Linking process indicators and clinical/safety outcomes to assess the effectiveness of abatacept (ORENCIA) patient alert cards in patients with rheumatoid arthritis

Esther Artime1 | Randip Kahlon2 | Ignacio Méndez1 | Tzuyung Kou3 | Macarena Garrido-Estepa1 | Nawab Qizilbash1,4

1Epidemiology & Risk Management, OXON Epidemiology, Madrid, Spain
2Worldwide Patient Safety, Bristol-Myers Squibb, Uxbridge, UK
3Worldwide Patient Safety, Bristol-Myers Squibb, Hopewell, New Jersey
4Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK

Correspondence
Nawab Qizilbash, OXON Epidemiology, Madrid, Spain.
Email: n.qizilbash@oxonepi.com

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Abstract
Purpose: Patient alert cards (PACs) for abatacept (ORENCIA) inform patients and healthcare professionals (HCPs) about the risk of infections and allergic reactions. The study evaluates the effectiveness of the PACs in rheumatoid arthritis patients and HCPs, using process indicators (awareness, receipt, utility, knowledge, behaviour) and outcomes.

Methods: Surveys of patients and HCPs in five European countries. A retrospective chart review permitted linking clinical and safety outcomes with survey responses.

Results: Data on 190 patients and 79 HCPs (50 physicians and 29 nurses) were analysed. Sixty percent of patients were aware of the PAC, of whom 95% had received it. Knowledge of risk of infection was higher among patients who had received the PAC vs those who had not (64% vs 46%; P = .013). Infections leading to hospitalisation increased with decreasing patient survey global scores: scores of ≥67%, 34%-67% and ≤33% were associated with hospitalisation rates of 2.5%, 5.2% and 8.4%, respectively (P = .4). Among HCPs 90% were aware and 68% had accessed the PAC. More nurses than physicians were aware (93% vs 88%), had accessed (78% vs 74%), read (90% vs 59%), distributed (81% vs 66%) and explained the content (94% vs 43%) of the PAC. Knowledge of risk of infection was higher among HCPs who had (91%) vs those who had not (73%) accessed the PAC (P = .053).

Conclusions: PACs were effective in improving knowledge of key safety messages in patients and HCPs. This novel study design bridges the gap of linking process indicators with outcomes in the same patients, thereby strengthening the clinical relevance of patient surveys.

KEYWORDS
educational material, effectiveness evaluation, PASS, patient alert card, pharmacoepidemiology, risk minimisation, survey

1 | INTRODUCTION

Abatacept (ORENCIA) is a selective immunosuppressant indicated for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis and psoriatic arthritis. As part of a regulatory commitment to the European Medicines Agency (EMA), patient alert cards (PACs) were developed for each formulation (intravenous [IV] and subcutaneous [SC]), to help inform patients and healthcare professionals...
(HCPs) of the potential risks and actions required during treatment with the product, specifically for infections and allergic reactions. The only difference between the two PACs, both provided in each medicine pack, is that the IV PAC includes a field to indicate the date of the most recent injection, while the SC PAC does not. The principal aim of the PACs is to ensure appropriate action by patients and HCPs when an infection occurs, with the ultimate goal of reducing the occurrence of undesirable outcomes (e.g., hospitalisations), or severity (e.g., reducing delays in seeking medical care). HCPs are expected to be active key players to provide and explain the contents of the PAC to RA patients.

The marketing authorisation holder (MAH), Bristol-Myers Squibb (BMS), commissioned OXON epidemiology (OXON) to conduct a study to evaluate the effectiveness of the abatacept PACs in RA patients and HCPs using process indicators. The study design also linked these process indicators with clinical and safety endpoints in the same patients.

2 | METHODS

2.1 | Study design

The study consisted of three sub-studies:

- Two cross-sectional surveys of HCPs and patients to assess process indicators (awareness, receipt, utility, utilisation, knowledge and behaviour related to the PACs) and
- A retrospective chart review of patient data to assess clinical and safety outcomes.

The study was conducted in France, Germany, Spain, Sweden and the UK.

