aibling
Department of Rheuma-Surgery, Kreuznacher Diakonie; Bad Kreuznach
Department of Rheuma-Surgery, Red Cross Hospital; Bremen
Department of Rheuma-Orthopedics, St. Elisabeth-Hospital, University hospital (Ruhr University-Bochum); Bochum
Orthopedics, Traumatology and Rheuma-Orthopedics Clinic, Katholic Hospital Dortmund-West; Dortmund
Orthopedics and Traumatology Clinic, Agaplesion Markus hospital; Frankfurt / Main
Orthopedics, Traumatology and Rheuma-Orthopedics Clinic, Westpfalzclinic Kusel; Kusel
Orthopedic and Policlinic, University hospital Leipzig; Leipzig
Rheuma-ortphopedics, Rheinisches Center for Rheumatology Meerbusch; Meerbusch
Orthopedic Department, Collm-Clinic Oschatz; Oschatz
Rheuma-orthopedics, North-western Center for Rheumatology St. Josef-Stift Sendenhorst; Sendenhorst

Table 1: Departments participating in the pilot-study.

	Aldalimumab	Ertanecept	Tocilizumab	Rituximab	Infliximab	Abatecept	Golimumab	MTX	Leflunomide	Azathioprine	Sulfasalazine	Hydroxy-cloroquine	Others	Corticoids	Total:
Aldalimumab	28	0	0	0	0	0	0	106	6	1	2	1	4	0	**68**
Ertanecept	0	47	0	0	0	0	0	41	17	1	4	3	1	24	**121**
Tocilizumab	0	0	12	0	0	0	0	4	1	0	2	0	0	3	**20**
Rituximab	0	0	0	16	0	0	0	11	2	0	2	2	0	6	**35**
Infliximab	0	0	0	0	3	0	0	5	0	0	1	0	0	2	**9**
Abatecept	0	0	0	0	0	3	0	6	2	0	0	1	0	2	**9**
Golimumab	0	0	0	0	0	0	3	7	0	0	0	0	0	6	**15**
MTX	106	41	4	11	5	6	7	191	43	2	31	24	10	109	**453**
Leflunomide	6	17	1	2	0	2	0	43	67	1	15	5	5	40	**179**
Azathioprine	1	1	0	0	0	0	0	2	1	10	0	1	0	5	**18**
Sulfasalazine	2	4	2	2	1	0	0	31	15	0	34	8	0	19	**99**
Hydroxy-cloroquine	1	3	0	2	0	1	0	24	5	1	8	11	1	22	**57**
Others	4	1	0	0	0	0	0	10	5	0	0	1	10	1	**32**
Corticoids	**6**	**24**	**3**	**6**	**2**	**2**	**6**	**109**	**40**	**5**	**19**	**22**	**1**	**60**	**253**

Table 2: Pharmacological therapy: steroids, DMARDs, Biologicals and their combinations as reported. MTX = Metothrexate.

	Teno-synovectomy	Synovectomy	Fusion or resections-arthroplasty	Total joint replacement	Others	Total:
Vertebra column			3	1	2	**6**
Shoulder	7	8	6	17		**38**
Elbow	1	14	7	6	5	**33**
Wrist		26	55	2	11	**94**
Flexor tendons (hand)	12					**12**
Extensor tendons (hand)	19					**19**
MCP-joints		5	9	17	1	**32**
DIP-/PIP-joints (hand)		4	19	4	7	**34**
Hip			3	148		**151**
Knee	1	56	4	175	4	**240**
Ankle joint	4	4	21	9	5	**43**
Subtalar joint	2	1	27		2	**32**
Toes	3	9	167	1	14	**194**
Tendons foot	6		3		5	**14**
Others					58	**58**
Total:	**55**	**127**	**324**	**380**	**114**	**1000**

Table 3: Addressed areas and kind of surgery performed in the 1000 pilot-patients, MCP-joints = metacarpo-phalangeal joints, DIP-/PIP-joints = distal interphalangeal / proximal interphalangeal joints.

Types of complications	Number of patients	Type of surgery	Risk factor cortico-steroids >1 year	Risk factor cortico-steroid > 5 mg perdnisolone-equivalent	Further risk factors as postulated	Immune modulating drugs
Wound disorder stitches in situ > 14 days	5	2 total hip replacement 1 ankle arthrodesis 2 forefoot surgery with osteosynthesis	2	0	0	2 mono 3 combination
	6	2 bursectomy or synovectomy (elbow) 2 total joint replacement (hip/knee) 2 procedures in ankle and forefoot	3	2	2 (diabetes and / or carcinoma) in patietns with elbow- or ankle-surgery	3 mono 2 combination 1 none
Seroma without re-operation	2	1 total elbow replacement with synovectomy 1 synovectomy	1	1	0	2 combination

		hip				
Revision due to seroma	1	1 bursectomy knee	1	1	0	1 combination
Deep infection with revision	11	3 handsurgery 1 total knee replacement 1 total knee replacement 1 open synovectomy knee 4 forefoot surgery with osteosynthesis or total joint replacement 1 osteosynthesis forearm	7	5	4 patients: 2 diabetes 2 vascular disease 1 carcinoma 1 history with infection in addressed area and infection alio loco	5 mono 3 combination
Palsy peroneal nerve	1	1 total knee replacement				1 mono

Table 4: Patients with postoperative reported complications. Wound disorders/infections postoperatively were the most reported complications. Number of patients is given in each group. Median age at surgical treatment 64.9 years (IQR 48.8-72.0; min. 13.5; max. 78.0). Median duration of rheumatic disease, 20.0 years (IQR 11.5-29.0; min. 5.0; max. 46.0). Wound disorders were observed more often in patients not receiving immune modulating medication. The percentage of patients with infection was slightly higher in those not receiving immune modulating medications (0.9 vs. 1%). One patient with a palsy of the peroneal nerve was reported, which has so be considered as a mechanical problem.

