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ORIGINAL RESEARCH

Patients' perspectives on a drug safety monitoring system for immune-mediated inflammatory diseases based on patient-reported outcomes

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ABSTRACT

Background: Patient-reported outcomes (PROs) on adverse drug reactions (ADRs) are increasingly used in cohort event monitoring (CEM) to obtain a better understanding of patients' real-world experience with drugs. Despite the leading role for patients, little is known about their perspectives on CEM systems.

Research design and methods: In a cross-sectional open survey following the rationale of the Technology Acceptance Model, we aimed to obtain insight in patients' perspectives on the perceived usefulness, ease of use and attitude toward using a PRO-based drug safety monitoring system for ADRs attributed to biologics.

Results: Patients considered structural reporting of ADRs in web-based questionnaires as useful and not burdensome. It was preferred to link the questionnaire frequency to regular hospital consultations or the biologic administration schedule. Various respondents were interested in sharing questionnaires with their medical specialist (49.0%) or pharmacist (34.2%), and suggested to minimize the questionnaire frequency in case of an unaltered situation or absence of ADRs.

Conclusions: Patients' perspectives should be considered in the setup of PRO-based CEM studies, as this contributes to data quality and patient centeredness. Since incorporation of patients' perspectives in CEM studies is indispensable, a delicate balance should be found between user-friendliness and study aims.

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Adverse drug reactions; biologics; immune-mediated inflammatory diseases; patient-reported outcomes; cohort event monitoring; patient perspective

1. Introduction

Patient participation has not always been common in the post-marketing surveillance of drugs. For many years, patients were left out of pharmacovigilance practices, as the reporting of adverse drug reactions (ADRs) to national pharmacovigilance centers was mainly reserved for healthcare providers (HCPs) [1]. Current trends stimulate patient participation in pharmacovigilance, as patients' perspectives are increasingly recognized as a valuable source of information [2]. In the European Union, patients have had a formal role in pharmacovigilance since the implementation of the pharmacovigilance legislation in 2012 [3]. From this point on, non-healthcare professionals were able and stimulated to report suspected ADRs directly to national pharmacovigilance centers.

The detection of new safety information after marketing is mainly based on spontaneous reporting of ADRs. Despite the vast amount of reports, complementary monitoring methods are required to obtain more insight in experiences with ADRs [4], for example via the systematic collection of patient-reported outcomes (PROs) on ADRs. Whereas spontaneous reporting is primarily aimed at the detection of new safety signals, PROs can be used to increase knowledge on the patient perspective on mostly known ADRs. Since PROs are directly reported by patients, the reports provide unfiltered information on subjective aspects of patients' health, including details on the course of ADRs and the resulting impact on their lives [5,6]. If collected systematically, PROs can contribute to the faster accumulation of knowledge on ADRs and thereby strengthen the pharmacovigilance system with more evidence about the impact of ADRs on patients.

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The Netherlands Pharmacovigilance Center Lareb has developed a framework for prospective cohort event monitoring (CEM) systems to capture patients' experiences with ADRs using web-based questionnaires. This framework can be used to monitor specific patient groups or specific drugs, and serves as an additional postmarketing surveillance tool. An example is the 'Dutch Biologic Monitor' [6,7], which is the first PRO-based CEM system that focuses on ADRs attributed to biologics indicated for immune-mediated inflammatory diseases (IMIDs). The Dutch Biologic Monitor serves as a pilot for a national drug safety monitoring system.

Since patients are the main source of information in PRO-based CEM systems, it is important to consider their perspectives regarding the perceived usefulness, ease of use and attitude toward using these systems. These insights can be used to reduce study withdrawal and to improve user-friendliness and reporting accuracy. In this study, we aimed to assess patients' experiences with the Dutch Biologic Monitor and their preferred design of a PRO-based national drug safety monitoring system for IMIDs.