The details of the study design are shown in Figure 1. Figure 1A shows the scenarios considered valid for inclusion in the patients sub-studies. In the retrospective chart review sub-study, follow-up data were collected for 2 years before the date of informed consent, or less if abatacept was commenced less than 2 years from the date of informed consent (Figure 1B).

Key messages contained in the PACs are listed in Table 1.

The study, classified as a Post-Authorisation Safety Study (PASS), was conducted according to GVP Modules XVI1 and VIII2 and best practices based on guidelines3-5 and publications6-14.

2.2 | Study population and sampling

Only patients treated with abatacept for RA in the 3 months preceding the date of completing the questionnaire were included. After informed consent patients received the survey questionnaire. Data were extracted from the clinical medical records of patients who had completed the survey questionnaire.

Physicians were selected using random sampling applied to lists of rheumatologists provided by the MAH and panels (Figure 1C).

Nurses were identified through physicians. Physicians and nurses who recruited patients were not eligible for the HCP survey. ‘Fair market’ fees were paid to HCPs for completed questionnaires.

Patients and HCPs were identified by a unique code in the OXON validated electronic data capture (EDC) platform, allowing linkage of patients between the survey and the retrospective chart review.

2.3 | Data collection tools

HCP and patient questionnaires were translated into local languages, and cognitively pretested by HCPs and patients. The questionnaires consisted of multiple-choice questions including conditional branching based on responses to previous questions to improve user friendliness and reduce missing data. Patient questionnaires were completed online or on paper. HCP questionnaires were only available online.

For the retrospective chart review, HCPs or data managers were trained to extract information from patient’s clinical medical records and enter it into the EDC platform. The EDC platform guided data extraction and contained edit checks and management of queries to improve data quality.

2.3.1 | Sample size

The study aimed to recruit 400 patients to allow precision of less than ±5% around plausible estimates (ranging from 50% to 90%) of correct responses for process indicators related to the PACs. This number would also permit the detection of a moderate decrease in the risk of infection-related hospitalisations (odds ratio < 0.23) between patients with ≥80% correct responses vs <80% correct response. A target of 80 HCPs would allow precision ±6.6% to 11.0% around plausible estimates (70%-90%) of correct responses for HCP process indicators.
FIGURE 1   Design features of the three related sub-studies. A, Patient scenarios valid for inclusion in the study. Horizontal arrows represent abatacept treatment periods for specific patients. Patients who received abatacept within the 3 months prior to the date of questionnaire completion were eligible for participation in the study. B, Retrospective data collection. Follow-up data were collected for the 2 years prior to the date of informed consent, or less if abatacept was commenced less than 2 years from the date of informed consent. C, Sampling and recruitment strategy.
2.4 | **Study endpoints and data analysis**

2.4.1 | **HCP and patient surveys**

HCPs and patients with questionnaires received before database closure were considered as ‘completers’. Participation rates were defined as the number of participants with completed questionnaires among the number invited in each category or among the number eligible.3,4

The definition of study endpoints and scores is provided in Table 2. Percentages were computed using the number of participants who answered specific questions as the denominator, excluding missing responses. All analyses were performed overall and by receipt vs no receipt of the PAC.

### TABLE 1

**Key messages in the abatacept patient alert cards**

| Safety concerns | Key messages |
|-----------------|-------------|
| Infections      | • Patients receiving abatacept are at increased risk of infections  
                 • Avoid abatacept in patients with severe infection  
                 • Need for screening for infections prior to abatacept: TB and VH  
                 • Seek medical attention if symptoms suggestive of infection occur for example, fever, persistent cough, weight loss, listlessness |
| Allergic reactions | Seek medical attention if symptoms of allergic reactions occur including chest tightness, wheezing, severe dizziness and light headedness |
| Others          | • Show the PAC to any doctor who may treat them  
                 • Take a full list of medicines on visiting a HCP  
                 • Keep the PAC for 3 months after the last dose of abatacept  
                 • Document the abatacept start date (IV and SC)  
                 • Document the date of the most recent abatacept treatment (IV only)  
                 • Complete patient’s name and the doctor’s name and phone number |

Abbreviations: HCP, healthcare professional; IV, intravenous; PAC, patient alert card; SC, subcutaneous; TB, tuberculosis; VH, viral hepatitis.