Legend figures 1-3:

Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients

Figure 2: Wound disorders and infections occurred more than two times as often as in patients not receiving immune-modulating medication, compared to treated patients. There was no statistical significance (Fisher's exact test, p= 0.168, 5%-level) in the occurrence of wound complications between patients treated with immune-modulating drugs and those not treated.

Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of the register.

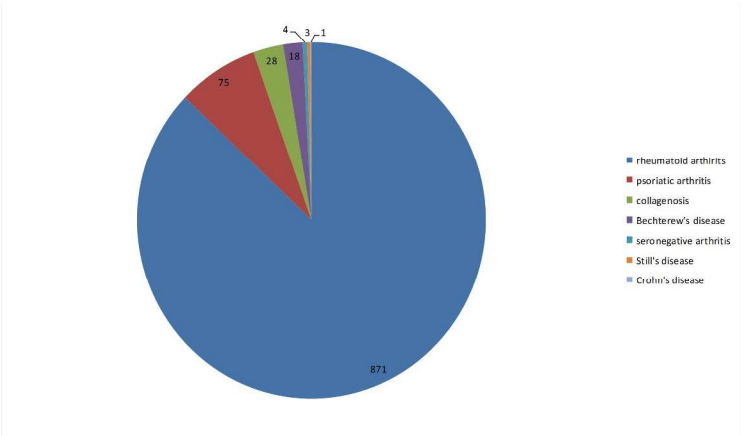
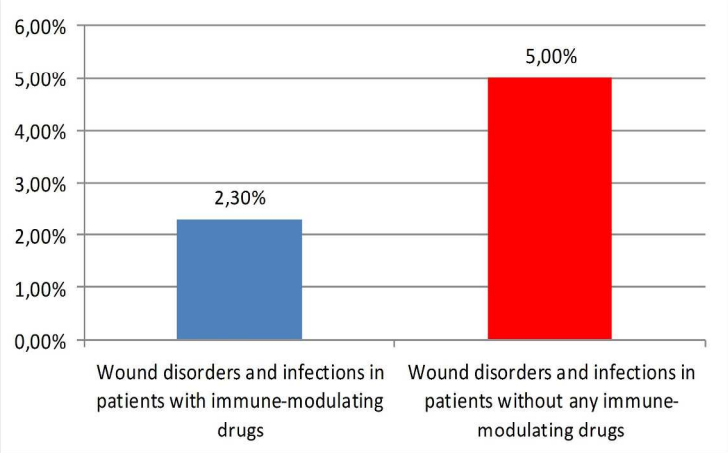


Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients.

209x297mm (300 x 300 DPI)



	No wound complications	Wound complications	
No immune-modulating drugs	n= 93 (94.9%)	n= 5 (5.1%)	n= 98
Immune-modulating drugs	n= 881 (97.7%)	n= 21 (2.3%)	n= 902
	n= 974	n= 26	n=1000

Figure 2: Wound disorders and infections occurred more than two times as often as in patients not receiving immune-modulating medication, compared to treated patients. There was no statistical significance (Fisher's exact test, p= 0.168, 5%-level) in the occurrence of wound complications between patients treated with immune-modulating drugs and those not treated.

209x297mm (300 x 300 DPI)

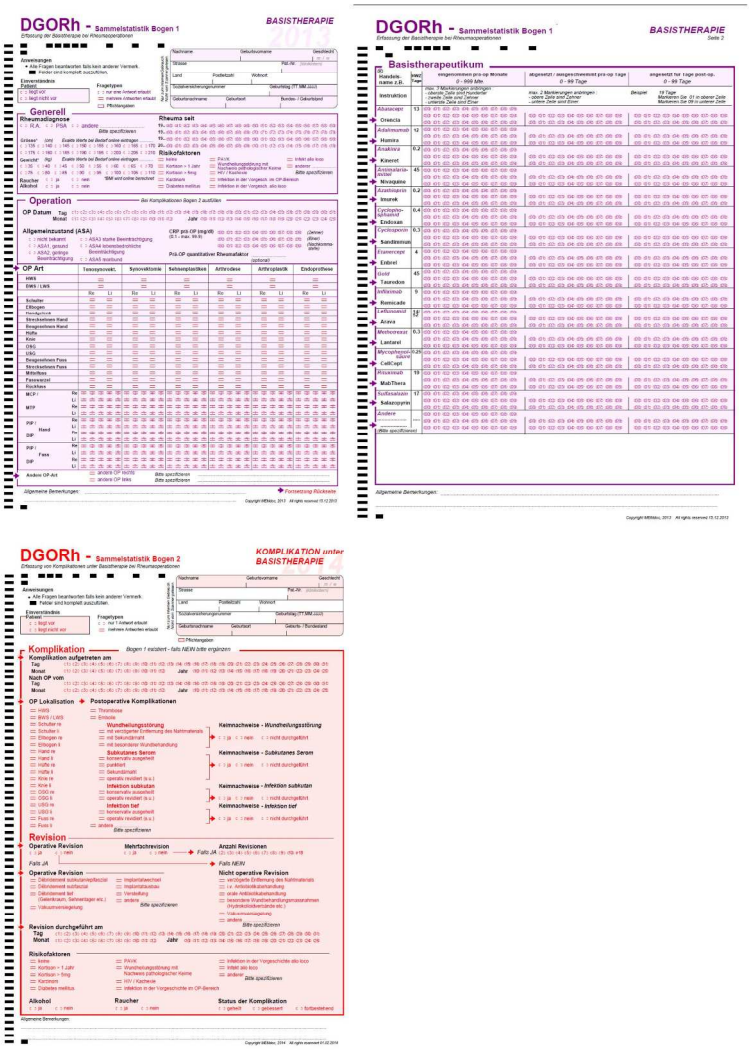


Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of the register.

