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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

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5 1 **Pilot study for the Registry of Complications of the German Society for Surgery in Rheumatic-Diseases**
6 2 **(DGORh) – Evaluation of methods and data from the first 1000 patients**
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38 30 **On behalf of the study-group “complication-register of the DGORh”**
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23 43

24 44 **The authors declare the following potential conflicts of interests:**

25 45 TK: Shares of pharmaceutical industry or medical devices manufacturers might be included in a fond – but details are not known to
26 46 the author.

27 47 SR: Has received speaker fees from the companies Abbvie / Grünenthal / MSD / implantcast / medac

28 48 CB: Has received speaker fees from the companies Link and Abbot

29 49 The remaining authors declare no potential conflict of interest.
30
31

32 50

33 51

34 52 **The authors declare the following contribution of authorship:**

35 53 TK: writing of manuscript, data analysis, modification of questionnaires for real time registry

36 54 SR: design of pilot questionnaires, review of questionnaires for real time registry, review of manuscript

37 55 RMH: data-collection and data analysis
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5 56 CB: providing of references, review of manuscript
6 57 REW: providing of references, approval ethics committee
7
8 58 KS: design of pilot questionnaires, data-collection, review of manuscript
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10 59

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71 This work was not supported.

72
73 **Data sharing:**

74 No additionally data are available.

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76
77 **Abstract:**

78 **Objective:**

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5 79 Most of the patients with rheumatic diseases, undergoing surgical treatments, are receiving immune-modulating therapy. Based on
6
7 80 the confusion if those medications affect their outcomes a national registry is established. Data from the first 1000 patients were
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9 81 used as a pilot study to identify relevant co-risk factors and to analyze, if a registry is suitable to develop accurate and relevant
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11 82 recommendations.
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15 84 **Design and participants:**

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18 85 Patient's data were collected in a consent form all patients undergoing surgical treatments. A second consent form was used, if a
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20 86 complication occurred. During the pilot study the risk-factors were considered only in patients where complications occur in order to
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22 87 obtain a quicker overview.
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25 88 In this pilot study only descriptive statistical analysis were appropriate due to the inhomogeneous type of surgery and the
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27 89 medications used, as well as the limited number of observed complications. Analytic statistics of the confirmatory questions in
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29 90 midterm-outcome can be expected later on.
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34 35 92 **Results:**

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5 93 Complications occurred in 26 patients and were nearly equally contributed in the different types of surgeries. 21 of these patients
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7 94 received immune-modulating therapy, 5 did not. Infections were observed in 2.3% of patients receiving and in 5.1% with no
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9 95 immune-modulating therapy.
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16 98 **Conclusions:**

18
19 99 Due to the inhomogeneity in the diseases and the treatments received by those patients it is difficult to develop standardized best-
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21 100 practice recommendations to optimize their care. Therefore, such a national registry has to include the most important and relevant
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23 101 variables that impact the care and outcomes of these patients to be suitable to develop accurate and relevant recommendations.
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25 102

27 103 **Article summary**

30 104 **Article focus:**

- 32 105 • Do we find indicators that administration of immune-modulating medications appears to impact wound complications in
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34 106 different types of elective orthopedic surgery?
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5 107 • Due to the inhomogeneity in the different types of rheumatic diseases itself as well as the treatments received by patients it is
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7 108 difficult to develop standardized best-practice recommendations. Is a registry suited to collect and analyze data from these
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9 109 inhomogeneous groups of patients?
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14 111 **Key message:**

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16 112 • The administration of immune-modulating medications appears to impact wound complications.
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18 113 • The creation of a large, comprehensive national registry that includes the most important and relevant variables that impact
19 114 the care and outcomes of these patients is essential.
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25 116 **Strengths and limitations of the study:**

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27 117 • The number of 1000 datasets from twelve centers with different structures were available to test, if a register is suited to
28 118 analyze a possible impact of immune-modulating medications on wound complications to adapt the questionnaires for the
29 119 use in the “real time” register.
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31
32 120 • Due to the small number of patients with complications, the inhomogeneity in the different types of rheumatic diseases itself
33 121 as well as the treatments received by patients so far extended statistical analyzes cannot be done with these first 1000
34 122 datasets and only tendencies can be derived.
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124 **Keywords:**

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

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5 129 **Main text:**
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8 130 **Introduction:**
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10 131 Rheumatoid arthritis (RA) has a prevalence of approximately 1% in Western Europe and the United States, with a cumulative
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12 132 prevalence for all types of rheumatic diseases being 2%, while the incidence of inflammatory-arthritis diseases in Germany is 3%
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14 133 (about 2.5 billion patients). About 25 years ago approximately 25% of these patients underwent total joint replacement, yet recently
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16 134 the number of these procedures as well and the number of surgical treatments in general in RA patients has decreased in Europe,
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18 135 the United States and Japan [1-8]. This trend could be the result of the recently introduced, very early “treat-to-target“-treatment
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20 136 and/or the use of modern anti-inflammatory medications [9], which have increased during the same time period. Actually, about
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22 137 70% of the patients with RA are receiving, so called, disease modifying anti-rheumatic drugs (DMARDs), while about 20% are
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24 138 treated with biologicals such as immune-modulating therapy [10]. This means that most of these patients, undergoing surgical
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26 139 treatments, are receiving immune-modulating therapy, for their inflammatory arthritic diseases. This raises the questions “do
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28 140 immune-modulating medications affect the outcomes of these surgical treatments?”, or “do they contribute to an increase in the
29
30 141 number of wound complications?” Interestingly, for most of the 20 DMARDs or biologicals, being routinely administered, there are
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32 142 surprisingly few evidence-based recommendations for their perioperative use when complications occur [2, 9]. For example, in the
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34 143 case of methotrexate, when wound complications occur, the recommendation, based on the “expert opinion of a broad international
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36 144 panel of rheumatologists” is to continue administration [11]. National medical societies in France, the Netherlands, the US, UK and
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38 145 Japan, recommend that - concerning tumor-necrosis-factor alpha (TMF- α)- therapy should be substituted until wounds are healed
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5 146 [12-15]. Based on this confusion the German Society for Orthopedics in Rheumatic-Diseases (DGORh) is conducting a pilot study,
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7 147 using data from its national registry, to answer the following questions:

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10 148 • Can data in the DGORh national registry be suitable to develop accurate and relevant recommendations?
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12 149 • What other risk factors, beside RA and medications, should be considered as it relates to wound disorders?
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16 150 This report presents the methods used in this pilot-study and the preliminary results, from the first 1000 patients.
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21 152 **Methods and Material:**
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25 154 ***Risk adjustment***
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28 155 Based on rheumatology textbooks, published studies [2,15-19], and clinical experience of study group members, the following risk-
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30 156 factors were identified as being possible confounders as it relates to wound-disorders or non-unions in arthrodesis: diabetes
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32 157 mellitus, atherosclerosis, malignant tumors, cachexia due to HIV or other consuming diseases, corticoid therapy with more than 5
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34 158 mg prednisolone-equivalent and/or administration for more than one year, current or history of bacterial infection in the wound or
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36 159 alio loco. In addition, other risk factors that were included were; sex, age, body mass-index (BMI), ASA's-classification, alcohol and
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38 160 smoking history.
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5 161 In order to obtain a quicker overview of these possible risk-factors/possible confounders they were only considered in those patients
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7 162 who had wound disorders during the pilot-study.
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13 164 ***Number and structure of centers involved in the pilot-study***
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16 165 A total number of twelve centers were included in the pilot-study (table 1).
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19 166 Each center had an orthopedic surgeon with experience treating patients with inflammatory arthritic diseases. In order to have a
20 167 representative cross section of the different types of provider's in Germany, different types of departments, which treat patients with
21 168 rheumatic diseases, were asked to participate: hospitals specialized in rheumatology, university-based hospitals, departments
22 169 whose focus was elective orthopedic surgery and departments that focus on treating trauma-patients.
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32 171 ***Ethical approval:***
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35 172 Approval to conduct the study was obtained from the ethics-committee at Ruhr-University in Bochum (No.: 4138-11). The study was
36 173 carried out in accordance with the Helsinki Declaration. All patients included in the study were asked and gave their written informed
37 174 consent in an initial consent form. This form included, information about different types of rheumatic diseases, their onset, types of
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5 175 medications administered to patients with rheumatic disease, details about medication regimens (continued or interrupted,
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7 176 estimated time for re-starting medication, etc.), and surgical treatments (date and type of surgery).