### TABLE 2

**Study endpoints**

| Study endpoint   | Definition                                                                 |
|------------------|-----------------------------------------------------------------------------|
| **Awareness**    | Proportion of HCPs/patients who were aware of the PAC                         |
| **Receipt**      | • Proportion of HCPs who had access or received the PAC                      |
|                  | • Proportion of patients who recalled receiving the PAC                      |
| **Utilisation**  | • Proportion of HCPs/patients who recalled having read the PACs              |
|                  | • Proportion of HCPs who explained contents to their patients               |
|                  | • Overall utilisation score, computed as the percentage of correct responses to variables that assessed utilisation, that is, 100 times the sum of all variables, divided by the number of variables. |
| **Utility**      | • Assessments of understandability and readability of the PACs (clarity, conciseness, completeness, brevity)  
                 • Overall utility score  
                 In the patient survey, the utility score was computed as 100 times the sum score of items assessing clarity, conciseness, completeness and brevity (recoded as 0 = worst value to 4 = best value) and understandability (ranging from 0 to 4), divided by the maximum possible score of 20.  
                 In the HCP survey, the utility score was computed as 100 times the sum score of items assessing helpfulness, clarity, conciseness, completeness and brevity (recoded as 0 = worst value to 4 = best value), divided by the maximum possible score of 20. |
| **Knowledge**    | • Proportion of HCPs/patients with correct responses to questions related to the important identified risks of infections and allergic reactions associated with abatacept treatment  
                 • Overall knowledge score, computed as the percentage of correct responses to variables that assessed knowledge, that is, 100 times the sum of all variables, divided by the number of variables. |
| **Behaviour**    | • Proportion of HCPs/patients with correct responses to behavioural questions  
                 • Overall behavioural score, computed as the percentage of correct responses to variables that assessed behaviour, that is, 100 times the sum of all variables, divided by the number of variables. |
| **Global score** | An average score that summarises the overall correct utilisation of the PAC, correct knowledge, correct behaviour and utility.  
                 This score is presented in three categories by tertiles: high level (scores ≥67%), medium level (scores 34%-67%) and low level (scores 0%-33%). |

**Correlation of global score of the patient survey with:**

| Percentage of patients with:  
| Results of any test to screen for TB prior to administration of abatacept therapy  
| Results of any test to screen for VH before administration of abatacept therapy  
| Infections leading to hospitalization  
| Infections leading to emergency room visits  
| Average number of days per patient from first symptom onset of infection until receiving medical attention. |

Abbreviations: HCP, healthcare professional; PAC, patient alert card; TB, tuberculosis; VH, viral hepatitis.
2.4.2 | Retrospective chart review

The extracted outcomes included (Table 2): availability of results of screening tests for tuberculosis (TB) and viral hepatitis (VH) prior to abatacept use (yes/no), occurrence of infections due to abatacept leading to hospitalisation and/or infections due to abatacept leading to emergency room visits (yes/no), and time from occurrence of infection to receiving medical attention. Numbers and percentages were calculated for each outcome. The mean number of days between the dates of first symptom onset of the infection and receiving medical attention was calculated.

Univariate analyses correlated within-patient clinical and safety outcomes responses to process indicators in the patient survey. The primary analysis assessed the frequency of infections leading to hospitalisation in patients by tertiles of the patient survey global score of the PAC using a two-sided chi-square test.

3 | RESULTS

3.1 | Patient survey

Participation rates calculated by completers/invited was 59.7% (190/318) and by completers/eligible was 67.9% (190/280). The disposition of patients is shown in Figure 2 and patient characteristics in Table 3.

From those with information, 59.7% (111/186) of patients were aware of the PAC, of whom 94.6% (105/111) recalled having received or accessed it, mainly through the specialist nurse (44.8%, 47/105) and in the medication box (30.5%, 32/105); and 83.8% (88/105) had read the material. By route of administration, 65.6% (40/61) of patients were aware of the PAC for the IV formulation and 56.9% (70/123) for the SC formulation.