209x297mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,4,9
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4/5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9/10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10/11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10/11*
Bias	9	Describe any efforts to address potential sources of bias	10/11
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	---
		(*c*) Explain how missing data were addressed	---
		(*d*) If applicable, explain how loss to follow-up was addressed	---
		(*e*) Describe any sensitivity analyses	---
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	---
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	---
		(c) Summarise follow-up time (eg, average and total amount)	---
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	---
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	---
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	---
Discussion			
Key results	18	Summarise key results with reference to study objectives	15/16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pilot study for the Registry of Complications in Rheumatic-Diseases from the German Society of Surgery (DGORh) – Evaluation of methods and data from the first 1000 patients

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Complete List of Authors:	Kostuj, Tanja; Katholisches Klinikum Bochum Sankt Josef-Hospital, Klinik für Orthopädie und Unfallchirurgie Rehart, Stefan; Agaplesion Markus Hospital, Teaching Hospital of Johann Wolfgang-Goethe University, Clinic for orthopedics and traumatology Matta-Hurtado, Ronald; Catholic Hospital Dortmund-West, Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic Biehl, Christoph; Universitätsklinikum Giessen und Marburg , Klinik für Hand- Wiederherstellungs- und Unfallchirurgie Willburger, Roland; Katholisches Klinikum Bochum Sankt Elisabeth-Hospital, Department of Rheumatic-Orthopedics Schmidt, Klaus; Catholic Hospital Dortmund-West, Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Public health, Patient-centred medicine, Rheumatology, Pharmacology and therapeutics
Keywords:	Inflammatory-arthritis, immune-modulating therapy, disease modifying anti-rheumatic drugs, biologicals, wound complications, registry

Pilot study for the Registry of Complications in Rheumatic-Diseases from the German Society of Surgery (DGORh) – Evaluation of methods and data from the first 1000 patients

Dr. med. Tanja Kostuj[1,2], - **Corresponding author**
[1]Catholic Hospital Bochum, St. Josefs-Hospital, University hospital of Ruhr-University-Bochum, Department of Orthopedics and traumatology, Gudrunstraße 56, 44791 Bochum, Germany
[2] Institute for Medical Biometry and Epidemiology, University of Witten / Herdecke, Alfred-Herrhausen-Straße 50, 58448 Witten, Germany
E-mail: tanja.kostuj@t-online.de; Phone: +49 170 3835773

Prof Dr. med. Stefan Rehart
Agaplesion Markus Hospital, Teaching Hospital of Johann Wolfgang-Goethe University, Clinic for orthopedics and traumatology, Wilhelm-Epstein-Str. 4, 60431 Frankfurt am Main, Germany

Mr. Ronald Matta-Hurtado,
Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic, Catholic Hospital Dortmund-West, Zollernstraße 40, 44379 Dortmund, Germany

Dr. med. Christoph Biehl,
Orthopedic and Rheumaorthopedic Clinic - Diakonie hospital, Ringstraße 64, 55543 Bad Kreuznach, Germany

Prof. Dr. med. Roland E. Willburger
Catholic Hospital Bochum, St. Elisabeth-Hospital, University hospital of Ruhr-University-Bochum, Department of Rheumatic-Orthopedics, Bleichestraße 15, 44787 Bochum, Germany

PD Dr. med. Klaus Schmidt
Orthopedics, Rheumatic-Orthopedics and Traumatology Clinic, Catholic Hospital Dortmund-West, Zollernstraße 40, 44379 Dortmund, Germany

On behalf of the study-group "complication-register of the DGORh"

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The authors declare the following potential conflicts of interests:

TK: Pharmaceutical or medical device companies may be involved in some of the included studies however the details are unknown to the author.

SR: Has received speaker fees from the companies Abbvie / Grünenthal / MSD / implantcast / medac

CB: Has received speaker fees from the companies Link and Abbot

The remaining authors declare no conflicts of interest.

The authors declare the following contribution of authorship:

TK: writing of manuscript, data analysis, modification of questionnaires for real time registry

SR: design of pilot questionnaires, review of questionnaires for real time registry, review of manuscript

RMH: data-collection and data analysis

CB: providing of references, review of manuscript

REW: providing of references, approval ethics committee

KS: design of pilot questionnaires, data-collection, review of manuscript

Further members from the pilot-study group are (listed alphabetically):

Dr. med. Ingo Arnold, Red Cross hospital, Bremen, Department of Rheumatology and Orthopedics

Dr. med. Ludwig Bause, St. Josef-Stift Sendenhorst, Department of Orthopedic Rheumatology

Dr. med Harald Dinges, Westpfalzklinikum Kusel, Clinic of Orthopedics, Traumatology and Rheumatic Orthopedics

PD Dr. med. Thomas Pauly, Rheinisches Rheumazentrum St. Elisabeth-Hospital, Department of Orthopedic Surgery/Rheumatology, Meerbusch-Lank

Dr. med. Stefan Schill, Joint-center, Rosenheim GmbH and Harthausen Bad Aibling Clinic

Dr. med. Roger Scholz, Department of Orthopedics, Collm-Clinic Oschatz

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Data sharing:

No additionally data are available.

Abstract:

Objective:

Most patients suffering with rheumatic diseases, that undergo surgical treatment, are receiving immune-modulating therapy. To determine whether these medications affect their outcomes a national registry was established in Germany by the German Society of Surgery (DGORh). Data from the first 1000 patients was used in a pilot study to identify relevant co-risk factors and to determine whether such a registry is suitable for developing accurate and relevant recommendations.

Design and participants:

Data was collected from patients undergoing surgical treatments with their written consent. A second consent form was used, if complications occurred. During this pilot study in order to obtain a quicker overview, risk-factors were considered only in patients with complications.

Only descriptive statistical analysis was employed in this pilot study due to limited number of observed complications, and inhomogeneous data regarding the surgery and the medications the patients received. Analytical statistics will be performed to confirm the results in a future outcome study.

Results:

Complications, occurred in 26 patients and were distributed equally among the different types of surgeries. Twenty-one of these patients were receiving immune-modulating therapy at the time, while five were not. Infections were observed in 2.3% of patients receiving, and in 5.1% not receiving immunosuppression.

Conclusions:

Due to the low number of cases, inhomogeneity in the diseases and the treatments received by the patients in this pilot study it is not possible to develop standardized best-practice recommendations to optimize their care. Based on this observation we conclude that in order to be suitable to develop accurate and relevant recommendations a national registry must include the most important and relevant variables that impact the care and outcomes of these patients.