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10 177 If a complication occurred, a second consent form was used, that included information about risk-factors, date and type of observed
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12 178 complication as well as indicated treatments.

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19 180 ***Patients***

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21 181 Each patient suffering from an inflammatory-arthritis disease and getting surgical treatment in one of the centers was asked to
22 182 participate in this study and included after written informed consent was given. No drop-outs / withdraws of consent occurred during
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24 183 this pilot study. The majority of the patients included in this pilot study (871 cases, 87%) suffered from RA, while 7.5% had a
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26 184 psoriatic arthritis, 2.8% suffered from a collagenosis and 1.8% from Bechterew's disease. Other rare diagnoses included not
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28 185 differentiated inflammatory-arthritis (four cases, 0.4%), Morbus Still (three cases, 0.3%) and Morbus Crohn (one case, 0.1%)
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30 186 (Figure1).

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36 187 The median period of time from onset to the procedure leading to their inclusion in the study was 16 years, with an interquartile
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38 188 range (IQR) of 10-25 years, with a maximum of 64 years and a minimum of one year.

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41 189 ***Statistical Methods***

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5 190 This article focuses on the methods and the adaption of the questionnaires for use in the registry and reports on the initial results
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7 191 from the first 1000 subjects included in the database.

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10 192 Due to the inhomogeneous type of the surgical treatments and the medications used, as well as the limited number of observed
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12 193 complications, only descriptive statistical analysis were appropriate in this pilot study, however, analytic statistics of the confirmatory
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14 194 questions in midterm-outcome can be expected from the registry, which has started in the summer of 2014.

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18 195 Medians, interquartile ranges, confidence intervals and significance (at 5%-level) for the incidence of wound complications in
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20 196 patients treated with immune-modulating medication, compared to those not treated, were computed using SPSS 22.0 for
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22 197 Windows™ (IBM Corporation, NY, USA).

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28 199 **Results:**

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31 200 ***Anti-inflammatory-drugs***

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34 201 More than 90% of patients (902) received pharmacological therapy, with 6% (60 patients) treated with corticosteroids as a
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36 202 monotherapy and 20% (197 patients) receiving a combination of DMARDS or biologicals and steroids. The majority 84% (840
37
38 203 patients) were treated with immune-modulating therapy based on DMARDS or biologicals, with 45% (453 patients) receiving
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40 204 methotrexate, either as a monotherapy (19%, 191 patients) or in combination with corticosteroids (11%, 109 patients) or

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5 205 adalimumab (11%, 106 patients). Other common drugs were leflunomide in (18%, 179 patients) of which 7% (67 patients) received
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7 206 monotherapy, and etanercept (12%, 121 patients) of which 5% (47 patients) received monotherapy.
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10 207 Over all more than half of all patients received monotherapy (51%, 507 patients), while 32% were treated with two different types of
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12 208 medication. Combinations of three (68 patients) or four different types of immune-modulating medications (2 patients) were rare and
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14 209 were reported in 7% and 0.2% respectively. The reported combinations are given in table 2.
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20 211 ***Types of surgery***

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24 212 Nearly one third of all procedures can be categorized as bone and joint procedures: total joint replacements, arthrodeses and
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26 213 resection arthroplasty. Different types of synovectomies were performed in 18% of patients. Surgeries in the lower extremity were
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28 214 represented far more often (67%, 674 cases) than those in the upper extremities (26%, 262 cases). Only two patients with surgical
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30 215 treatment of the vertebral column were included (0.2%). The different types of surgical treatments are listed in table 3.
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36 217 ***Complications occurred***

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5 218 Complications, summarized as “wound-disorders”, and infections occurred in 26 patients (2.6%) and were nearly equally
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7 219 contributed in the upper limbs, total hip- or knee-replacement, and foot and ankle surgeries. Twenty-one of these patients received
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9 220 pharmacological immune-modulating therapy, (interrupted perioperatively in 11 cases), while five of the patients did not receive a
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11 221 specific medication. 2.3% of patients with an immuno-modulating therapy had wound complaints, while 5.1% with no
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13 222 pharmacotherapy, due to their rheumatoid disease, experienced wound complications in the form of infections.
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17 223 Deep infections, requiring revision surgery, occurred in nine patients; eight (0.9%) of which were patients treated with immune-
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19 224 modulating drugs, and one (0.1%) was not receiving medication.
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22 225 Of the 26 patients with wound complications: 14 (54%) were being treated with corticosteroids for more than one year and nine
23
24 226 patients (35%) were receiving doses greater than 5mg prednisolone-equivalent. Four patients (15%) had diabetes mellitus, two
25
26 227 patients (8%) had vascular disease in the treated limb, two patients (8%) had carcinoma (none with cachexia) and one patient (4%)
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28 228 had a history of infection at the time of surgery. The average age of the patients with wound disorders/infections, at the time of
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30 229 surgery was 65 (IQR 49-72 minimum 14 maximum 78) years. The duration of the inflammatory-arthritic disease was 18 (IQR 10-29
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32 230 minimum five maximum 46) years (95%-CI 11-27 years). Details for these 26 patients with wound complications/infections are given
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34 231 in table 4.
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5 233 **Discussion:**
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7 234 These initial results in this pilot study show, that wound complications occurred two times as often in patients not receiving immune-
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9 235 modulating medication, while deep infections were nearly equally distributed in patients receiving and not receiving drug therapy.

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11 236 This finding seems to be clinically relevant – even if there is no statistically significant difference by performing the fisher’s exact test
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13 237 ($p= 0.168$) (figure 2). But due to the inhomogeneous group of surgical procedures, considerable variance of pharmacotherapy and
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15 238 the surprisingly low number of complications within the pilot-data it has to be interpreted with care.

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19 239 With respect to the limited number of patients, the inhomogeneity in the types of surgeries and the pharmacotherapy received by
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21 240 the patients, analytic statistics cannot yet be performed on this initial set of data. These initial observations support the need to
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23 241 collect additional data that include risk factors, types of surgeries and pharmacotherapy in order to be able to formulate evidence-
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25 242 based recommendations for these patients.

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29 243 This pilot study has helped to identify possible confounders, such as risk-factors and loss to follow-up due to missing patient
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31 244 identification, both important factors that must be taken into consideration as data collection moved forward.

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34 245 The postulated risk-factors were found in patients with wound disorders, indicating, that these risk-factors will have to be considered
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36 246 as possible confounders in order to evaluate the influence of pharmacotherapy on wound complications. Based on this observation
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38 247 going forward these risk-factors have been included in the initial patient inclusion recording forms (“basic questionnaire”), This will
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5 248 make it possible to perform risk-adjusted analyses combined with age, sex, BMI, ASA's classification, alcohol and smoking history,
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7 249 type and onset of rheumatic disease, in the real-time-registry (Figure 3). Taking these confounders into account, will help formulate
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9 250 more accurate and relevant preoperative recommendations related to the influence of pharmacotherapy in these patients.
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12 251 The unexpected low number of patients with postoperative wound disorders and infection – compared to the considerably higher
13 252 figure published in literature [10, 20, 21] – can be explained by the loss to follow-up for those patients with minor wound
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15 253 complications, treated with local therapy outside the hospital. These patients were not included in this pilot study because their
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17 254 patient ID was lost in the system as they received care both as ambulant and hospital-based patients. To remedy this a patient's
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19 255 pseudonym was generated based on non-changing patient data consisting of; date and location they were attended, place of birth -
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21 256 city and state -, Christian name and maiden name. This so called "salt-protected hash-code" ensures that, even the most
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23 257 complicated forms and between different institutions, patients can be linked to their individual data set helping to avoid a loss to
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25 258 follow-up in the real-time registry.
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31 259 Finally, based on this pilot study additional data will be collected documenting in more detail the type of treatment wound disorders
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33 260 received and the final status of the wound complication, thus being able to distinguish between minor and major wound
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35 261 complications in the registry.
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5 263 **Limitations:**
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7 264 Due to the small number of patients with observed complications as well as due to the inhomogeneity in the different types of
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9 265 rheumatic diseases itself as well as the elective surgical treatments received by patients so far extended analytical statistics cannot
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11 266 be done. Thus so far no recommendations for the perioperative management of anti-inflammatory drugs but only tendencies can be
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13 267 derived from these first 1000 datasets.
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20 269 **Conclusion:**
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23 270 Besides age, sex, risk-factors, type and duration of the rheumatic disease, the administration of immune-modulating medications
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25 271 appears to impact wound complications. Due to the inhomogeneity in the disease itself and the treatments received by patients with
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27 272 rheumatic diseases it is difficult to develop standardized best-practice recommendations to optimize their care. Therefore, the
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29 273 creation of a large, comprehensive national registry that includes the most important and relevant variables that impact the care and
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31 274 outcomes of these patients is essential. This pilot study has helped to identify these variables and in doing so will contribute to
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33 275 improving the national registry so that its data can be used to formulate accurate and relevant recommendations for the care of this
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35 276 vulnerable patient population.
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41 278 **Acknowledgement:**
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7
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9
10 281 Biometry and Epidemiology)-Congress 2014 in Göttingen / Germany

11
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13
14 283 (DGOOC).
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345 **Tables:**

346

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Orthopedic and Policlinic, University hospital Leipzig; Leipzig
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349 **Table 1: Departments participating in the pilot-study.**

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351

	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 = Methotrexate.