2. Methods

2.1. Dutch Biologic Monitor

The Dutch Biologic Monitor is a pilot for a PRO-based prospective CEM system for IMIDs [6–9]. Nine Dutch hospitals and four patient registries participated in the monitor between January 2017 and December 2020. Patients using one of the monitored biologics, mainly for an IMID, were selected and invited by HCPs of the respective hospitals by means of consecutive sampling. Patients were eligible if they were proficient in Dutch and minimally 18 years of age. The perspective of patients was incorporated in the design of the monitor, since the questionnaires, information for patients and study website were pretested by patients. Moreover, representatives of two Dutch patient associations for rheumatic diseases and inflammatory bowel diseases were involved in the design of the monitor.

Patients could register via the study website (www.mijnbiologischmedicijn.nl). After registration, participants were asked to complete a comprehensive baseline questionnaire covering demographic information (gender, date of birth, weight, height, smoking habits), drug use (biologic and combination therapy), indication for biologic therapy, comorbidities and experienced ADRs that they attributed to the biologic. The questions concerning ADRs focused on the type of ADR, start and stop date, course, burden on patients (using a five-point Likert-type scale), contact with HCPs and treatment steps. Patients could elaborate on the type of ADR, treatment steps and burden of ADRs in free-text fields. Postbaseline questionnaires included a follow-up on drug use and newly experienced and previously reported ADRs. The provided answer options for biologics, indication, combination therapy and comorbidities are described elsewhere [6]. Moreover, the baseline and postbaseline questionnaires are translated into English and added to the electronic supplementary material (Supplementary item 1).

Participants were invited for the bimonthly questionnaires using an automated e-mail invitation. Login to the monitor's website was required to access new questionnaires. No more invitations for a subsequent questionnaire were sent in case the previous questionnaire had expired (after 21 days) or if the patient voluntarily withdrew from the study.

2.2. Survey on patients' experiences and preferences

2.2.1. Design

A cross-sectional survey following the rationale of the Technology Acceptance Model [10] was developed to obtain insight in patients' perspectives on the Dutch Biologic Monitor. The survey focused on the perceived usefulness, ease of use, attitude toward using and the preferred design of a national drug safety monitoring system for IMIDs. Participants were eligible for the survey in case they were still enrolled in the Dutch Biologic Monitor at the time of the survey opening and if they had completed at least one questionnaire of the monitor.

An invitation to the survey (Supplementary item 2) was integrated in the automated invitation e-mails for postbaseline questionnaires of the Dutch Biologic Monitor. Additionally, a hyperlink to the survey was available on the homepage of the study website (Figure 1). The survey was accessible from January 2019 until February 2020. Personal details were not included in the survey, and responses could not be linked to participants of the Dutch Biologic Monitor. The study adhered to the Checklist for Reporting Results of Internet E-surveys (CHERRIES) [11].

2.2.2. Informed consent

The regional medical ethics committee declared that the Medical Research Involving Human Subjects Act is not applicable to the Dutch Biologic Monitor (METC Brabant, NW2016-66). Additionally, the study was approved by the medical ethics committees of the participating hospitals. All participants received information about the study prior to participation and signed a web-based informed consent form that included a statement that permitted the invitation for additional surveys. The purpose of the additional survey, the duration, anonymity and the investigating agency were mentioned in the survey introduction. The survey was voluntary and no incentives were offered.

2.2.3. Survey development

The survey was developed by authors LK, GW and NJ, and was thoroughly assessed by an independent employee of Netherlands Pharmacovigilance Center Lareb. The survey was built in SurveyMonkey® (San Mateo, CA, USA) and was pretested for usability and functionality by the developing authors. The survey followed the rationale of the Technology Acceptance Model [10], and focused on patients' perspectives on the perceived usefulness, ease of use and attitude toward using the Dutch Biologic Monitor. Moreover, questions were added on patients' preferences toward the design of a national drug safety monitoring that is based on the Dutch Biologic Monitor.