Article summary

Strengths and limitations of the study:

- Data from 1000 patients, from twelve health care centers with varying organizational structures was available to test.
- Due to the small number of patients with complications, the inhomogeneity in the different types of rheumatic diseases, and the treatments received by patients extended statistical analyses was not possible and only tendencies could be derived.

Keywords:

Inflammatory-arthritis, immune-modulating therapy, disease modifying anti-rheumatic drugs, biologicals, wound complications, registry

Main text:

Introduction:

Rheumatoid arthritis (RA) has a prevalence of approximately 1% in Western Europe and the United States, with a cumulative prevalence for all types of rheumatic diseases being 2%, and the incidence of inflammatory-arthritis diseases in Germany is 3% (about 2.5 billion patients). About 25 years ago approximately 25% of these patients underwent total joint replacement, yet recently the number of these procedures as well as the number of surgical treatments in general in RA patients has decreased in Europe, the United States and Japan [1-8]. This trend could be the result of the recently introduced, very early “treat-to-target“-treatment and/or the use of modern anti-inflammatory medications [9], which have increased during the same time period. Actually, about 70% of the patients with RA are receive, so called, disease modifying anti-rheumatic drugs (DMARDs), while about 20% are treated with biologicals such as immune-modulating therapy [10]. This means that most of these patients, undergoing surgical treatments, are receiving immune-modulating therapy for their inflammatory arthritic diseases. However, it remains unclear whether immune-modulating medications affect the outcomes of these surgical treatments or if they contribute to an increase in the number of wound complications.

Interestingly, for most of the 20, routinely administered DMARDs or biologicals, there are surprisingly few evidence-based recommendations for their perioperative use when complications occur [2, 9]. For example, in the case of methotrexate, the recommendation to continue administration was based on the expert opinion of a broad international panel of rheumatologists [11]. National medical societies in France, the Netherlands, the US, UK and Japan, recommend that - concerning tumor-necrosis-factor alpha (TMF-α)- therapy should be substituted until wounds are healed [12-15].

Based on this confusion the German Society for Orthopedics in Rheumatic-Diseases (DGORh) established a national registry that included surgical patients suffering with inflammatory-arthritis disease. The aim of this pilot study was to determine if data from this national registry could be used to identify risk factors to develop accurate and relevant treatment recommendations. For example in RA patients receiving medications who have subcutaneous or deep wound infections.

This report presents the methods used in this pilot-study and the preliminary results, from the first 1000 patients.

Methods and Material:

Risk adjustment

Based on rheumatology textbooks, published studies [2,15-19], and the clinical experience of study group members, the following risk-factors were identified as being possible confounders as it relates to wound-disorders or non-unions in arthrodesis: diabetes mellitus, atherosclerosis, malignant tumors, cachexia due to HIV or other consuming diseases, corticoid therapy with more than 5 mg prednisolone-equivalent and/or administration for more than one year, current or history of bacterial infection in the wound or alio loco. In addition, other risk factors that were included were; sex, age, body mass-index (BMI), ASA's-classification, alcohol and smoking history.

In order to obtain a quicker overview of these possible risk-factors/possible confounders these were only considered in those patients who had wound disorders during the pilot-study. While this might have caused a bias in statistical analyses and interpretation of data concerning wound disorders, seroma, and infection we accept this, since the main

focus of this pilot study was to see if risk factors are present, and since we did not expect to have enough data to perform statistical analyses. In the actual registry data this bias would not occur since all risk factors and confounders must be reported in the basic form, in order to obtain valid statistical data.

Number and structure of centers involved in the pilot-study

A total number of twelve centers were included in the pilot-study (table 1).

Each center had an orthopedic surgeon with experience treating patients with inflammatory arthritic diseases. In order to have a representative cross section of the different types of provider's in Germany, different types of departments, which treat patients with rheumatic diseases, were asked to participate: hospitals specialized in rheumatology, university-based hospitals, departments whose focus was elective orthopedic surgery and departments that focus on treating trauma-patients.

Ethical approval:

Approval to conduct the study was obtained from the ethics-committee at Ruhr-University in Bochum (No.: 4138-11). The study was carried out in accordance with the Helsinki Declaration. All patients included in the study were invited and gave their written informed consent in an initial consent form. This form, administered by the attending physician, included information about different types of rheumatic diseases, their onset, types of medications administered to patients with rheumatic disease, details about medication regimens (continued or interrupted, estimated time for re-starting medication, etc.), and surgical treatments (date and type of surgery).

If a complication occurred, a second consent form was used that included information about risk factors, date, and type of observed complication, as well as indicated treatments. This pilot study focused on the following complications and treatments: wound disorders and skin necrosis (delayed removal of stiches, type of local treatment, local suture), seroma (evacuation, local suture, re-operation), subcutaneous infections (CDC A1) (with i.v. antibiotics treatment or re-operation), deep infections (CDC A2 + A3) (i.v. antibiotics and re-operation). Minor complications, that did not result in an appointment at the outpatient department or readmission, but instead were treated in a doctor's office were not taken into account.

Patients

Every patient suffering from inflammatory-arthritis disease and receiving surgical treatment in one of the centers was asked to participate in this study and was included after written informed consent was given. Inflammatory arthritis and elective surgical treatment in the musculoskeletal system was the only inclusion criteria. No exclusion criteria were defined. No drop-outs / withdraws of consent occurred during this pilot study. The majority of the patients included in this pilot study (871 cases, 87%) suffered from RA, while 7.5% had a psoriatic arthritis, 2.8% suffered from a collagenosis and 1.8% from ankylosing spondylosis. Other rare diagnoses included not differentiated inflammatory-arthritis (four cases, 0.4%), Still's disease (three cases, 0.3%) and Crohn's disease (one case, 0.1%) (Figure1).

The median period of time from onset of the disease to the procedure leading to their inclusion in the study was 16 years, with an interquartile range (IQR) of 10-25 years, with a maximum of 64 years and a minimum of one year.