	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

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

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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	Eterncept	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	Hydroxychloroquine + Corticosteroid	36

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Patient	Wound disorder stitches in situ > 14 days	Wound disorder – secondary suture	Seroma	Revision due to seroma	Deep infection with revision	Risk factor Corticosteroids >1 year	Risk factor Corticosteroid > 5 mg perdnisolone-equivalent	Risk factor diabetes mellitus	Risk factor chronicl vascular disease	Carcinoma	HIV / cachexia	History of infection in addressed area	Infection alio loco
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360 **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).**
 361 **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**
 362 **receiving immune modulating medication. The percentage of patients with infection was slightly higher in those not receiving immune modulating**
 363 **medications (0.9 vs. 1%). R.A. = rheumatoid arthritis.**

For peer review only

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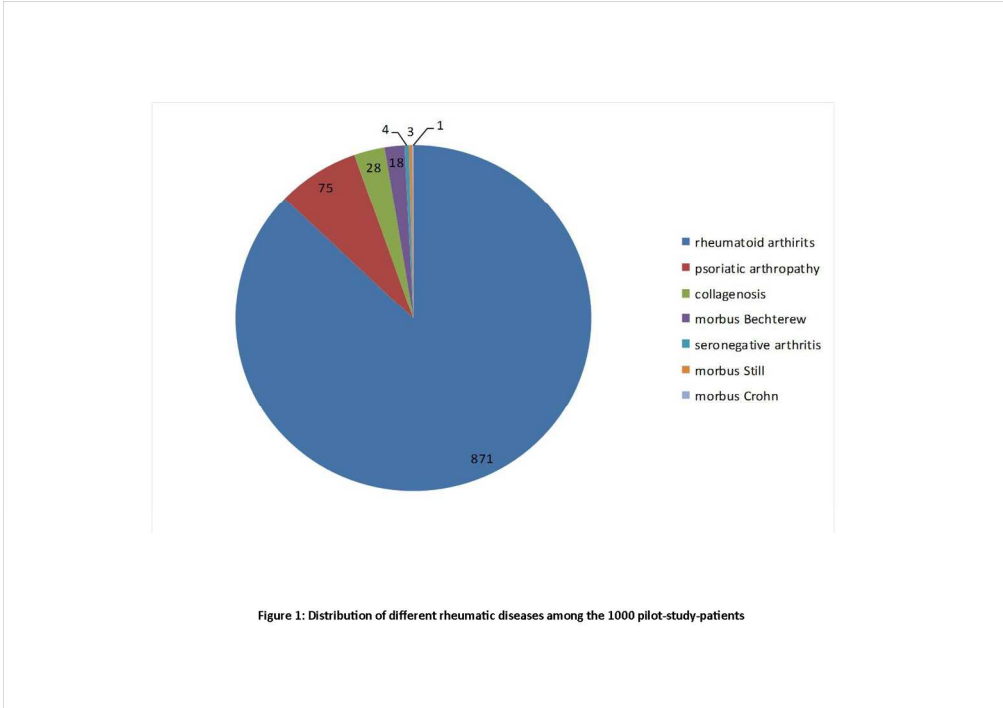


Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients

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

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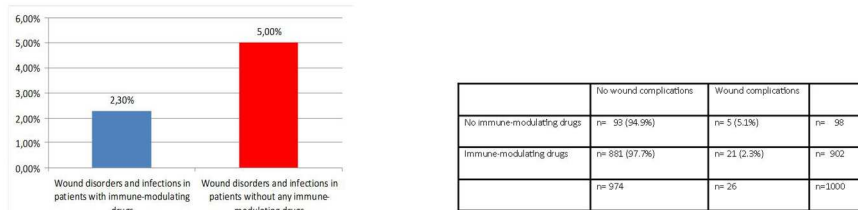


Figure 2: Wound disorders and infections occurred more than two times as often as in patients not receiving immune-modulating medication, compared to treated patients. There was no statistical significance (Fisher's exact test, $p=0.168$, 5%-level) in the occurrence of wound complications between patients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

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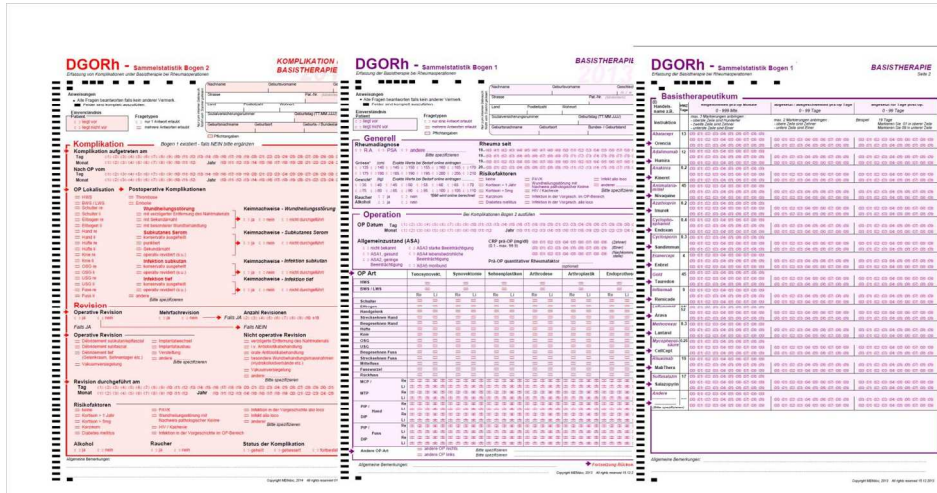


Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of the register.

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

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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-015987.R1
Article Type:	Research
Date Submitted by the Author:	20-Apr-2017
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

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Manuscripts

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2
3 **Pilot study for the Registry of Complications in Rheumatic-Diseases**
4 **(DGORh) from the German Society of Surgery– Evaluation of methods**
5 **and data from the first 1000 patients**
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44 **On behalf of the study-group “complication-register of the DGORh”**
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9

10 **The authors declare the following potential conflicts of interests:**

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

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

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

16 The remaining authors declare no conflicts of interest.
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22 **The authors declare the following contribution of authorship:**

23
24
25 TK: writing of manuscript, data analysis, modification of questionnaires for real time
26 registry

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

29 RMH: data-collection and data analysis

30 CB: providing of references, review of manuscript

31 REW: providing of references, approval ethics committee

32 KS: design of pilot questionnaires, data-collection, review of manuscript
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50
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56 **Funding:**
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3 This work was not supported.
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7 **Data sharing:**

8 No additionally data are available.
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13 **Abstract:**

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15 **Objective:**

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

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35 Data was collected from patients undergoing surgical treatments with their written
36 consent. A second consent form was used, if a complication occurred. During this pilot
37 study risk-factors were considered only in patients with complications in order to obtain
38 a quicker overview.
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46 In this pilot study only descriptive statistical analysis were employed due to
47 inhomogeneous data regarding the surgery and the medications they received, as well
48 as the limited number of observed complications. Analytic statistics will be performed to
49 confirm the questions asked in a future outcome study.
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57 **Results:**
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3 Complications, distributed equally among the different types of surgeries, occurred in 26
4 patients. Twenty one of these patients were receiving immune-modulating therapy and
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6
7 5 were not. Infections were observed in 2.3% of patients receiving, and in 5.1% not
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9 receiving immunosuppression.
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11 12 13 14 15 16 **Conclusions:**