The survey consisted of 20 categorial and 1 open-ended questions, including three questions that focused on socio-

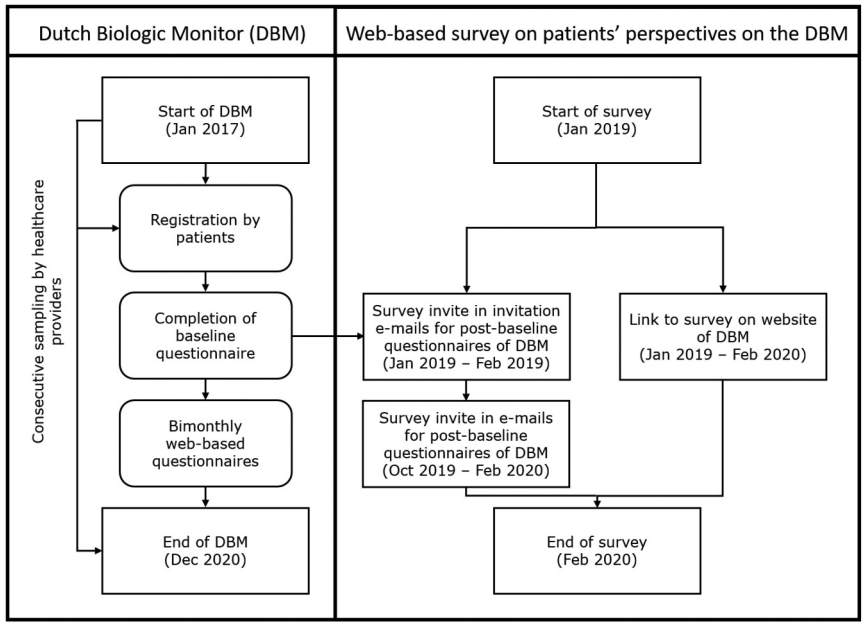

Figure 1. Flowchart of the study design. The left panel describes the study design of the Dutch Biologic Monitor,whereas the recruitment process for the additional survey on patients' perspectives on the Dutch Biologic Monitor is depicted on the right.

demographics (gender, birth year, level of education). Seven categorical questions contained a text field for additional comments. Categorical questions were either multiple select, multiple choice or Likert-type. An overview of the survey questions is provided in Supplementary item 3.

The majority of the questions were mandatory, with the exception of questions on demographic information. The answer options 'Do not know' and 'No opinion' were added to mandatory questions to provide for respondents without an opinion or respondents that did not know the answer. The questions were distributed over ten pages with a maximum of four questionnaire items per page. Each page was automatically checked for completeness after submission. Answers could be reviewed and changed through a back button.

2.2.4. Quantitative analysis

Duplicate database entries were identified using Internet Protocol (IP) addresses and only the most recent entry was stored for analysis. Descriptive statistics were provided using median (Q1-Q3) values. Fisher-Freeman-Halton tests with Monte Carlo simulation were used to compare the distribution of Likert-type items per group. To assess representativeness of the survey population in comparison to the Dutch Biologic Monitor, differences in median age were tested with Mann-Whitney U test, and gender and ADR presence with Chi-Square Goodness-of-Fit tests. Descriptive statistics, Mann-Whitney U test and Chi-Square Goodness-of-Fit tests were performed in IBM SPSS Statistics version 22. Fisher-Freeman-Halton test was performed in RStudio with R version 3.5.2. p-values below 0.05 were considered statistically significant.

2.2.5. Qualitative analysis

Text fields were analyzed using theoretical thematic analysis [12]. The first two authors (LK and GW) independently familiarized themselves with the data and independently coded the open-ended survey responses. The authors met on several occasions to review the codes and to resolve discrepancies. Next, the authors independently identified subthemes and corresponding themes, and subdivided the codes into the corresponding subthemes. After discussing and resolving discrepancies, themes and subthemes were visualized per survey question using mind maps.

3. Results

3.1. Respondent characteristics

At the start of the survey a total of 1,255 participants had participated in the Dutch Biologic Monitor. Almost half (47.9%) of the participants had reported one or more ADRs. The majority (82.1%) used a TNF-alpha inhibitor, including adalimumab (35.6%), etanercept (30.5%) and infliximab (10.7%). Approximately 70% of the participants used a biologic indicated for an inflammatory rheumatic disease.

