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Stakeholders' perspectives on a patient-reported outcome measure-based drug safety monitoring system for immune-mediated inflammatory diseases

Leanne J. Kosse¹, Naomi T. Jessurun¹, Harald E. Vonkeman², Sander W. Tas³, Mike T. Nurmohamed⁴, Frank Hoentjen⁵, Martijn B.A. van Doorn⁶, Eugène P. van Puijenbroek^{1,7}, Bart J.F. van den Bemt⁸, Marieke de Vries⁹

¹Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands

²Department of Rheumatology, Medisch Spectrum Twente and University of Twente, Enschede, the Netherlands

³Department of Rheumatology & Clinical Immunology, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam Infection & Immunity Institute and Amsterdam Rheumatology & immunology Center (ARC), Amsterdam, the Netherlands

⁴Department of Rheumatology, Amsterdam Rheumatology & Immunology Center (ARC), location Reade, Amsterdam, the Netherlands

⁵Department of Gastroenterology, Radboud University Medical Center. Nijmegen, the Netherlands

⁶Department of Dermatology Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

⁷Department of PharmacoTherapy, Epidemiology and Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, the Netherlands

⁸Department of Pharmacy, Sint Maartenskliniek, Nijmegen, the Netherlands. Department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands

⁹Institute for Computing and Information Sciences, Radboud University, Nijmegen, the Netherlands

Corresponding author:

Leanne J. Kosse,
Netherlands Pharmacovigilance Centre Lareb
Goudsbloemvallei 7
5237MH 's-Hertogenbosch
The Netherlands
Email: l.kosse@lareb.nl
Phone: +3173 64 69 700

Fax: +3173 64 26 136

Leanne J. Kosse ORCID 0000-0002-9358-2286

Naomi T. Jessurun ORCID 0000-0002-8267-1259

Harald E. Vonkeman ORCID 0000-0003-3792-7718

Sander W. Tas ORCID 0000-0002-8940-1788

Mike T. Nurmohamed ORCID 0000-0002-6274-1934

Bart J.F. van den Bemt ORCID 0000-0002-8560-9514

Marieke de Vries ORCID 0000-0003-2112-1664

ACCEPTED MANUSCRIPT

Abstract

Background: Biologics are used as effective therapeutics to treat a variety of diseases. Even though biologics are widely used, knowledge on the post-marketing experience of patients is limited. Therefore, a framework was established for a patient-reported outcome measure (PROM)-based drug safety monitoring system for ADRs attributed to biologics, known as the 'Dutch Biologic Monitor'.

Objective: Generation of a multi-stakeholder perspective on the preferred setup, potential and added value of a PROM-based national drug safety monitoring system.

Methods: Nineteen stakeholders were interviewed following a structured interview guide. Transcribed data were coded and analyzed to count frequencies and to generate recurring themes.

Results: Stakeholders (84.2%) support the establishment of a national drug safety monitoring system, but the feasibility depends on the implementation process. The need for integration and assessment of PROMs on ADRs in clinical practice and the preference to monitor small molecules and new drugs was emphasized. Preferably, all pharmacological options per indication should be monitored.

Conclusions: Stakeholders recommend to establish a PROM-based national drug safety monitoring system focused on ADRs attributed to biologics, small molecules and new drugs. Moreover, PROMs on ADRs ideally need to become integrated in clinical practice to provide healthcare providers more insight in patients' perspectives.

Key words: adverse drug reactions, biologics, cohort event monitoring, immune-mediated inflammatory diseases, patient-reported outcome measures, stakeholder analysis

1.0 Introduction

Biological drugs, also known as biologics, serve as effective therapy options to treat a variety of diseases, such as immune-mediated inflammatory diseases (IMiDs). The introduction of biosimilars has led to a rapid increase in the number of biologics, and this is expected to grow even further in the nearby future^{1,2}. Despite the growing market share, knowledge on the post-marketing experience of patients that use biologics remains limited. For this reason, the safety of biologics is continuously monitored after market authorization using the spontaneous reporting system, where case reports of adverse drug reactions (ADRs) by patients and healthcare providers are collected. In an effort to complement the spontaneous reporting system, Netherlands Pharmacovigilance Centre Lareb (hereinafter: Lareb) developed a patient-reported outcome measure (PROM)-based cohort event monitoring (CEM) system for ADRs attributed to biologics, also known as the 'Dutch Biologic Monitor'³.