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19 Due to the inhomogeneity in the diseases and the treatments received by the patients in
20
21 this pilot study it is difficult to develop standardized best-practice recommendations to
22
23 optimize their care. Therefore, such a national registry has to include the most important
24
25 and relevant variables that impact the care and outcomes of these patients to be
26
27 suitable to develop accurate and relevant recommendations.
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32 **Article summary**

33 34 **Strengths and limitations of the study:**

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37 • Data from 1000 patients, from twelve centers, with different structures were
38
39 available to test, if a register is suited to analyze the possible impact of immune-
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41 modulating medications on wound complications to adapt the questionnaires for
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43 the use in the “real time” register.
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- 45
46 • Due to the small number of patients with complications, the inhomogeneity in the
47
48 different types of rheumatic diseases, and the treatments received by patients
49
50 extended statistical analyses could not be performed on this first 1000 datasets
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52 and only tendencies could be derived.
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55 56 57 **Keywords:** 58 59 60

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

For peer review only

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 (TNF- α)- therapy should be substituted until wounds are healed [12-15].

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3 Based on this confusion the German Society for Orthopedics in Rheumatic-Diseases
4 (DGORh) established a national registry that included surgical patients suffering with
5 inflammatory-arthritis disease. The aim of this pilot study was to determine if data from
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10 this national registry could be used to identify risk factors to develop accurate and
11
12 relevant treatment recommendations. For example in RA patients receiving medications
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14 who have subcutaneous or deep wound infections.

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17 This report presents the methods used in this pilot-study and the preliminary results,
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19 from the first 1000 patients.
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24 **Methods and Material:**

25 ***Risk adjustment***

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29 Based on rheumatology textbooks, published studies [2,15-19], and clinical experience
30
31 of study group members, the following risk-factors were identified as being possible
32
33 confounders as it relates to wound-disorders or non-unions in arthrodesis: diabetes
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35 mellitus, atherosclerosis, malignant tumors, cachexia due to HIV or other consuming
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37 diseases, corticoid therapy with more than 5 mg prednisolone-equivalent and/or
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39 administration for more than one year, current or history of bacterial infection in the
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41 wound or alio loco. In addition, other risk factors that were included were; sex, age,
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43 body mass-index (BMI), ASA's-classification, alcohol and smoking history.
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50 In order to obtain a quicker overview of these possible risk-factors/possible confounders
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52 they were only considered in those patients who had wound disorders during the pilot-
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54 study. This might cause a bias in statistical analyses and interpretation of data
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56 concerning wound disorders, seroma, and infection however we accept this, since the
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3 main focus of this pilot study was to see if risk factors are present, and did not expect to
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5 have enough data to perform statistical analyses. In the actual registry data this type of
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7 bias would not be possible since all risk factors and confounders must to be reported in
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9 the basic form, in order to obtain valid statistical data.
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11 12 13 14 15 16 ***Number and structure of centers involved in the pilot-study***

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19 A total number of twelve centers were included in the pilot-study (table 1).
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22 Each center had an orthopedic surgeon with experience treating patients with
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24 inflammatory arthritic diseases. In order to have a representative cross section of the
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26 different types of provider's in Germany, different types of departments, which treat
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28 patients with rheumatic diseases, were asked to participate: hospitals specialized in
29
30 rheumatology, university-based hospitals, departments whose focus was elective
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32 orthopedic surgery and departments that focus on treating trauma-patients.
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35 36 ***Ethical approval:***

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39 Approval to conduct the study was obtained from the ethics-committee at Ruhr-
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41 University in Bochum (No.: 4138-11). The study was carried out in accordance with the
42
43 Helsinki Declaration. All patients included in the study were invited and gave their
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45 written informed consent in an initial consent form. This form, administered by the
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47 attending physician, included information about different types of rheumatic diseases,
48
49 their onset, types of medications administered to patients with rheumatic disease,
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51 details about medication regimens (continued or interrupted, estimated time for re-
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53 starting medication, etc.), and surgical treatments (date and type of surgery)
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3 If a complication occurred, a second consent form was used, that included information
4 about risk factors, date, and type of observed complication, as well as indicated
5 treatments. This pilot study focused on the following complications and treatments:
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7 wound disorders and skin necrosis (delayed removal of stiches, type local treatment,
8 suture), seroma (evacuation, local suture, re-operation), subcutaneous infections (CDC
9 A1) (with i.v. antibiotics treatment or re-operation), deep infections (CDC A2 + A3) (i.v.
10 antibiotics and re-operation). Minor complications, that did not result in an appointment
11 at the outpatient department or to readmission, but instead were treated in a doctor's
12 office were not taken into account.
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27 ***Patients***

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29 Each patient suffering from inflammatory-arthritis disease and receiving surgical
30 treatment in one of the centers was asked to participate in this study and was included
31 after written informed consent was given. Inflammatory-arthritis and elective surgical
32 treatment in the musculoskeletal system was the only inclusion criteria. No exclusion
33 criteria were defined. No drop-outs / withdraws of consent occurred during this pilot
34 study. The majority of the patients included in this pilot study (871 cases, 87%) suffered
35 from RA, while 7.5% had a psoriatic arthritis, 2.8% suffered from a collagenosis and
36 1.8% from ankylosing spondylosis. Other rare diagnoses included not differentiated
37 inflammatory-arthritis (four cases, 0.4%), Still's disease (three cases, 0.3%) and Crohn's
38 disease (one case, 0.1%) (Figure1).
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52 The median period of time from onset to the procedure leading to their inclusion in the
53 study was 16 years, with an interquartile range (IQR) of 10-25 years, with a maximum of
54 64 years and a minimum of one year.
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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

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3 patients) of which 7% (67 patients) received monotherapy, and etanercept (12%, 121
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5 patients) of which 5% (47 patients) received monotherapy.
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8 Overall more than half of all patients received monotherapy (51%, 507 patients), while
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10 32% were treated with two different types of medication. Combinations of three (68
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12 patients) or four different types of immune-modulating medications (2 patients) were
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14 rare and were reported in 7% and 0.2% respectively. The reported combinations are
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16 given in table 2.
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23 ***Types of surgery***

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26 Nearly one third of all procedures can be categorized as bone and joint procedures:
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28 total joint replacements, arthrodeses and resection arthroplasty. Different types of
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30 synovectomies were performed in 18% of patients. Surgeries in the lower extremity
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32 were represented far more often (67%, 674 cases) than those in the upper extremities
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34 (26%, 262 cases). Only two patients with surgical treatment of the vertebral column
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36 were included (0.2%). The different types of surgical treatments are listed in table 3.
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43 ***Complications occurred***

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46 Complications, summarized as “wound-disorders”, and infections occurred in 26
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48 patients (2.6%) and were nearly equally contributed in the upper limbs, total hip- or
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50 knee-replacement, and foot and ankle surgeries. Twenty-one of these patients received
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52 pharmacological immune-modulating therapy, (interrupted perioperatively in 11 cases),
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54 while five of the patients did not receive a specific medication. 2.3% of patients with an
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56 immuno-modulating therapy had wound complaints, while 5.1% with no
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3 pharmacotherapy, due to their rheumatoid disease, experienced wound complications in
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5 the form of infections.
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8 Deep infections, requiring revision surgery, occurred in nine patients; eight (0.9%) of
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10 which were patients treated with immune-modulating drugs, and one (0.1%) was not
11
12 receiving medication.
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15 Of the 26 patients with wound complications: 14 (54%) were being treated with
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17 corticosteroids for more than one year and nine patients (35%) were receiving doses
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19 greater than 5mg prednisolone-equivalent. Four patients (15%) had diabetes mellitus,
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21 two patients (8%) had vascular disease in the treated limb, two patients (8%) had
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23 carcinoma (none with cachexia) and one patient (4%) had a history of infection at the
24
25 time of surgery. The average age of the patients with wound disorders/infections, at the
26
27 time of surgery was 65 (IQR 49-72 minimum 14 maximum 78) years. The duration of
28
29 the inflammatory-arthritic disease was 18 (IQR 10-29 minimum five maximum 46) years
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31 (95%-CI 11-27 years). Details for these 26 patients with wound complications/infections
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33 are given in table 4.
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42 **Discussion:**