Statistical Methods

This article focuses on the methods and the adaption of the questionnaires for use in the registry and reports on the initial results from the first 1000 subjects included in the database.

Due to the limited number of observed complications and the inhomogeneous type of the surgical treatments and the medications used, only descriptive statistical analysis were appropriate in this pilot study. However, analytical statistics of the confirmatory questions in midterm-outcome can be expected from the registry, which was established in the summer of 2014.

Medians, interquartile ranges, confidence intervals and significance (at 5%-level) for the incidence of wound complications in patients treated with immune-modulating medication compared to those not treated were computed using SPSS 22.0 for Windows™ (IBM Corporation, NY, USA).

Results:

Anti-inflammatory-drugs

More than 90% of patients (902) received pharmacological therapy, with 6% (60 patients) treated with corticosteroids as a monotherapy and 20% (197 patients) receiving a combination of DMARDs or biologicals and steroids. The majority (84%, 840 patients) were treated with immune-modulating therapy based on DMARDS or biologicals, with 45% (453 patients) receiving methotrexate, either as a monotherapy (19%, 191 patients) or in combination with corticosteroids (11%, 109 patients) or adalimumab (11%, 106 patients). Other common drugs were leflunomide in (18%, 179

patients) of which 7% (67 patients) received a monotherapy, and etanercept (12%, 121 patients) of which 5% (47 patients) received a monotherapy.

Overall, more than half of all patients received a monotherapy (51%, 507 patients), while 32% were treated with two different types of medication. Combinations of three (68 patients) or four different types of immune-modulating medications (2 patients) were rare and were reported in 7% and 0.2% of patients respectively. The reported combinations are shown in table 2.

Types of surgery

Nearly one third of all procedures can be categorized as bone and joint procedures: total joint replacements, arthrodeses and resection arthroplasty. Different types of synovectomies were performed in 18% of patients. Surgeries in the lower extremity were represented far more often (67%, 674 cases) than those in the upper extremities (26%, 262 cases). Only two patients with surgical treatment of the vertebral column were included (0.2%). The different types of surgical treatments are listed in table 3.

Complications occurred

Complications, summarized as “wound-disorders”, and infections occurred in 26 patients (2.6%) and were nearly equally distributed among upper limb, total hip- or knee-replacement, and foot and ankle surgeries. Twenty-one of these patients received pharmacological immune-modulating therapy, (interrupted perioperatively in 11 cases), while five did not receive a specific medication. 2.3% of patients with an immuno-modulating therapy had wound complications, while 5.1% receiving no

pharmacotherapy for their rheumatoid disease, experienced wound complications in the form of infections.

Deep infections requiring revision surgery occurred in nine patients; eight (0.8%) of which were being treated with immune-modulating drugs, and one (0.1%) who was not receiving medication.

Of the 26 patients with wound complications: 14 (54%) had been treated with corticosteroids for more than one year and nine patients (35%) were receiving doses greater than a 5mg prednisolone-equivalent. Four patients (15%) had diabetes mellitus, two patients (8%) had vascular disease in the treated limb, two patients (8%) had carcinoma (none with cachexia) and one patient (4%) had a history of infection at the time of surgery. The average age of the patients with wound disorders/infections at the time of surgery was 65 (IQR 49-72, minimum 14, maximum 78) years. The duration of the inflammatory-arthritic disease was 18 (IQR 10-29, minimum five, maximum 46) years (95%-CI 11-27 years). Details for these 26 patients with wound complications/infections are given in table 4.

Discussion:

Our initial results in this pilot study show that wound complications occurred twice as often in patients not receiving immune-modulating medication, while deep infections were nearly equally distributed in patients receiving and not receiving drug therapy. This finding seems to be clinically relevant – even if the statistical significance was not demonstrated, using the fisher's exact test (p= 0.168) (figure 2). However, due to the surprisingly low number of complications, the inhomogeneous surgical procedures, and

the variance of pharmacotherapy within the pilot-data this observation must be interpreted with care and analytical statistics cannot yet be performed.

That said, these initial observations support the need to collect additional data that include risk factors, types of surgeries and pharmacotherapy in order to be able to formulate evidence-based recommendations for these patients.

This pilot study has helped to identify possible confounders such as risk-factors and loss to follow-up due to missing patient identification, both important factors that must be taken into consideration as data collection moves forward.

The postulated risk-factors were found in patients with wound disorders, indicating, that these risk-factors will have to be considered as possible confounders in order to evaluate the influence of pharmacotherapy on wound complications. Based on this observation, these risk-factors have been included in the initial patient inclusion criteria forms (“basic questionnaire”), This will make it possible to perform risk-adjusted analyses combined with age, sex, BMI, ASA’s classification, alcohol and smoking history, type and onset of rheumatic disease, in the actual registry (Figure 3). Taking these confounders into account will help formulate more accurate and relevant preoperative recommendations related to the influence of pharmacotherapy in these patients.

The surprisingly low number of patients with postoperative wound disorders and infection compared to the considerably higher figure published in literature [10, 20, 21] can be explained by the loss to follow-up of patients with minor wound complications treated with local therapy outside the hospital. These patients were not included in this study because the ID assigned to them by their respective hospitals made follow up impossible as they received care elsewhere. To remedy this a patient pseudonym was

generated based on non-changing patient data consisting of; date and location they were attended, place of birth -city and state -, Christian name and maiden name. This so called “salt-protected hash-code” ensures that, even in the most complicated forms and between different institutions, patients can be linked to their individual data set helping to avoid a loss to follow-up in the actual registry.

Finally, based on this pilot study additional data will be collected documenting in more detail, the type of treatment wound disorders received and the final status of the wound complication, thus being able to distinguish between minor and major wound complications in the registry.

Limitations:

Due to the small number of patients with observed complications as well as the inhomogeneity in the surgical and pharmacological treatments they received extended analytical statistics could not be performed. Accordingly, at this time no recommendations for perioperative management of anti-inflammatory drugs could be derived from these first 1000 datasets.