In recent years, the patient perspective is increasingly quantified and incorporated in pharmacovigilance and clinical research due to the ongoing shift towards a more patient-centered approach. This is mostly achieved using PROMs, which are tools - such as questionnaires - to collect health outcomes that are directly reported by patients. Patient-reported outcomes (PROs) can comprise various aspects of a patient's treatment or disease, such as symptoms, frequency and severity of disease, the presence of ADRs, and the perceived impact on daily life⁴. These subjective components are difficult to evaluate or assess by healthcare providers, and therefore provide valuable insights in the perspectives of patients towards their health status or treatment. For this reason, it is not surprising that PROs are increasingly collected alongside clinician reports to obtain a comprehensive assessment of the health status of a patient⁵.

In pharmacovigilance, patient reporting of ADRs has been increasingly embraced to contribute to the ongoing safety assessment of marketed drugs. However, patient reports can also be used to enhance the knowledge on ADRs attributed to biologics.

Given the expanding number of biologics (and prescriptions) and the relatively little real-life experience with these drugs, it is important that the safety of biologics is continuously monitored after market authorization. This will not only contribute to rational and safe pharmacotherapy, but might also stimulate the public trust and acceptance of biosimilars. More insight in the patient perspective on ADRs can also facilitate healthcare providers to timely identify, treat or prevent problems, and will provide them with a better understanding of the impact of ADRs on patients^{3,6}. This can result in a better quality of care and improved therapy adherence.

In light of the need to monitor biologic safety after market authorization, and the wish for more insight in patients' experiences with biologics, we have developed a framework for a PROM-based prospective CEM system to monitor ADRs attributed to biologics indicated for IMiDs, also known as the 'Dutch Biologic Monitor'³. Since this is an unexplored concept, the pilot was primarily aimed to determine whether a PROM-based system is a suitable model for a national drug safety monitoring system. In this study, we aimed to obtain insight in the perspectives of external stakeholders of the Dutch Biologic Monitor on the preferred methodology, potential and its added value. Their views are crucial for a successful design.

2.0 Methods

This stakeholder analysis was performed in context of the 'Dutch Biologic Monitor' to obtain insight in the multi-stakeholder perspective on the preferred methodology, feasibility and added value of a national drug safety monitoring system. An overview of the study design is provided in Figure 1.

2.1 The Dutch Biologic Monitor

The Dutch Biologic Monitor is a pilot for a PROM-based prospective CEM system focused on ADRs attributed to biologics (www.mijnbiologischmedicijn.nl). Nine Dutch hospitals and four patient registries participated from 1 January 2017 onwards. Eligible patients were selected and invited by healthcare providers. Patients were eligible in case they were 18 years or older and used a biologic indicated for an IMiD. After online registration, the participants were asked to complete bimonthly web-based questionnaires that covered their demographic information (gender, date of birth, weight, height, smoking habits), drug therapy (biologic and combination therapy), indication for biologic therapy, comorbidities and potential ADRs attributed to biologics. All participants received information about the study prior to participation and were required to sign a web-based informed consent form. The Dutch Medical Research Involving Human Subjects Act (WMO) was not applicable, as a 'non-WMO' declaration was received by the regional medical ethics committee (METC Brabant, NW2016-66). Furthermore, approval was obtained from the medical ethics committees of the participating hospitals. Additional information on the pilot is described elsewhere³.

2.2 Stakeholder selection

Stakeholder analysis of the Dutch Biologic Monitor identified five stakeholder categories: patients (organizations), medical specialists, pharmacists (associations), governmental organizations and research institutes that are experienced with PROMs focused on ADRs. Stakeholders of all categories were recruited using convenience sampling, as individuals from Lareb's network, including the expert committee and supervisory committee of the Dutch Biologic Monitor, were invited to participate in the stakeholder analysis. Potential participants were recruited by the second author using an email that explained the research aims. Nineteen out of 35 contacted individuals consented to participate, others did not respond or declined due to time constraints. Nine participants actively included patients in the Dutch Biologic Monitor and/or were member of the pilot's expert committee or supervisory committee. An overview of the participating stakeholders is provided in Table 1.