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44 These initial results in this pilot study show, that wound complications occurred two
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46 times as often in patients not receiving immune-modulating medication, while deep
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48 infections were nearly equally distributed in patients receiving and not receiving drug
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50 therapy. This finding seems to be clinically relevant – even if there is no statistically
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52 significant difference by performing the fisher's exact test ($p= 0.168$) (figure 2). But due
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54 to the inhomogeneous group of surgical procedures, considerable variance of
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3 pharmacotherapy and the surprisingly low number of complications within the pilot-data
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5 it has to be interpreted with care.
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9 With respect to the limited number of patients, the inhomogeneity in the types of
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11 surgeries and the pharmacotherapy received by the patients, analytic statistics cannot
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13 yet be performed on this initial set of data. These initial observations support the need
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15 to collect additional data that include risk factors, types of surgeries and
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17 pharmacotherapy in order to be able to formulate evidence-based recommendations for
18
19 these patients.
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23 This pilot study has helped to identify possible confounders, such as risk-factors and
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25 loss to follow-up due to missing patient identification, both important factors that must
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27 be taken into consideration as data collection moved forward.
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31 The postulated risk-factors were found in patients with wound disorders, indicating, that
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33 these risk-factors will have to be considered as possible confounders in order to
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35 evaluate the influence of pharmacotherapy on wound complications. Based on this
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37 observation going forward these risk-factors have been included in the initial patient
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39 inclusion recording forms (“basic questionnaire”), This will make it possible to perform
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41 risk-adjusted analyses combined with age, sex, BMI, ASA’s classification, alcohol and
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43 smoking history, type and onset of rheumatic disease, in the real-time-registry (Figure
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45 3). Taking these confounders into account, will help formulate more accurate and
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47 relevant preoperative recommendations related to the influence of pharmacotherapy in
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49 these patients.
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53 The unexpected low number of patients with postoperative wound disorders and
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55 infection – compared to the considerably higher figure published in literature [10, 20, 21]
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57 – can be explained by the loss to follow-up for those patients with minor wound
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3 complications, treated with local therapy outside the hospital. These patients were not
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5 included in this study because the ID assigned to them their respective hospitals would
6
7 not make follow up possible as they received care anywhere else. To remedy this a
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9 patient's pseudonym was generated based on non-changing patient data consisting of;
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11 date and location they were attended, place of birth -city and state -, Christian name
12
13 and maiden name. This so called "salt-protected hash-code" ensures that, even the
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15 most complicated forms and between different institutions, patients can be linked to
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17 their individual data set helping to avoid a loss to follow-up in the real-time registry.
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21 Finally, based on this pilot study additional data will be collected documenting in more
22
23 detail the type of treatment wound disorders received and the final status of the wound
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25 complication, thus being able to distinguish between minor and major wound
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27 complications in the registry.
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30 31 **Limitations:**

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33 Due to the small number of patients with observed complications as well as due to the
34
35 inhomogeneity in the different types of rheumatic diseases itself as well as the elective
36
37 surgical treatments received by patients so far extended analytical statistics cannot be
38
39 done. Thus so far no recommendations for the perioperative management of anti-
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41 inflammatory drugs but only tendencies can be derived from these first 1000 datasets.
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45 In the actual registry, analysis of data reported in high volumes, like monotherapy and
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47 single surgeries will be considered first line, while those occurring in low-volumes like
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49 multiple surgeries or combinations of medication will be designated second line and will
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51 be analyzed taking the first line into consideration.
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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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Tables:

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Orthopedics and Traumatology Clinic, Agaplesion Markus hospital; Frankfurt / Main
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Orthopedic and Policlinic, University hospital Leipzig; Leipzig
Rheuma-orthopedics, 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.

	Aldalim umab	Ertane cept	Tociliz umab	Rituxi mab	Inflix mab	Abate cept	Golimu mab	M TX	Lefluno mide	Azathio prine	Sulfasal azine	Hydro xy- cloroq uine	Oth ers	Cortic oids	Tot al:
Aldalim umab	28	0	0	0	0	0	0	10 6	6	1	2	1	4	0	68
Ertanec ept	0	47	0	0	0	0	0	41	17	1	4	3	1	24	12 1
Tocilizu mab	0	0	12	0	0	0	0	4	1	0	2	0	0	3	20
Rituxim ab	0	0	0	16	0	0	0	11	2	0	2	2	0	6	35
Inflixim ab	0	0	0	0	3	0	0	5	0	0	1	0	0	2	9
Abatece pt	0	0	0	0	0	3	0	6	2	0	0	1	0	2	9
Golimu mab	0	0	0	0	0	0	3	7	0	0	0	0	0	6	15
MTX	106	41	4	11	5	6	7	19 1	43	2	31	24	10	109	45 3
Lefluno mide	6	17	1	2	0	2	0	43	67	1	15	5	5	40	17 9
Azathio prine	1	1	0	0	0	0	0	2	1	10	0	1	0	5	18
Sulfasal azine	2	4	2	2	1	0	0	31	15	0	34	8	0	19	99
Hydrox y- cloroqui ne	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
Corticoi ds	6	24	3	6	2	2	6	10 9	40	5	19	22	1	60	25 3

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

	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 patients 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

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3 **Table 4: Patients with postoperative reported complications. Wound disorders/infections**
4 **postoperatively were the most reported complications. Number of patients is given in each group.**
5 **Median age at surgical treatment 64.9 years (IQR 48.8-72.0; min. 13.5; max. 78.0). Median duration of**
6 **rheumatic disease, 20.0 years (IQR 11.5-29.0; min. 5.0; max. 46.0). Wound disorders were observed**
7 **more often in patients not receiving immune modulating medication. The percentage of patients with**
8 **infection was slightly higher in those not receiving immune modulating medications (0.9 vs. 1%). One**
9 **patient with a palsy of the peroneal nerve was reported, which has so be considered as a mechanical**
10 **problem.**
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20 **Legend figures 1-3:**

21
22 **Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients**

23
24 **Figure 2: Wound disorders and infections occurred more than two times as often as in patients not**
25 **receiving immune-modulating medication, compared to treated patients. There was no statistical**
26 **significance (Fisher's exact test, $p= 0.168$, 5%-level) in the occurrence of wound complications**
27 **between patients treated with immune-modulating drugs and those not treated.**
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29 **Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of**
30 **the register.**
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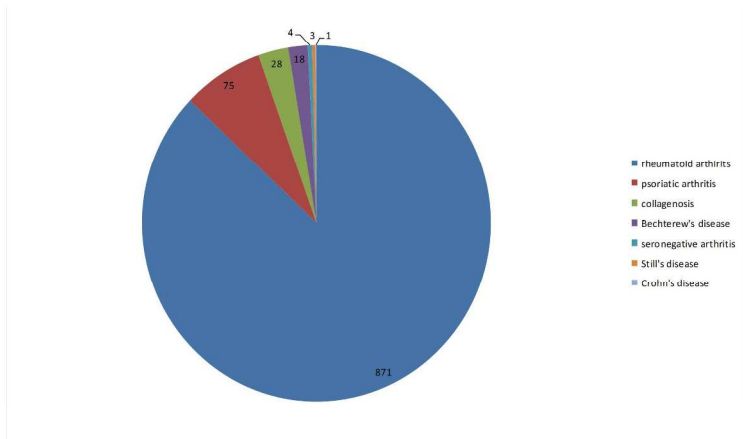
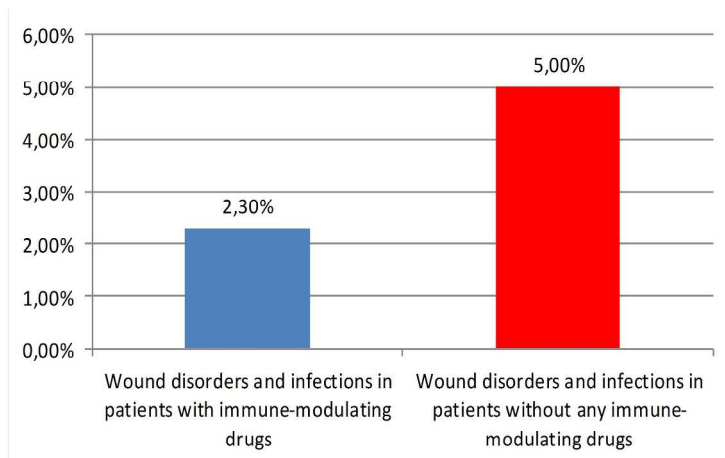


Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients.