More than half the patients who received the PAC or selected ‘I do not remember’ (56.6%; 60/106) indicated that the information...

| TABLE 3  | Patient characteristics |
|----------|-------------------------|
|          | Patients                |
| N = 190  |                         |

| Country   | n (%) |
|-----------|-------|
| France    | 16 (8.42) |
| Germany   | 30 (15.79) |
| Spain     | 75 (39.47) |
| UK        | 59 (31.05) |
| Sweden    | 10 (5.26) |

| Type of questionnaire | n (%) |
|-----------------------|-------|
| Paper                 | 169 (88.95) |
| Electronic            | 21 (11.05) |

| Age group       | n (%) |
|-----------------|-------|
| 18-25 years     | 0 (0.00) |
| 26-35 years     | 6 (3.16) |
| 36-45 years     | 21 (11.05) |
| 46-55 years     | 29 (15.26) |
| 56-65 years     | 55 (28.95) |
| >65 years       | 79 (41.58) |

| Gender         | n (%) |
|----------------|-------|
| Male           | 44 (23.16) |
| Female         | 146 (76.84) |

| Educational level | n (%) |
|-------------------|-------|
| No schooling completed | 12 (6.38) |
| Primary school    | 42 (22.34) |
| No schooling completed/Primary school | 0 (0.00) |
| Secondary school  | 81 (43.09) |
| Some college further education (eg, at a college) | 24 (12.77) |
| Bachelor's degree | 8 (4.26) |
| Master's degree or doctorate | 15 (7.98) |
| Other professional qualification | 6 (3.19) |
| Missing           | 2     |
**FIGURE 3** Level of correct knowledge in patient survey. Positive correct responses (=Yes) are displayed in dark grey and negative correct responses (=No) in light grey.

**FIGURE 4** Proportion differences in level of correct knowledge in patient survey according to receipt/non-receipt of the patient alert card. Abbreviations: HCP, healthcare professional; IV, intravenous; PAC, patient alert card; RA, rheumatoid arthritis; SC, subcutaneous.
contained in the material had been explained to them. Among 76 patients who received explanation of the contents of PAC or who selected ‘I do not remember’, the source of the explanation was primarily a specialist nurse for 53.9% and a doctor in 35.5%.

The PAC was carried at all times by 64.5% (69/107) of patients and 59.6% (62/104) were aware that they should present it to every physician involved in their healthcare. The mean (SD) scores were 65.2% (29.5) for utilisation, 87.2% (22.7) for understandability, 65.5% (42.3) for clarity, 64.2% (41.8) for conciseness, 61.1% (40.2) for completeness, 56.3% (42.3) for brevity, resulting in an overall mean utility score of 60.5% (32.8).

Levels of correct knowledge in patients are shown in Figure 3. The mean knowledge score (across all knowledge questions) was higher among those who recalled receiving the PAC compared with those who did not (64.5% vs 36.9%; \(P < .001\)). As shown in Figure 4, knowledge about the risk of infections was higher among those who recalled having received the PAC compared with those who did not (63.8% vs 45.9%; \(P = .013\)). Knowledge about pre-screening for TB and VH were correctly indicated by 77.9% and 47.4% of patients, respectively. In both cases, this knowledge was among those who recalled having received the PAC compared with those who did not: 87.6% vs 65.9% for TB (\(P < .01\)) and 55.2% vs 49.2% for VH (\(P = .016\)). While only 28.4% of patients identified the PAC as a source where to find information about the benefits and risks of abatacept, it was higher among those who recalled receiving the PAC than those who did not (35.2% vs 26.2%; \(P = .021\)).

The percentage of patients who were aware that a list of all other medicines being taken with abatacept should be carried at any visit to a HCP was higher among those who recalled having received the PAC than in those who did not (85.7% vs 72.9%; \(P = .029\)). By contrast, the recommendation to keep the PAC for 3 months after the last dose of abatacept was only known by 26.2% of patients who received the PAC vs 0.0% of those who did not.

The majority of patients reported that HCPs informed them about the side effects of abatacept (66.1%; 125/189). Implementation of behaviour was also assessed through hypothetical scenarios of when to seek immediate medical attention: correct responses were 68.9% (131/190) for fever, 80.5% (153/190) for chest tightness, 66.3% (126/190) for wheezing and 64.2% (122/190) for severe dizziness or feeling light-headed.