A total of 652 eligible Dutch Biologic Monitor participants were invited for the web-based preference survey using the invitation e-mails for postbaseline questionnaires of the Dutch Biologic Monitor. The survey was subsequently filled in by 310 Dutch Biologic Monitor participants (response rate: 47.5%) with a median completion time of 5:42 (IQR 4:12–8:18) minutes. Respondents that had not completed the survey or that did not comply with the inclusion criteria were excluded (n = 18), resulting in 292 study participants.

Over half of the respondents (n = 168, 58.9%) were female. Median age was 62 (IQR 54–69) years. Approximately half had a higher education qualification (48.2%). The majority of the

Table 1. Respondent characteristics. Data is represented as the number of respondents (n) or median age and corresponding quartiles (Q). ADR: Adverse drug reaction.

Variable	All participants (n = 292)		ADRs reported (n = 225)		No ADRs reported (n = 54)		ADR reporting unknown (n = 13)	
Gender, n (%)								
Female	168	(57.5)	136	(60.4)	26	(48.1)	6	(46.2)
Male	117	(40.1)	83	(36.9)	28	(51.9)	6	(46.2)
Missing	7	(2.4)	6	(2.7)	0	(0.0)	1	(7.7)
Median age at survey, years (Q1-Q3)	62	(54–69)	61	(54–68)	64	(53.3–72)	59	(52.5–63.3)
18–35 years	8	(2.7)	7	(3.1)	1	(1.9)	0	(0.0)
36–50 years	36	(12.3)	25	(11.1)	9	(16.7)	2	(15.4)
51–65 years	141	(48.3)	115	(51.1)	18	(33.3)	8	(61.5)
>66 years	104	(35.6)	76	(33.8)	26	(48.1)	2	(15.4)
Missing	3	(1.0)	2	(0.9)	0	(0.0)	1	(7.7)
Education, n (%)								
Primary school	9	(3.1)	7	(3.1)	2	(3.7)	0	(0.0)
Secondary school	57	(19.5)	44	(19.6)	10	(18.5)	3	(23.1)
Vocational education	83	(28.4)	59	(26.2)	20	(37.0)	4	(30.8)
Higher professional education	109	(37.3)	89	(39.6)	17	(31.5)	3	(23.1)
Academic	30	(10.3)	23	(10.2)	5	(9.3)	2	(15.4)
Missing	4	(1.4)	3	(1.3)	0	(0.0)	1	(7.7)
Completed questionnaires, n (%)								
1	11	(3.8)	8	(3.6)	2	(3.7)	1	(7.7)
2–5	62	(21.2)	48	(21.3)	12	(22.2)	2	(15.4)
6–10	91	(31.2)	75	(33.3)	12	(22.2)	4	(30.8)
>10	63	(21.6)	52	(23.1)	10	(18.5)	1	(7.7)
Do not know	65	(22.3)	42	(18.7)	18	(33.3)	5	(38.5)

respondents had completed two or more Dutch Biologic Monitor questionnaires (74.0%), and 77.1% indicated to have reported one or more ADRs (Table 1).

The survey population was representative for the participants of the Dutch Biologic Monitor based on gender (58.9% vs. 58.2% female; p = 0.80). Median age and ADR reporting were not fully representative, since the survey population's median age was higher compared to the monitor population (62.0 vs. 56.0 years; p < 0.001), and a higher percentage of survey respondents had reported at least one ADR attributed to a biologic (77.1% vs. 52.0%; p < 0.001).