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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.

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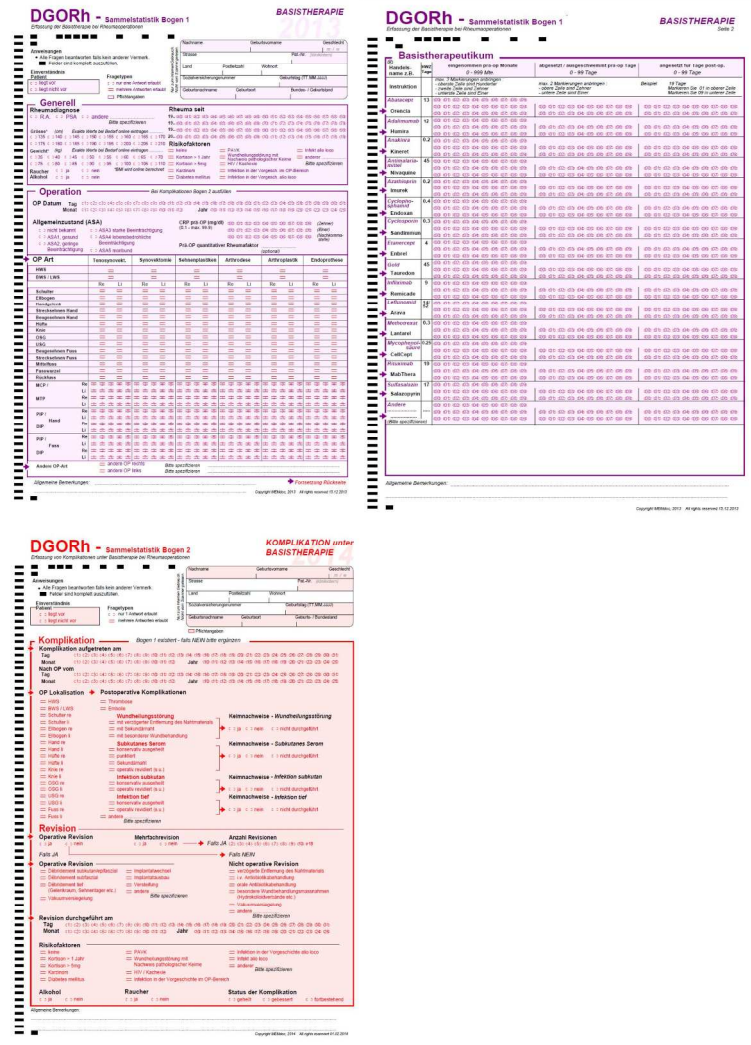


Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of the register.

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-015987.R2
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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

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Manuscripts

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3 **Pilot study for the Registry of Complications in Rheumatic-Diseases**
4 **from the German Society of Surgery (DGORh) – Evaluation of**
5 **methods and data from the first 1000 patients**
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44 **On behalf of the study-group “complication-register of the DGORh”**
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51 **Copyright for authors**
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10 **The authors declare the following potential conflicts of interests:**

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

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

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

16 The remaining authors declare no conflicts of interest.
17
18
19
20
21

22 **The authors declare the following contribution of authorship:**

23
24
25 TK: writing of manuscript, data analysis, modification of questionnaires for real time
26 registry

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

29 RMH: data-collection and data analysis

30 CB: providing of references, review of manuscript

31 REW: providing of references, approval ethics committee

32 KS: design of pilot questionnaires, data-collection, review of manuscript
33
34
35
36
37

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50
51
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55

56 **Funding:**
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1
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3 This work was not supported.
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7 **Data sharing:**

8 No additionally data are available.
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13 **Abstract:**

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16 **Objective:**

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

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36 Data was collected from patients undergoing surgical treatments with their written
37 consent. A second consent form was used, if complications occurred. During this pilot
38 study in order to obtain a quicker overview, risk-factors were considered only in patients
39 with complications.
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46 Only descriptive statistical analysis was employed in this pilot study due to limited
47 number of observed complications, and inhomogeneous data regarding the surgery and
48 the medications the patients received. Analytical statistics will be performed to confirm
49 the results in a future outcome study.
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57 **Results:**
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3 Complications, occurred in 26 patients and were distributed equally among the different
4 types of surgeries. Twenty-one of these patients were receiving immune-modulating
5 therapy at the time, while five were not. Infections were observed in 2.3% of patients
6 receiving, and in 5.1% not receiving immunosuppression.
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11 **Conclusions:**

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

35 **Strengths and limitations of the study:**

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38 • Data from 1000 patients, from twelve health care centers with varying
39 organizational structures was available to test.
- 40
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42 • Due to the small number of patients with complications, the inhomogeneity in the
43 different types of rheumatic diseases, and the treatments received by patients
44 extended statistical analyses was not possible and only tendencies could be
45 derived.
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52 **Keywords:**

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

For peer review only

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 (TNF- α)- therapy should be substituted until wounds are healed [12-15].

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3 Based on this confusion the German Society for Orthopedics in Rheumatic-Diseases
4 (DGORh) established a national registry that included surgical patients suffering with
5 inflammatory-arthritis disease. The aim of this pilot study was to determine if data from
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10 this national registry could be used to identify risk factors to develop accurate and
11
12 relevant treatment recommendations. For example in RA patients receiving medications
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14 who have subcutaneous or deep wound infections.

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17 This report presents the methods used in this pilot-study and the preliminary results,
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19 from the first 1000 patients.
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24 **Methods and Material:**

25 ***Risk adjustment***

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29 Based on rheumatology textbooks, published studies [2,15-19], and the clinical
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31
32 experience of study group members, the following risk-factors were identified as being
33
34 possible confounders as it relates to wound-disorders or non-unions in arthrodesis:
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36 diabetes mellitus, atherosclerosis, malignant tumors, cachexia due to HIV or other
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38 consuming diseases, corticoid therapy with more than 5 mg prednisolone-equivalent
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40 and/or administration for more than one year, current or history of bacterial infection in
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42 the wound or alio loco. In addition, other risk factors that were included were; sex, age,
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44 body mass-index (BMI), ASA's-classification, alcohol and smoking history.
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50 In order to obtain a quicker overview of these possible risk-factors/possible confounders
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52 these were only considered in those patients who had wound disorders during the pilot-
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54 study. While this might have caused a bias in statistical analyses and interpretation of
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56 data concerning wound disorders, seroma, and infection we accept this, since the main
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3 focus of this pilot study was to see if risk factors are present, and since we did not
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5 expect to have enough data to perform statistical analyses. In the actual registry data
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7 this bias would not occur since all risk factors and confounders must be reported in the
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9 basic form, in order to obtain valid statistical data.
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11 12 13 14 15 16 ***Number and structure of centers involved in the pilot-study***

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19 A total number of twelve centers were included in the pilot-study (table 1).
20

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22 Each center had an orthopedic surgeon with experience treating patients with
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24 inflammatory arthritic diseases. In order to have a representative cross section of the
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26 different types of provider's in Germany, different types of departments, which treat
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28 patients with rheumatic diseases, were asked to participate: hospitals specialized in
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30 rheumatology, university-based hospitals, departments whose focus was elective
31
32 orthopedic surgery and departments that focus on treating trauma-patients.
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35 36 ***Ethical approval:***

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39 Approval to conduct the study was obtained from the ethics-committee at Ruhr-
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41 University in Bochum (No.: 4138-11). The study was carried out in accordance with the
42
43 Helsinki Declaration. All patients included in the study were invited and gave their
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45 written informed consent in an initial consent form. This form, administered by the
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47 attending physician, included information about different types of rheumatic diseases,
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49 their onset, types of medications administered to patients with rheumatic disease,
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51 details about medication regimens (continued or interrupted, estimated time for re-
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53 starting medication, etc.), and surgical treatments (date and type of surgery).
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3 If a complication occurred, a second consent form was used that included information
4 about risk factors, date, and type of observed complication, as well as indicated
5 treatments. This pilot study focused on the following complications and treatments:
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7 wound disorders and skin necrosis (delayed removal of stiches, type of local treatment,
8 local suture), seroma (evacuation, local suture, re-operation), subcutaneous infections
9 (CDC A1) (with i.v. antibiotics treatment or re-operation), deep infections (CDC A2 + A3)
10 (i.v. antibiotics and re-operation). Minor complications, that did not result in an
11 appointment at the outpatient department or readmission, but instead were treated in a
12 doctor's office were not taken into account.
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27 ***Patients***