The mean (SD) global score was 46.1% (23.1) overall and higher among patients who indicated having received the PAC than in those who did not (65.6% vs 26.9%; \(P < .001\)).

### TABLE 4 Correlation analysis

| Categorical variables | Level of understanding and implementation of the PAC | Test | \(P\)-value\(^b\) |
|-----------------------|-----------------------------------------------|------|-----------------|
|                       | High | Medium | Low |                      |
|                       | Valid n | n | % col | n | % col | n | % col |                      |
| Patients with results of any pre-screening test for TB before abatacept | Yes | 116 | 24 | 60.00 | 47 | 81.03 | 45 | 54.22 | Chi-square test | .004\(^c\) |
| No | 65 | 16 | 40.00 | 11 | 18.97 | 38 | 45.78 | |
| Patients with results of any pre-screening test for viral hepatitis before abatacept | Yes | 111 | 23 | 57.50 | 41 | 70.69 | 47 | 56.63 | Chi-square test | .206 |
| No | 70 | 17 | 42.50 | 17 | 29.31 | 36 | 43.37 | |
| Patients with infections leading to unplanned hospitalisation during the follow-up | Yes | 11 | 1 | 2.50 | 3 | 5.17 | 7 | 8.43 | Fisher exact test | .440 |
| No | 170 | 39 | 97.50 | 55 | 94.83 | 76 | 91.57 | |
| Patients with infections leading to emergency room visit during the follow-up | Yes | 7 | 1 | 2.50 | 2 | 3.45 | 4 | 4.82 | Fisher exact test | 1.000 |
| No | 174 | 39 | 97.50 | 56 | 96.55 | 79 | 95.18 | |
| Continuous variables | Valid n | n | Mean | Std. error | n | Mean | Std. error | n | Mean | Std. error | Test | Statistic | Value | \(P\)-value\(^e\) |
| Number of days from first symptom onset of infection until receiving medical attention (average per patient)* | 16 | 3 | 7.0 | 3.464 | 5 | 3.6 | 2.619 | 8 | 8.8 | 2.725 | Mann-Whitney U | 8.50 | .103 |

Abbreviations: PAC, patient alert card; TB, tuberculosis.

*The univariate analysis was performed among groups with at least five cases.

\(^b\)Bold values correspond to statistical significance of the differences between groups (\(p<0.05\)).

\(^c\)Yes is associated with 'Medium Level' and No with 'Low Level'.
3.2 Correlation of patient survey process indicators with clinical/safety outcomes from retrospective chart review

Of the 190 patients who completed the patient questionnaire, 181 had outcomes data extracted. The nine patients without outcomes data was due mainly to closure of the study before the data could be collected. Pre-treatment screening tests for TB and for VH were available in 83.4% (151/181) and 69.1% (125/181) of patients, respectively; 76.8% (116/151) had the results available for TB and 88.8% (111/125) for VH before abatacept. The mean (SD) time from symptom onset of the infection to receiving medical attention (per patient), in 16 patients with data available, was 6.8 (± 6.9) days. Seven of 181 patients (3.9%) had infections leading to emergency room attendance and 11 (6.1%) had infections leading to hospitalisation. In the correlation analysis (Table 4), the percentage of patients with infections leading to hospitalisation increased as patient survey global scores decreased: scores of ≥67%, 34%-67% and ≤33% were associated with hospitalisation rates of 2.5% (1/40), 5.2% (3/58) and 8.4% (7/83), respectively (P = .44). A statistically significant association was observed for the correlation of the global composite score and screening for TB: global scores of ≥67%, 34%-67% and ≤33% were associated with screening for TB scores of 60.0%, 81.0% and 54.2%, respectively (P = .004). No significant correlation was found for screening for VH: global composite scores of ≥67%, 34%-67% and ≤33% were associated with screening for VH scores of 57.5%, 70.7% and 56.6%, respectively. There was no correlation for emergency room visits and by days from first onset of symptoms of infection to receiving medical attention with global scores.