2.3 Data collection and setting

A structured interview guide was developed by the first two authors following the methodology described by Schmeer⁷. The intent of the questions were discussed with five professionals (including authors EvP and MdV), after which questions were modified when necessary. The interview guide (summarized in Table 2) included four main themes: the Dutch Biologic Monitor, and the preferred methodology, feasibility and added value of a national drug safety monitoring system for ADRs. The interview guide consisted of both open-ended and close-ended questions. The added value of this monitoring system was classified using a five-point Likert-type scale that ranged from 'very high' to 'very low', and focused on good healthcare quality, health improvement and efficient care, as further defined in Supplementary Table 1. The positions of the stakeholders towards the establishment of a national drug safety monitoring system were categorized using a five-point Likert-type scale ranging from 'strongly support' to 'strongly oppose'.

The interviews were conducted between May 2018 and August 2018. Interview guides were sent to the interviewees preferably one week before the interviews to optimize the quality of the responses and to enable participants to receive input from colleagues when needed. As a result, the representative of the Dutch Medicines Evaluation Board also provided insight in the vision of two colleagues. Interviews were conducted in Dutch, and were conducted, audio recorded and summarized by the first author (master's student, female). Field notes were made during the interviews. Seventeen stakeholders were interviewed in person, including one duo interview with two representatives of a patient association. Two stakeholders were questioned by email, as they were unable to meet. Additionally, the written responses of one stakeholder were subsequently discussed by phone. The

face-to-face interviews took place in private at the interviewee's workplace or at the office of Lareb. Interviewees gave permission for audio recording and anonymity was guaranteed. The duration of the interviews varied between 30 to 60 minutes. Saturation of the large majority of the themes was achieved after the last interview. Interview summaries were sent to each interviewee for verification and to allow interviewees to provide feedback on the data.

2.4 Data analysis

The summaries were coded according to the procedures of content analysis and were analyzed to count frequencies and to generate recurring themes relating to the study aims⁸. Codes were added by the first researcher in Microsoft Excel 2016 (Microsoft Corporation, Richmond, WA, USA), and were reviewed by the second researcher in five randomly chosen summaries. The researchers agreed on 94.2% of the codes and resolved the remaining discrepancies by consensus. Themes were generated based on the open codes and were sorted into the previously defined main themes as used in the interview guide following selective coding. For clarification, the outcomes of main theme A ('Dutch Biologic Monitor') were added to main theme B ('Preferred methodology of a national drug safety monitoring system for ADRs'). Lastly, a position map of the stakeholders' opinions on the potential of a PROM-based national drug safety monitoring system focused on ADRs was generated following the methodology developed by Schmeer⁷.

3.0 Results

3.1 Preferred methodology

The stakeholders were asked to share their vision on the methodology of the Dutch Biologic Monitor and its extension into a PROM-based national drug safety monitoring system for ADRs. The stakeholders reflected upon the strengths and weaknesses of the Dutch Biologic Monitor, the use of PROMs, whether PROs on ADRs (PRO-ADRs) should be connected to clinical parameters, and if and how the completed questionnaires should be shared with treating healthcare providers. The main recommendations are presented in Table 3.

3.1.1 PROMs and its applications

The use of PROMs was consistently supported by all stakeholders, as it was stated that more insight in how patients experience their treatment can contribute to patient-centered care. PRO-ADRs are expected to result in more insight in the post-marketing experience with new drugs, including the spectrum of potential ADRs, ADR frequencies and discrepancies in ADRs between drugs and patient groups and, importantly, the impact of ADRs on a patients' daily life. Critical remarks were also given, as several stakeholders stated that PROs are difficult to interpret and analyze, and often result in heterogeneous data. Additionally, the stakeholders see a lingering risk of reporting bias, since the ADRs are not medically validated and patients might not report all experienced ADRs. With this in mind, it is possible that patients mistakenly report non-drug-related health complaints (false positives).