In the actual registry, the analysis of data reported in high volumes, like monotherapy and single surgeries will be considered first line, while those occurring in low-volumes like multiple surgeries or combinations of medication will be designated second line and will be analyzed taking the first line into consideration.

Conclusion:

Besides age, sex, risk-factors, type and duration of the rheumatic disease, the administration of immune-modulating medications may impact wound complications.

Due to the inhomogeneity in the disease itself and the treatments received by patients with rheumatic diseases it is difficult to develop standardized best-practice recommendations to optimize their care. Therefore, the creation of a large, comprehensive national registry that includes the most important and relevant variables that impact the care and outcomes of these patients is essential. This pilot study has helped to identify these variables and in doing so will contribute to improving the national registry so that its data can be used to formulate accurate and relevant recommendations for the care of this vulnerable patient population.

Acknowledgement:

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References:

[1] Weiss R J, Stark A, Wick M C *et al.* Orthopaedic surgery of the lower limbs in 49, 802 rheumatoid arthritis patients: results from the Swedish National Inpatient Registry during 1987 to 2001. Ann Rheum Dis. 2006; 65: 335–341

[2] Weiss RJ, Ehlin A, Montgomery SM *et al.* Decrease of RA-related orthopaedic surgery of the upper limbs between 1998 and 2004: data from 54,579 Swedish RA inpatients.
Rheumatology (Oxford). 2008; 47:491-494

[3] da Silva E, Doran MF, Crowson CS *et al.* Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment.
Arthritis Rheum. 2003; 49: 216–220

[4] Shourt CA, Crowson CS, Gabriel SE *et al.*Orthopedic Surgery Among Patients with Rheumatoid Arthritis 1980–2007: a population-based study focused on surgery rates, sex, and mortality. J Rheumatol. 2012; 39: 481-485. doi: 10.3899/jrheum.111056.

[5] Grant HL, Ward M, Changes in the rates of joint surgery among patients with Rheumatoid Arthritis in California, 1983–2007.
Ann Rheum Dis. 2010; 69: 868–871.

[6] Momohara S, Inoue E, Ikari K *et al.* Decrease in orthopaedic operations, including total joint replacements, in patients with rheumatoid arthritis between 2001 and 2007: data from Japanese outpatients in a single institute-based large observational cohort (IORRA). Ann Rheum Dis. 2010; 69:312-313.

[7] Krüger K, Albrecht K, Rehart S *et al.* [Recommendations of the German Society for Rheumatology on the perioperative approach under therapy with DMARDs and biologicals in inflammatory rheumatic diseases.] Z Rheumatol. 2014; 73: 77-84. doi: 10.1007/s00393-013-1301-z.

[8] Louie GH, Ward MM, Changes in the rates of joint surgery among patients with Rheumatoid Arthritis in California, 1983–2007. Ann Rheum Dis. 2010 May; 69(5):868-71. doi: 10.1136/ard.2009.112474.

[9] Gaubitz M. [Biologicals 2012.] Orthopäde. 2012; 41: 526-532; doi 10.1007/s00132-012-1931-x

[10] Welcker M, Sternad P, Krüger K. Aktuelle Empfehlungen der Deutschen Gesellschaft für Rheumatologie - Peroperatives Management klassischer und neuer Antirheumatika, Orthopädie & Rheuma. 2014; 17: 24-29

[11] Visser K, Katchamart W, Loza E *etal.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E-Initiative. Ann Rheum Dis. 2009; 68: 1086-1093. doi: 10.1136/ard.2008.094474.

[12] Heldmann F, Dybowski F, Baraliakos X *et al.* Perioperativer Umgang mit Biologika bei rheumatoider Arthritis. Z Rheumatol. 2011; 70: 14-20. doi: 10.1007/s00393-010-0680-7.

[13] Goh L, Laversuch C, Samanta A. Should anti-TNF therapy be discontinued in rheumatoid arthritis patients undergoing elective orthopaedic surgery? A systematic review of the evidence. Rheumatol Int. 2012; 32:5-13. doi: 10.1007/s00296-011-2040-6.

[14] Pieringer H , Danninger K, Tzaribachev N *et al.* Patients with arthritis undergoing surgery: how should we manage tumour necrosis factor blocking agents perioperatively?-A systematic literature review 14 of 1249 -2011. Yonsei Med J. 2013; 54: 253–257. doi: 10.3349/ymj.2013.54.1.253.

[15] Krüger K. Perioperative medikamentöse Therapie rheumatischer Erkrankungen – Aktuelle Empfehlung der DGRh. Arthritis Rheum. 2014; 60: 158-162

[16] Ravi B, Escott B, Shah PS *et al.* A systematic review and meta-analysis comparing complications following total joint arthroplasty for rheumatoidarthritis versus for osteoarthritis. 40 Studies 1990-2011. Arthritis Rheum. 2012; 64: 3839-3849

[17] Den Broeder AA, Creemers MC, Fransen J *et al.* Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol. 2007; 34: 689-695

[18] Strangfeld A, Eveslage M, Schneider M *et al.* Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF

inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011; 70: 1914-1920

[19] Combe B, Landewe R, Lukas C *et al.* EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for international Clinical Sudies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007; 66: 34-45

[20] Doran MF, Crowson CS, Pond GR *et al.* Frequency of infection in patients with rheumatoid arthritis compared with controls: a population based study. Arthritis Rheum. 2002; 46: 2287-2293

[21] Rehart S, Petak N. [Modern disease modifying drugs in rheumatoid arthritis in the perioperative period. Patients with rheumatic diseases under therapy with methotrexate, leflunomide or TNF-alpha blockers in the perioperative period.] Akt Rheumatol. 2007; 32: 74-77

Tables:

Orthopedic Hospital Harthausen; Bad Aibling
Department of Rheuma-Surgery, Kreuznacher Diakonie; Bad Kreuznach
Department of Rheuma-Surgery, Red Cross Hospital; Bremen
Department of Rheuma-Orthopedics, St. Elisabeth-Hospital, University hospital (Ruhr University-Bochum); Bochum
Orthopedics, Traumatology and Rheuma-Orthopedics Clinic, Katholic Hospital Dortmund-West; Dortmund
Orthopedics and Traumatology Clinic, Agaplesion Markus hospital; Frankfurt / Main
Orthopedics, Traumatology and Rheuma-Orthopedics Clinic, Westpfalzclinic Kusel; Kusel
Orthopedic and Policlinic, University hospital Leipzig; Leipzig
Rheuma-ortphopedics, Rheinisches Center for Rheumatology Meerbusch; Meerbusch
Orthopedic Department, Collm-Clinic Oschatz; Oschatz
Rheuma-Orthopedics, North-western Center for Rheumatology St. Josef-Stift Sendenhorst; Sendenhorst

Table 1: Departments participating in the pilot-study.