**Figure 5** Healthcare professional disposition. Abbreviations: HCP, healthcare professional

**Table 5** Healthcare professional characteristics

| HCPs | N = 79 |
|------|--------|
| Country | |
| France | n (%) 23 (29.11) |
| Germany | n (%) 14 (17.72) |
| Spain | n (%) 17 (21.52) |
| UK | n (%) 21 (26.58) |
| Sweden | n (%) 4 (5.06) |
| Age group | |
| 18-25 years | n (%) 0 (0.00) |
| 26-35 years | n (%) 10 (12.66) |
| 36-45 years | n (%) 30 (37.97) |
| 46-55 years | n (%) 28 (35.44) |
| 56-65 years | n (%) 11 (13.92) |
| >65 years | n (%) 0 (0.00) |
| Gender | |
| Male | n (%) 29 (36.71) |
| Female | n (%) 50 (63.29) |
| Type of HCP | |
| Rheumatologist | n (%) 49 (62.03) |
| Rheumatologist in training | n (%) 1 (1.27) |
| Specialist nurse | n (%) 29 (36.71) |
| Internist | n (%) 0 (0.00) |
| Years managing RA patients | |
| <5 years | n (%) 3 (3.80) |
| 5-10 years | n (%) 19 (24.05) |
| 11-20 years | n (%) 36 (45.57) |
| >20 years | n (%) 21 (26.58) |
| Number of RA patients managed personally with abatacept in previous 12 months | |
| n (n missing) | 79 (0) |
| Mean (SD) | 29.3 (62.6) |
| Median (Q1-Q3) | 12.0 (6.0-24.0) |
| Min - Max | 2.0-400.0 |

Abbreviations: HCP, healthcare professional; RA, rheumatoid arthritis.
3.3 | HCP survey

Only 320 HCPs were evaluable among 2385 HCPs invited to participate. From these 320 HCPs, only 107 were eligible and 79 (50 physicians and 29 nurses) completed the questionnaire. The percentage of completers/evaluable invitees was 24.7% (79/320) and that of completers/eligible was 73.8% (79/107). The disposition of HCPs in the study is shown in Figure 5 and characteristics of the 79 HCPs in Table 5.

The majority of HCPs (89.7%; 70/78) were aware of the PAC, of whom 68.0% (53/78) reported having had access or receiving it. Half of those who had received the PAC offered it to patients with the first prescription (50.0%; 19/38) and 47.4% (18/38) did at or before first administration. The PAC was mainly provided by nurses (66.7%; 52/78). Among HCPs who received or had access to the PAC, 71.7% (38/53) also read it. Most HCPs explained the content of the PAC to their patients at least sometimes (65.8%; 25/38). More nurses than physicians were aware (93.1% vs 87.8%), had accessed (77.8% vs...
74.4%), read (90.5% vs 59.4%), distributed (80.9% vs 65.6%) and explained the content (94.1% vs 42.9%) of the PAC.

Among readers of the PAC, the mean (SD) utilisation score was 50.9% (37.3). The level of helpfulness of the PAC was 70.4% (20.0), clarity 75.0% (25.3), conciseness 73.7% (23.2), completeness 71.1% (25.0) and brevity 66.4% (25.5), resulting in an overall mean utility score of 71.3% (20.4).

Knowledge about the risk of infections was 84.8% (67/79) (Figure 6). The recommendations of pre-screening for TB and VH were known by 84.8% and 73.4% of HCPs, respectively (Figure 6). Figure 7 shows the differences in knowledge levels between HCPs who received the PAC compared with those who did not. No statistically significant differences in knowledge of any safety concerns were found between HCPs who did and did not receive the PAC. The mean (SD) knowledge score was 72.3% (17.0), and non-statistically significantly higher among those who remembered receiving the PAC compared with those who did not (74.8% vs 67.2%; P = .274).

Most HCPs (96.2%) informed patients about the side effects of abatacept. The mean behaviour score was higher among HCPs who recalled having received the PAC compared with those who did not (79.2% vs 63.5%; P = .027).

The mean global score was higher among HCPs who reported having received the PAC compared with those who did not (68.8% vs 33.1%; P < .001).

4 | DISCUSSION

The study employed a hybrid design to evaluate the effectiveness of the abatacept PACs using both process indicators and clinical/safety outcomes in the same patients, and is the first published study of its type of which we are aware.