To obtain more insight in clinical events, a combination with clinician-reported outcomes (CROs) is preferred (89.5%) to contribute to the medical verification and explanation of the reported ADRs. Moreover, the stakeholders emphasized that PRO-ADRs should ideally become incorporated in clinical practice to learn more about patients' experiences with biologics, resulting in a more patient-centered healthcare system. After all, the availability of PRO-ADRs in electronic health records will allow healthcare providers to act on the reports when necessary, through timely treatment or prevention of ADRs, or by educating patients to distinguish drug-related complaints from disease-related complaints. For this reason, the integration of PRO-ADRs in electronic health records is

regarded as the most prominent feature of a PROM-based drug safety monitoring system, and is highly desired by 94.7% of the stakeholders.

3.1.2 Recommended drugs for monitoring

The Dutch Biologic Monitor was a pilot for a PROM-based national drug safety monitoring system focused on ADRs that were exclusively attributed to biologics. However, to obtain insight in what drugs should be monitored in the national rollout, the stakeholders were asked what drug selection criteria they would recommend, and what (classes of) drugs, besides biologics, they would preferably incorporate. Drugs with new mechanisms of action (n=57.9%) and drugs with uncertain safety risks (n=36.8%, i.e. uncertainty at registration, conditional market approval or additional monitoring requirements) were the most frequently mentioned selection criteria. Interestingly, all but one stakeholder within the rheumatology domain indicated that they highly preferred to monitor all pharmacological options for inflammatory rheumatic diseases, as this would enable comparison between ADR profiles of different drugs and can provide more insight in the ADR profiles of well-established drugs.

The majority of drugs that are eligible for monitoring comprised drugs indicated for IMiDs, and mainly consisted of small molecule tyrosine kinase inhibitors, such as the Janus kinase inhibitors baricitinib, tofacitinib and upadacitinib (Supplementary Table 2). Oncology drugs, again with a slight preference for tyrosine kinase inhibitors, were recommended by five stakeholders (26.3%). Anti-interleukin-5 therapies for severe asthma and drugs indicated for metabolic diseases and cardiovascular diseases were also mentioned by respectively two or more stakeholders. Despite the nomination of non-IMiD drugs, various stakeholders advocated to continue with IMiDs drugs and to include other diseases and drugs at later stages of the monitor.

3.2 Feasibility

The stakeholders were asked to express their position towards the establishment of a national drug safety monitoring system that is based on the Dutch Biologic Monitor using a five-point scale (Fig. 2). All stakeholders had a supporting or neutral stand towards a PROM-based national drug safety monitoring system, and agreed on the necessity to monitor the safety of drugs and to obtain more insight in the patient perspective on ADRs. Three stakeholders (13.2%) had a neutral position due to the proposed methodology. Among these stakeholders were two representatives of the national oncology association, who discouraged the incorporation of oncology drugs due to the presence of various (Dutch) initiatives and registries to monitor PRO-ADRs attributed to oncology drugs. However, they did support a national system for non-oncology indications.

All stakeholders expected that the establishment of a PROM-based drug safety monitoring system will be feasible, but that its success largely depends on the implementation and operation of the system. The feasibility is said to increase if the system merely focuses on a limited number of diseases and if PRO-ADRs are integrated in electronic health records. The latter will serve as an incentive for patients and healthcare providers, as they otherwise would not directly benefit from participating in the monitor.

3.3 Added value

To obtain insight in the perceived value of a PROM-based national drug safety monitoring system for ADRs with respect to good healthcare quality, health benefits and the facilitation of efficient care, the stakeholders were requested to rate the added value for each of the respective parameters. An overview of the ratings is presented in Fig. 3.

Approximately two thirds of the stakeholders (68.5%) estimated that a PROM-based national drug safety monitoring system focused on ADRs will positively impact quality of care. For the facilitation

of efficient care, the added value is expected to be either high (44.7%) or moderate (42.1%). Opinions were more divided on the generation of health benefits, as only half (44.7%) mentioned that a national system can contribute, albeit indirectly, to the generation of health benefits for patients. For all three aspects, it was recurrently stated that PRO-ADRs need to be shared with treating healthcare providers to increase the added value even further.