	Aldalimumab	Ertanecept	Tocilizumab	Rituximab	Infliximab	Abatecept	Golimumab	MTX	Leflunomide	Azathioprine	Sulfasalazine	Hydroxy-cloroquine	Others	Corticoids	Total:
Aldalimumab	28	0	0	0	0	0	0	106	6	1	2	1	4	0	**68**
Ertanecept	0	47	0	0	0	0	0	41	17	1	4	3	1	24	**121**
Tocilizumab	0	0	12	0	0	0	0	4	1	0	2	0	0	3	**20**
Rituximab	0	0	0	16	0	0	0	11	2	0	2	2	0	6	**35**
Infliximab	0	0	0	0	3	0	0	5	0	0	1	0	0	2	**9**
Abatecept	0	0	0	0	0	3	0	6	2	0	0	1	0	2	**9**
Golimumab	0	0	0	0	0	0	3	7	0	0	0	0	0	6	**15**
MTX	106	41	4	11	5	6	7	191	43	2	31	24	10	109	**453**
Leflunomide	6	17	1	2	0	2	0	43	67	1	15	5	5	40	**179**
Azathioprine	1	1	0	0	0	0	0	2	1	10	0	1	0	5	**18**
Sulfasalazine	2	4	2	2	1	0	0	31	15	0	34	8	0	19	**99**
Hydroxy-cloroquine	1	3	0	2	0	1	0	24	5	1	8	11	1	22	**57**
Others	4	1	0	0	0	0	0	10	5	0	0	1	10	1	**32**
Corticoids	**6**	**24**	**3**	**6**	**2**	**2**	**6**	**109**	**40**	**5**	**19**	**22**	**1**	**60**	**253**

Table 2: Pharmacological therapy: steroids, DMARDs, Biologicals and their combinations as reported. MTX = Metothrexate.

	Teno-synovectomy	Synovectomy	Fusion or resections-arthroplasty	Total joint replacement	Others	Total:
Vertebra column			3	1	2	**6**
Shoulder	7	8	6	17		**38**
Elbow	1	14	7	6	5	**33**
Wrist		26	55	2	11	**94**
Flexor tendons (hand)	12					**12**
Extensor tendons (hand)	19					**19**
MCP-joints		5	9	17	1	**32**
DIP-/PIP-joints (hand)		4	19	4	7	**34**
Hip			3	148		**151**
Knee	1	56	4	175	4	**240**
Ankle joint	4	4	21	9	5	**43**
Subtalar joint	2	1	27		2	**32**
Toes	3	9	167	1	14	**194**
Tendons foot	6		3		5	**14**
Others					58	**58**
Total:	**55**	**127**	**324**	**380**	**114**	**1000**

Table 3: Type of surgery performed and affected areas in the 1 000 patients, MCP-joints = metacarpo-phalangeal joints, DIP-/PIP-joints = distal interphalangeal / proximal interphalangeal joints.

Types of complications	Number of patients	Type of surgery	Risk factor cortico-steroids >1 year	Risk factor cortico-steroid > 5 mg perdnisolone-equivalent	Further risk factors as postulated	Immune modulating drugs
Wound disorder stitches in situ > 14 days	5	2 total hip replacement 1 ankle arthrodesis 2 forefoot surgery with osteosynthesis	2	0	0	2 mono 3 combination
	6	2 bursectomy or synovectomy (elbow) 2 total joint replacement (hip/knee) 2 procedures in ankle and forefoot	3	2	2 (diabetes and / or carcinoma) in patietns with elbow- or ankle-surgery	3 mono 2 combination 1 none
Seroma without re-operation	2	1 total elbow replacement with synovectomy 1 synovectomy	1	1	0	2 combination

		hip				
Revision due to seroma	1	1 bursectomy knee	1	1	0	1 combination
Deep infection with revision	11	3 handsurgery 1 total knee replacement 1 total knee replacement 1 open synovectomy knee 4 forefoot surgery with osteosynthesis or total joint replacement 1 osteosynthesis forearm	7	5	4 patients: 2 diabetes 2 vascular disease 1 carcinoma 1 history with infection in addressed area and infection alio loco	5 mono 3 combination
Palsy peroneal nerve	1	1 total knee replacement				1 mono

Table 4: Patients with reported postoperative complications. Wound disorders/infections postoperatively were the most reported complications. The number of patients affected is given in each group. Median age at surgical treatment 64.9 years (IQR 48.8-72.0; min. 13.5; max. 78.0). Median duration of rheumatic disease, 20.0 years (IQR 11.5-29.0; min. 5.0; max. 46.0). Wound disorders were observed more often in patients not receiving immune-modulating medication. The percentage of patients with infection was slightly higher in those not receiving immune modulating medications (0.9 vs. 1%). One patient with a palsy of the peroneal nerve was reported, which hast so be considered as a mechanical problem.

Legend figures 1-3:

Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients

Figure 2: Wound disorders and infections occurred more than twice as often as in patients not receiving immune-modulating medication, compared to treated patients. There was no statistical significance (Fisher's exact test, p= 0.168, 5%-level) in the occurrence of wound complications between patients treated with immune-modulating drugs and those not treated.