3.2. Perceived usefulness

Generally, the respondents agreed (53.8%) or strongly agreed (34.3%) that it was useful to participate in the Dutch Biologic Monitor (Figure 2). More importantly, the majority (84.6%) would recommend the monitor to their peers. Patients' incentives to participate in the Dutch Biologic Monitor varied per respondent, but were mainly of an altruistic nature (Supplementary Table 1). The ability to share experiences with biologics (47.6%), active involvement of patients in safety studies on biologics (44.5%), and a request by the patients' HCP or hospital (39.4%) were the most frequently selected incentives. Moreover, a small number of respondents were driven by worries about drug safety (5.8%), while over a fourth perceived a lack of information on ADRs and long-term effects

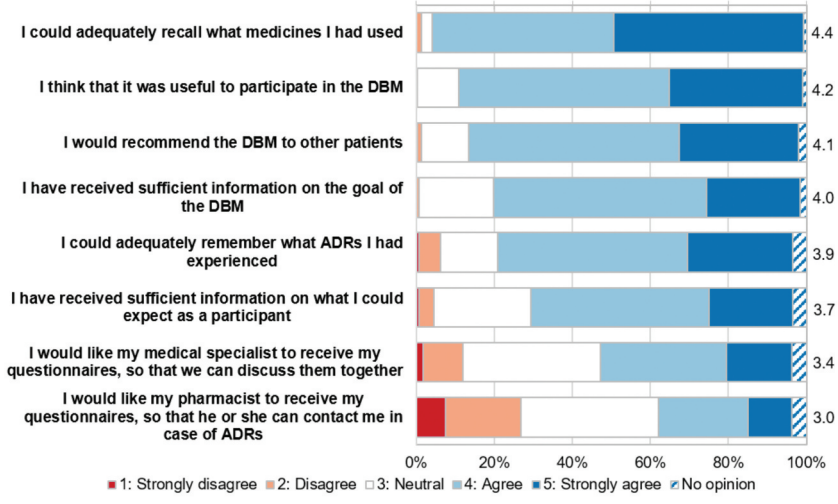

Figure 2. Stacked bar graph of user experiences. Agreement scores were measured using a five-point Likert-typescale, ranging from strongly disagree (1) to strongly agree (5). The average agreement score per statement is indicated on the far right. The percentages represent the share of respondents. DBM: Dutch BiologicMonitor; ADRs: adverse drug reactions.

(28.8%). Respondents illustrated their incentives using the following examples:

'I am very grateful for how biologics have improved my life. I think that I can give something back to the researchers if I share my experiences.' (female, 45 years)

'Patients can provide extensive information on adverse drug reactions and the use of biologics. I think that it is important that this is captured.' (male, 65 years)

'Every medicine has adverse drug reactions, but the severity can only become clear after a longer period of time.' (female, 69 years)

Furthermore, the respondents were requested to reflect upon their self-perceived ability to recall the drugs that they used and the ADRs that they had experienced during the two-month period preceding each questionnaire. The majority of the respondents regarded their recall-ability as sufficient (Figure 2).

3.3. Perceived ease of use

To obtain insight in patients' perceived burden of participating in the Dutch Biologic Monitor, the respondents were requested to score the experienced participation burden between 1 (no burden) to 5 (very high burden). The average burden was 1.2, as 76.7% of the respondents reported that they did not experience any burden while participating in the monitor (Supplementary Table 2). No discrepancies were found between the perceived participation burden of patients who had reported versus had not reported ADRs, or between patients with a higher versus a lower education level.

A large share of the respondents (81.2%) indicated that they generally completed the questionnaires in 10 minutes or less. This percentage was considerably higher among the respondents without reported ADRs (90.7%). The questionnaire duration was scored as 'well-balanced' by 79.5%, as most respondents were content and/or regarded the questionnaire duration as irrelevant for the study aims (Supplementary Figure 1).

3.4. Attitude toward using the Dutch Biologic Monitor

The questionnaires in the Dutch Biologic Monitor were sent out bimonthly. This frequency was preferred by 27.7% of the respondents (Supplementary Table 3). Half (55.5%) desired a lower frequency, since this was perceived as less time-consuming and more suitable in case of an unchanged situation or the absence of ADRs. Others stated that the two-month period was too short to adequately assess the causality of an ADR. Ideally, the questionnaire frequency should run parallel to regular contact moments with medical specialists or the biologic administration schedule (Supplementary Figure 2). On the contrary, a small share of patients preferred a more frequent questionnaire scheme (5.4%), as this would result in more detailed insight in ADRs and fewer recall problems. A self-adjustable questionnaire frequency was not highly preferred, as this would require continued dedication and the possibility of forgetting questionnaires. These points were illustrated using the following examples:

'I did not experience adverse drug reactions. Therefore [the questionnaires] can come less often.' (male, 72 years)

'I experienced [a questionnaire frequency of] two months as quite often, as I did not always had time. This is also the reason why I quit.' (female, 45 years)

'I visit my practitioner every 12 weeks, [the questionnaire frequency] can be linked to that.' (female, 53 years)

3.5. Additional preferences

The respondents were asked whether they would prefer to receive questionnaire feedback by HCPs. Almost half (49.0%) of the respondents were interested in sharing questionnaires with their medical specialist, as this would enable discussion of the questionnaire outcomes. In contrast, a third (34.2%) of the respondents advocated for sharing questionnaires with their pharmacist in order to be contacted if necessary (Figure 2). Some respondents stated that they preferred to directly consult their HCP themselves in case of reported abnormalities. Others expected no feedback or regarded the questionnaires as irrelevant for HCPs, as it was emphasized that pharmacists are not always involved in biologic therapy (Supplementary figure 3). Examples of statements are provided below:

'If I would experience adverse drug reactions of my biologic, then I would tell that to my doctor. By doing so, we can decide together what we are going to do about it. I would not consult my pharmacist.' (female, 54 years)

'It's not a bad thing if my medical specialist would receive my questionnaires, but it's not a necessity.' (female, 53 years)

'My medical specialist is allowed to see my questionnaire responses, but I do not expect him to respond or provide feedback.' (female, 75 years)

4. Discussion

The main outcome of this survey is that IMID patients that use biologics are generally supportive of the concept of a PRO-based CEM system. Respondents regarded it not burdensome to complete bimonthly questionnaires of approximately ten minutes or less, irrespective of the presence of ADRs. Ideally, the questionnaire frequency should be linked to the regular hospital consultations or the biologic administration schedule. Questionnaires should be shortened and sent less frequent in case of an unaltered situation or the absence of ADRs. Moreover, half of the respondents would like to share the questionnaires with their treating medical specialist or pharmacist. Given these points, we advocate to incorporate patients' perspectives in the design and evaluation of PRO-based CEM studies, as they provide valuable insights in the perceived usefulness, ease of use and preferred study design.

Although the perspective of patients should be considered in the development of CEM studies, their design also needs to match the primary objectives of the data collection. This requires a delicate balance between user-friendliness and the ability to capture sufficient volume of high-quality data. In the present survey, the respondents strongly recommended to shorten the questionnaires in case of an unaltered personal situation or the absence of ADRs. After all, it is known that

participation rate and questionnaire length are closely intertwined. A shorter questionnaire length is likely to have a lower participation burden, but also generates a less extensive data set [13]. Likewise, a short recall window length is more convenient for respondents, but can generate information loss. A longer window length provides researchers with more data, but may cause recall error [14]. With this in mind, it is recommended to design longitudinal questionnaires in such a way that they generate sufficient high-quality data, but simultaneously reduce redundancy for respondents, and to create a synergy between the perspectives of patients and the primary objective of the data collection.

PRO-based CEM studies currently mainly serve for pharmacovigilance purposes, but are not very common yet. The impact and potential of CEM studies is expected to increase when the patient-reported outcomes on ADRs are shared with the participants' treating HCPs in clinical practice [8]. By doing so, HCPs will become more aware of (non)serious ADRs with a high impact on patients and on subjective symptoms that are normally not so obvious. This will facilitate timely treatment and/or prevention of ADRs, and allows HCPs to help patients distinguish ADRs from disease-related symptoms [15]. Moreover, the implementation of PROs on ADRs in routine clinical care may contribute to improved acceptance and management of ADRs, which can result in improved medication adherence [16]. Correspondingly, it may be useful to standardize ADR screening and to empower patients [17]. This is already increasingly integrated in oncology care [18–22], cancer clinical trials [23–26] and pharmacies [27,28].