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29 Every patient suffering from inflammatory-arthritis disease and receiving surgical
30 treatment in one of the centers was asked to participate in this study and was included
31 after written informed consent was given. Inflammatory arthritis and elective surgical
32 treatment in the musculoskeletal system was the only inclusion criteria. No exclusion
33 criteria were defined. No drop-outs / withdraws of consent occurred during this pilot
34 study. The majority of the patients included in this pilot study (871 cases, 87%) suffered
35 from RA, while 7.5% had a psoriatic arthritis, 2.8% suffered from a collagenosis and
36 1.8% from ankylosing spondylosis. Other rare diagnoses included not differentiated
37 inflammatory-arthritis (four cases, 0.4%), Still's disease (three cases, 0.3%) and Crohn's
38 disease (one case, 0.1%) (Figure1).
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52 The median period of time from onset of the disease to the procedure leading to their
53 inclusion in the study was 16 years, with an interquartile range (IQR) of 10-25 years,
54 with a maximum of 64 years and a minimum of one year.
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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

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3 patients) of which 7% (67 patients) received a monotherapy, and etanercept (12%, 121
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5 patients) of which 5% (47 patients) received a monotherapy.
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8 Overall, more than half of all patients received a monotherapy (51%, 507 patients),
9
10 while 32% were treated with two different types of medication. Combinations of three
11
12 (68 patients) or four different types of immune-modulating medications (2 patients) were
13
14 rare and were reported in 7% and 0.2% of patients respectively. The reported
15
16 combinations are shown in table 2.
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23 ***Types of surgery***

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26 Nearly one third of all procedures can be categorized as bone and joint procedures:
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28 total joint replacements, arthrodeses and resection arthroplasty. Different types of
29
30 synovectomies were performed in 18% of patients. Surgeries in the lower extremity
31
32 were represented far more often (67%, 674 cases) than those in the upper extremities
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34 (26%, 262 cases). Only two patients with surgical treatment of the vertebral column
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36 were included (0.2%). The different types of surgical treatments are listed in table 3.
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43 ***Complications occurred***

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46 Complications, summarized as “wound-disorders”, and infections occurred in 26
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48 patients (2.6%) and were nearly equally distributed among upper limb, total hip- or
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50 knee-replacement, and foot and ankle surgeries. Twenty-one of these patients received
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52 pharmacological immune-modulating therapy, (interrupted perioperatively in 11 cases),
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54 while five did not receive a specific medication. 2.3% of patients with an immuno-
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56 modulating therapy had wound complications, while 5.1% receiving no
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3 pharmacotherapy for their rheumatoid disease, experienced wound complications in the
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5 form of infections.
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8 Deep infections requiring revision surgery occurred in nine patients; eight (0.8%) of
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10 which were being treated with immune-modulating drugs, and one (0.1%) who was not
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12 receiving medication.
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15 Of the 26 patients with wound complications: 14 (54%) had been treated with
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17 corticosteroids for more than one year and nine patients (35%) were receiving doses
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19 greater than a 5mg prednisolone-equivalent. Four patients (15%) had diabetes mellitus,
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21 two patients (8%) had vascular disease in the treated limb, two patients (8%) had
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23 carcinoma (none with cachexia) and one patient (4%) had a history of infection at the
24
25 time of surgery. The average age of the patients with wound disorders/infections at the
26
27 time of surgery was 65 (IQR 49-72, minimum 14, maximum 78) years. The duration of
28
29 the inflammatory-arthritic disease was 18 (IQR 10-29, minimum five, maximum 46)
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31 years (95%-CI 11-27 years). Details for these 26 patients with wound
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33 complications/infections are given in table 4.
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42 **Discussion:**

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44 Our initial results in this pilot study show that wound complications occurred twice as
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46 often in patients not receiving immune-modulating medication, while deep infections
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48 were nearly equally distributed in patients receiving and not receiving drug therapy. This
49
50 finding seems to be clinically relevant – even if the statistical significance was not
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52 demonstrated, using the fisher's exact test ($p= 0.168$) (figure 2). However, due to the
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54 surprisingly low number of complications, the inhomogeneous surgical procedures, and
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3 the variance of pharmacotherapy within the pilot-data this observation must be
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5 interpreted with care and analytical statistics cannot yet be performed.
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8 That said, these initial observations support the need to collect additional data that
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10 include risk factors, types of surgeries and pharmacotherapy in order to be able to
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12 formulate evidence-based recommendations for these patients.
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15 This pilot study has helped to identify possible confounders such as risk-factors and
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17 loss to follow-up due to missing patient identification, both important factors that must
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19 be taken into consideration as data collection moves forward.
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23 The postulated risk-factors were found in patients with wound disorders, indicating, that
24
25 these risk-factors will have to be considered as possible confounders in order to
26
27 evaluate the influence of pharmacotherapy on wound complications. Based on this
28
29 observation, these risk-factors have been included in the initial patient inclusion criteria
30
31 forms (“basic questionnaire”), This will make it possible to perform risk-adjusted
32
33 analyses combined with age, sex, BMI, ASA’s classification, alcohol and smoking
34
35 history, type and onset of rheumatic disease, in the actual registry (Figure 3). Taking
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37 these confounders into account will help formulate more accurate and relevant
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39 preoperative recommendations related to the influence of pharmacotherapy in these
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41 patients.
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46 The surprisingly low number of patients with postoperative wound disorders and
47
48 infection compared to the considerably higher figure published in literature [10, 20, 21]
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50 can be explained by the loss to follow-up of patients with minor wound complications
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52 treated with local therapy outside the hospital. These patients were not included in this
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54 study because the ID assigned to them by their respective hospitals made follow up
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56 impossible as they received care elsewhere. To remedy this a patient pseudonym was
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3 generated based on non-changing patient data consisting of; date and location they
4 were attended, place of birth -city and state -, Christian name and maiden name. This
5 so called “salt-protected hash-code” ensures that, even in the most complicated forms
6 and between different institutions, patients can be linked to their individual data set
7 helping to avoid a loss to follow-up in the actual registry.
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15 Finally, based on this pilot study additional data will be collected documenting in more
16 detail, the type of treatment wound disorders received and the final status of the wound
17 complication, thus being able to distinguish between minor and major wound
18 complications in the registry.
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23 24 25 **Limitations:**

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27 Due to the small number of patients with observed complications as well as the
28 inhomogeneity in the surgical and pharmacological treatments they received extended
29 analytical statistics could not be performed. Accordingly, at this time no
30 recommendations for perioperative management of anti-inflammatory drugs could be
31 derived from these first 1000 datasets.
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39 In the actual registry, the analysis of data reported in high volumes, like monotherapy
40 and single surgeries will be considered first line, while those occurring in low-volumes
41 like multiple surgeries or combinations of medication will be designated second line and
42 will be analyzed taking the first line into consideration.
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52 53 **Conclusion:**

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55 Besides age, sex, risk-factors, type and duration of the rheumatic disease, the
56 administration of immune-modulating medications may impact wound complications.
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3 Due to the inhomogeneity in the disease itself and the treatments received by patients
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5 with rheumatic diseases it is difficult to develop standardized best-practice
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7 recommendations to optimize their care. Therefore, the creation of a large,
8
9 comprehensive national registry that includes the most important and relevant variables
10
11 that impact the care and outcomes of these patients is essential. This pilot study has
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13 helped to identify these variables and in doing so will contribute to improving the
14
15 national registry so that its data can be used to formulate accurate and relevant
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17 recommendations for the care of this vulnerable patient population.
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22 **Acknowledgement:**

23
24
25 Special thanks to the native-speakers Prof. John Barker and Kirsten Hartmann for their
26
27 assistance editing the English content in this manuscript.
28
29

30 Results from 873 pilot study patients were presented as a poster at the GMDS
31
32 (German Society for Medical computer science, Biometry and Epidemiology)-Congress
33
34 2014 in Göttingen / Germany
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37 External funding to perform this pilot study was not made available, however
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39 permission to establish the online registry was granted by the German Orthopedic
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41 Society (DGOOC).
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Tables:

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Orthopedic and Policlinic, University hospital Leipzig; Leipzig
Rheuma-orthopedics, 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.