Figure 3: Questionnaires adapted for use in the registry based on the findings from the pilot-study.

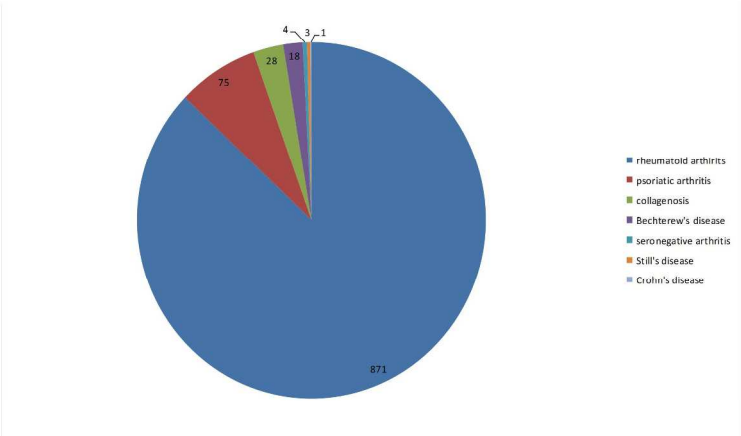
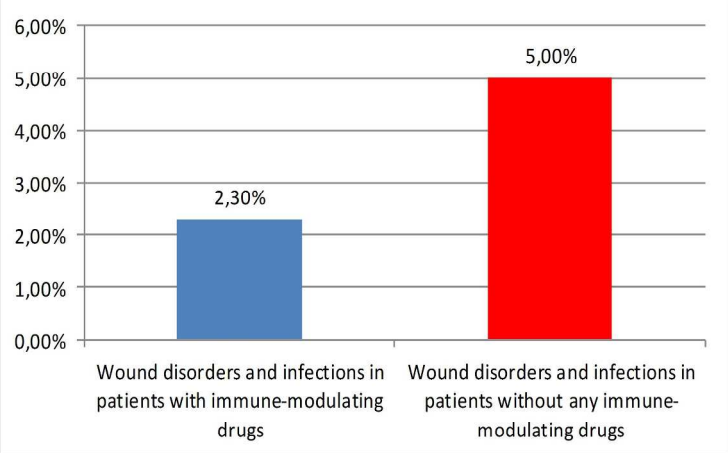


Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients.

209x297mm (300 x 300 DPI)



	No wound complications	Wound complications	
No immune-modulating drugs	n= 93 (94.9%)	n= 5 (5.1%)	n= 98
Immune-modulating drugs	n= 881 (97.7%)	n= 21 (2.3%)	n= 902
	n= 974	n= 26	n=1000

Figure 2: Wound disorders and infections occurred more than two times as often as in patients not receiving immune-modulating medication, compared to treated patients. There was no statistical significance (Fisher's exact test, p= 0.168, 5%-level) in the occurrence of wound complications between patients treated with immune-modulating drugs and those not treated.

209x297mm (300 x 300 DPI)

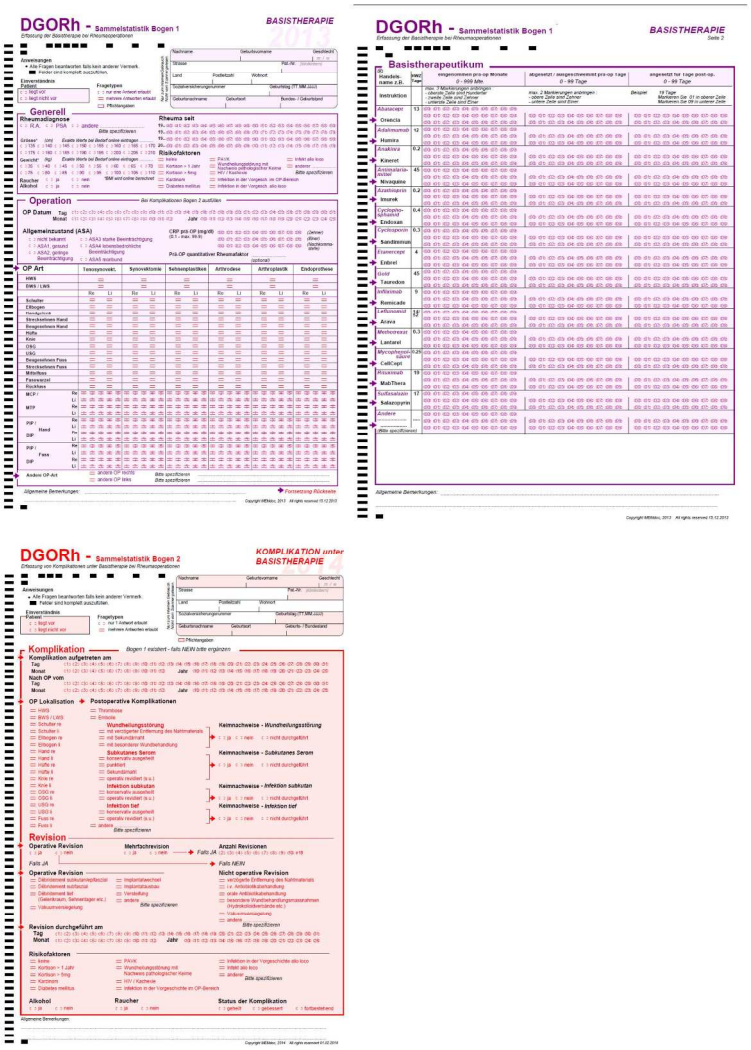


Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of the register.

209x297mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,4,9
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4/5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9/10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10/11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10/11*
Bias	9	Describe any efforts to address potential sources of bias	10/11
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	---
		(*c*) Explain how missing data were addressed	---
		(*d*) If applicable, explain how loss to follow-up was addressed	---
		(*e*) Describe any sensitivity analyses	---
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	---
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	---
		(c) Summarise follow-up time (eg, average and total amount)	---
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	---
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	---
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	---
Discussion			
Key results	18	Summarise key results with reference to study objectives	15/16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.