Patients were recruited via physicians and the lower than anticipated recruitment of patients appeared to be due low use of abatacept in the study centres.

Awareness of the PAC was moderate among patients. More reassuring is that if patients receive the PAC, they most often read it. Higher levels of correct knowledge about the risk of infections and pre-screening for TB and VH, behaviours around these messages and the global score were observed among patients who recalled having received the PAC compared with those who did not, which suggests that the PAC may have an effect on levels of knowledge and behaviour.

Despite low numbers of clinical and safety endpoints, a numerical increasing trend was observed in the primary endpoints of infections leading to hospitalisation and infections leading to emergency room visits as the patient survey global score decreased. However, these results are not statistically significant and would require a bigger sample for confirmation.

Most HCPs reported being aware of the PAC, with fewer accessing and reading it. Nurses were identified as the HCP responsible for providing the PAC by more than two-thirds of HCP respondents. Thus, the importance of the role of the rheumatology nurse responsible for handling and explaining the content of the PAC to the patient is clear. Most HCPs considered the PAC to be clear, concise, complete and helpful. Knowledge about the risk of infections was high among all HCPs, with no differences observed between HCPs who received the PAC and those who did not. HCPs who manage RA patients familiar with biologic therapy—infection is a known common risk—and may acquire most of their information about the use and risks of abatacept from sources other than the PACs. Behaviour and global scores were higher among HCPs who had access to the PAC, suggesting a potential impact around implementation of some key messages.

The main strength of this study was the ability to correlate survey responses with clinical and safety outcomes in the same patients. The study used a novel design that bridges the gap of linking process indicators with outcomes for the assessment of effectiveness of risk minimisation measures, strengthening the clinical relevance of results from surveys. Previous studies have been conducted to assess outcomes and process indicators, though no designs comprising within-person correlations have been reported in the published literature, as far as we are aware. However, the applicability of this approach to evaluate the effectiveness of risk minimisation interventions for other products needs to be assessed on a case-by-case basis.

The range of countries with different healthcare systems and multiple sites provides a global overall picture of the performance of the abatacept PACs among RA patients and HCPs in Europe.

The study has some limitations. While the planned number of HCPs was recruited, it involved a significant recruitment effort requiring invitations to 2385 potential HCPs. How many of the 2029 non-responders, despite several reminders, were not eligible is unknown but we do know that some two-thirds of all responders were not eligible. Thus, the generalisability of the results has some uncertainty. Nonetheless, low response rates in surveys involving HCPs is a well-known limitation and has been previously acknowledged in other studies of this kind.

While differences in results in those who receive and do not receive the PAC is the strongest evidence from the surveys alone, they may not be unconfounded comparisons. Thus, results need to be cautiously interpreted. There is potential bias in extrapolating current understanding and implementation in patient surveys with past events in this retrospective study. The scores were created to assess the impact of the PAC in the target populations, including those who reported being aware and having received the PAC vs never having received the PAC. Furthermore, it is possible that there may have been some information bias, particularly since behaviour was self-reported by the participant. However, the correlation of clinical outcomes of screening for TB with survey results indicate that the survey results may be valid. Potential response bias was minimised with ‘best practice’ qualitative techniques to develop the questions and their implementation in the online survey such as sequencing of questions, skipping questions was not permitted, questions could not be changed once submitted.

The practical impact of this study resulted in no modifications to the content of the PAC or further evaluations being requested by EMA regulators.
CONCLUSION

The study assessed the effectiveness of the abatacept PACs among patients and HCPs in five European countries, using process indicators and outcomes. This novel study design bridges the gap of linking process indicators with outcomes at the individual-patient level and strengthens the clinical relevance of results from surveys.

The results support the effectiveness of the abatacept PACs. The study results suggest that the distribution of the PAC to patients could be improved, despite already being included inside the abatacept product packaging and that nurses should be the main target of any strengthened distribution efforts, where feasible.

ETHICS STATEMENT

The protocol was approved by Ethics Committees in all five participating countries.

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CONFLICT OF INTEREST

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ORCID

Esther Artime https://orcid.org/0000-0003-4294-6462
Nawab Qizilbash https://orcid.org/0000-0001-6950-2322

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