	Aldalim umab	Ertane cept	Tociliz umab	Rituxi mab	Inflix mab	Abate cept	Golimu mab	M TX	Lefluno mide	Azathio prine	Sulfasal azine	Hydro xy- cloroq uine	Oth ers	Cortic oids	Tot al:
Aldalim umab	28	0	0	0	0	0	0	10 6	6	1	2	1	4	0	68
Ertanec ept	0	47	0	0	0	0	0	41	17	1	4	3	1	24	12 1
Tocilizu mab	0	0	12	0	0	0	0	4	1	0	2	0	0	3	20
Rituxim ab	0	0	0	16	0	0	0	11	2	0	2	2	0	6	35
Inflixim ab	0	0	0	0	3	0	0	5	0	0	1	0	0	2	9
Abatece pt	0	0	0	0	0	3	0	6	2	0	0	1	0	2	9
Golimu mab	0	0	0	0	0	0	3	7	0	0	0	0	0	6	15
MTX	106	41	4	11	5	6	7	19 1	43	2	31	24	10	109	45 3
Lefluno mide	6	17	1	2	0	2	0	43	67	1	15	5	5	40	17 9
Azathio prine	1	1	0	0	0	0	0	2	1	10	0	1	0	5	18
Sulfasal azine	2	4	2	2	1	0	0	31	15	0	34	8	0	19	99
Hydrox y- cloroqui ne	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
Corticoi ds	6	24	3	6	2	2	6	10 9	40	5	19	22	1	60	25 3

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

	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 = metacarpophalangeal joints, DIP-/PIP-joints = distal interphalangeal / proximal interphalangeal joints.

Types of complications	Number of patients	Type of surgery	Risk factor corticosteroids >1 year	Risk factor corticosteroid > 5 mg prednisolone 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 patients 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

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3 **Table 4: Patients with reported postoperative complications. Wound disorders/infections**
4 **postoperatively were the most reported complications. The number of patients affected is given in**
5 **each group. Median age at surgical treatment 64.9 years (IQR 48.8-72.0; min. 13.5; max. 78.0). Median**
6 **duration of rheumatic disease, 20.0 years (IQR 11.5-29.0; min. 5.0; max. 46.0). Wound disorders were**
7 **observed more often in patients not receiving immune-modulating medication. The percentage of**
8 **patients with infection was slightly higher in those not receiving immune modulating medications (0.9**
9 **vs. 1%). One patient with a palsy of the peroneal nerve was reported, which has to be considered as**
10 **a mechanical problem.**
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20 **Legend figures 1-3:**
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22 **Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients**
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24 **Figure 2: Wound disorders and infections occurred more than twice as often as in patients not**
25 **receiving immune-modulating medication, compared to treated patients. There was no statistical**
26 **significance (Fisher's exact test, $p= 0.168$, 5%-level) in the occurrence of wound complications**
27 **between patients treated with immune-modulating drugs and those not treated.**
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29 **Figure 3: Questionnaires adapted for use in the registry based on the findings from the pilot-study.**
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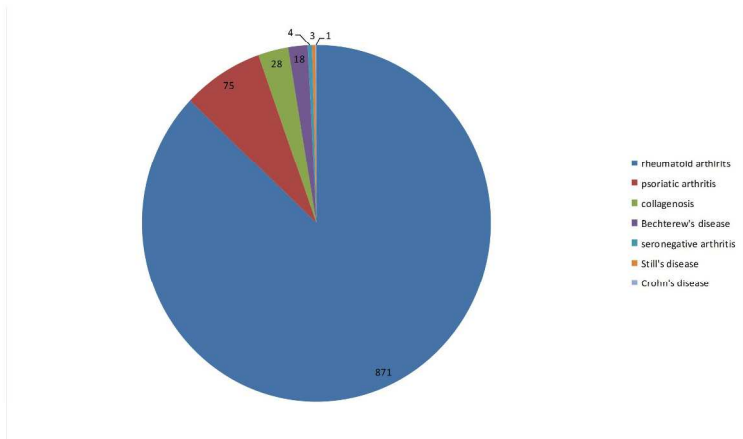
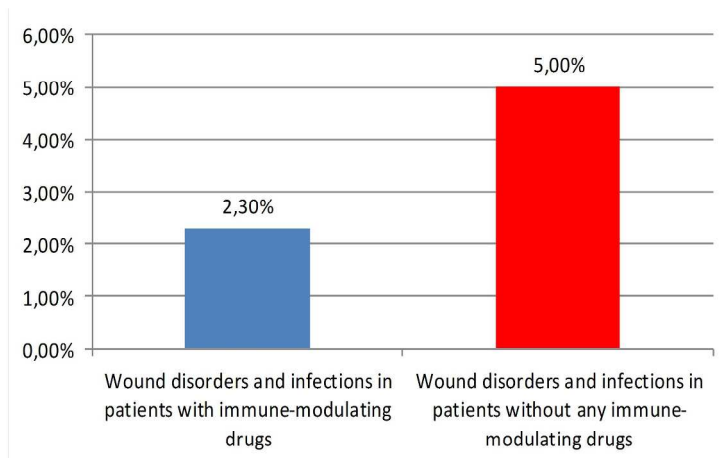


Figure 1: Distribution of different rheumatic diseases among the 1000 pilot-study-patients.

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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.

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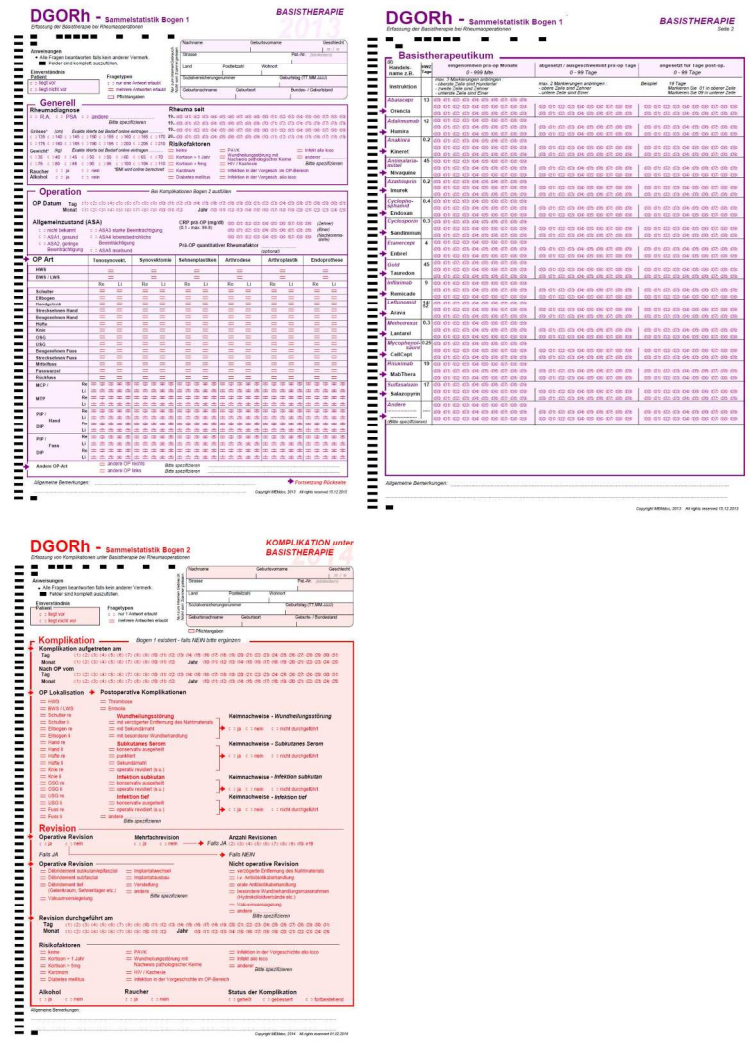


Figure 3: Based on the findings from the pilot-study adapted questionnaires for the real-time-work of the register.

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.