We found that almost half of our survey respondents (49.0%) were interested in sharing their questionnaires with their medical specialist, whereas a third (34.2%) advocated for sharing questionnaires with their pharmacist. Even though not all respondents were supportive, it is important to still consider this as an additional functionality of PRO-based CEM studies, and to clearly communicate the benefits to patients.

The most prevalent motives of patients to enroll in the Dutch Biologic Monitor were generally based on altruism, as respondents wanted to share their experiences with biologics (47.6%), to actively involve patients in safety studies on biologics (44.5%), and to satisfy the participation request of their HCPs or hospital (39.4%). Only 8.9% of the respondents indicated that they enrolled because they often experienced ADRs, despite the high share of respondents that had experienced one or more ADRs attributed to a biologic. These results are similar to those in comparable studies on patient-reported ADRs in pharmacovigilance [29–34]. At the same time, a fourth of our respondents (28.8%) were driven by a perceived information scarcity on ADRs and long-term effects, and wanted to contribute to more knowledge on ADRs. This is also seen in other studies, although more often in higher numbers [31,33].

This study has some limitations. Firstly, the respondent population is not fully representative for the Dutch Biologic Monitor, which correlates to the moderate response rate of the survey. It has previously been demonstrated that Dutch Biologic Monitor participants represent the hospital populations they were sampled from regarding age, gender and prescribed biologic [7,35]. In the current study we found that the gender distribution of the survey population was similar to the Dutch Biologic Monitor, while the median age and share of ADR-reporting patients were higher. It is expected that the impact of the age discrepancy (62.0 years vs. 56.0 years) is negligible, but that the relatively high share of ADR-reporting patients (77.1% vs. 52.0%) might have skewed the outcomes of this survey, even though no differences were found between the perceived participation burden of respondents with and without allegedly reported ADRs.

Secondly, almost half of the respondents had a higher education qualification (48.2%). This is not representative for the Dutch population, since only 30% of the adult population had completed a higher education in 2018 [36]. It possible that participants with a lower education level had different experiences and opinions about the Dutch Biologic Monitor. Due to this, the perceived usefulness and ease of use as experienced in this survey might be biased toward the positive.

Thirdly, the respondents have completed a varying number of questionnaires. This could have provoked bias, as it might suggest that respondents that completed more questionnaires have obtained a better impression of the Dutch Biologic Monitor. However, patients can also obtain a global impression of the Dutch Biologic Monitor after completing solely one questionnaire, as seen in a small group of survey respondents.

Since the survey was completed by half of the eligible patients (response rate: 47.5%), one can argue how representative our outcomes are toward PRO-based CEM studies in general, as only the most motivated and involved patients might have participated in the survey. It is not known why the nonresponders did not participate in the survey, what their characteristics are and how they experienced participating in the Dutch Biologic Monitor. The outcomes of this survey thus should be seen as a global indication of patients' perspectives on PRO-based CEM studies, and not as an accurate reflection of the whole population.

5. Conclusion

The outcomes of this survey provide valuable insights in patients' perspectives on a PRO-based drug safety monitoring system for IMIDs, and provide several useful starting points to further stimulate and improve PRO-based CEM systems. We showed that the survey respondents regard structural reporting of ADRs as useful and not burdensome. Furthermore, respondents indicated that it was highly preferable to link the questionnaires to the regular hospital consultations or the biologic administration schedule, and recommended that the questionnaires should be shortened and sent less frequent in case of an unchanged situation or the absence of ADRs. Altogether, it is feasible to establish a PRO-based drug safety monitoring system that monitors IMID patients' real-world experiences with ADRs and that is not burdensome to patients. Given the promising nature of PRO-based CEM systems, it is recommended to further stimulate the use of PROs on ADRs in pharmacovigilance.

Author contributions

All authors were involved in the conception and design of the study. LJ Kosse, G Weits and NT Jessurun collected, researched, analyzed and interpreted the data, and were involved in the drafting of this manuscript. All authors critical reviewed, revised the paper for intellectual content, provided detailed feedback, read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Declaration of interest

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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