ADR monitoring by itself is not expected to result in direct benefits for patients, as it will only become beneficial when healthcare providers can act on the reported ADRs. In contrast, indirect effects are likely to arise when more knowledge becomes available on ADRs and potential contraindications. This will allow healthcare providers to optimize drug doses and to improve therapy choices and guidelines. Another potential effect is that biosimilars might be prescribed more often when no safety concerns are found, thereby reducing costs while maintaining effectivity. Other stakeholders argued that the outcomes of a PROM-based national safety monitoring system focused on ADRs will not significantly impact therapy choices.

4.0 Discussion

We showed that the large majority of the external stakeholders (highly) support the establishment of a PROM-based national drug safety monitoring system that is based on the Dutch Biologic Monitor. All stakeholders expected that the establishment of a national system will be feasible, but that its success will largely depend on the method of implementation. Accessibility of PRO-ADRs for healthcare providers, preferably via direct access in electronic health records, was regarded as a crucial component, as this is expected to serve as an incentive for both patients and healthcare providers. Moreover, it will simultaneously contribute to the medical verification and explanation of the reported ADRs via the combination with CROs, thereby minimizing the amount of falsely reported ADRs. It was also recommended to broaden the scope of the Dutch Biologic Monitor with small molecules and other new compounds that are indicated for IMiDs, including drugs with new mechanisms of action and drugs with uncertain safety risks.

CEM systems, such as our proposed PROM-based drug safety monitoring system for ADRs, are regarded as one of the standard methods of active pharmacovigilance⁹ and are used to complement the spontaneous reporting system. Even though PRO-ADRs give valuable insight in the real-life experience with drugs¹⁰, they also are at risk of reporting bias. PRO-ADRs do not necessarily have a causal relationship with the monitored drugs, as patients can mistake non-drug-related complaints for ADRs. Furthermore, patients can also underreport ADRs due to unawareness, forgetfulness or a lack of compliance. Studies on PROMs and spontaneous reports have shown that patients make a valuable contribution to the generation of drug safety signals^{11,12} and can adequately report their medical information^{3,13}. Even though patients and healthcare providers do not fully agree on all (subjective) patient-reported ADRs due to differences in terminology and perspectives, they highly agree on easily observable ADRs^{14,15}. These discrepancies are very valuable, as they provide more insight in the unfiltered perspectives of patients on ADRs and their drug use. For this reason, it is essential for CEM systems that all PRO-ADRs are recorded to not miss new drug safety signals⁹.

CEM systems can increase their impact if the PRO-ADRs are also shared with healthcare providers. This will not only contribute to more knowledge on ADRs and the safety of drugs, but will also benefit the treatment of participating patients. Therefore, it is not surprising that the stakeholders regarded the integration of PRO-ADRs in clinical practice, preferably in electronic health records, as a pivotal factor for a PROM-based drug safety monitoring system for ADRs. The availability of the questionnaires for healthcare providers is highly desired, since the combination of PROs with CROs is expected to contribute to the medical verification and explanation of the reported ADRs, as healthcare providers can help patients to distinguish ADRs from disease-related complaints. Moreover,

healthcare providers will obtain more insight in the patient perspective if PRO-ADRs are discussed during consultations, since PRO-ADRs can reveal nonserious ADRs with a high impact on patients and subjective symptoms that normally are not obvious to healthcare providers. In doing so, healthcare providers become better placed to treat and/or prevent ADRs timely, as they will obtain a better understanding of the occurrence and course of the reported symptoms¹⁶. All things considered, implementation of PRO-ADRs in clinical practice can make the patient perspective more outspoken, and will simultaneously open possibilities for shared decision making. Several initiatives, mainly in oncology, already attempted to implement PROMs in clinical practice, and found that web-based symptom monitoring positively affected communication between patients and healthcare providers, symptom awareness, symptom management, quality of life, survival and patient satisfaction¹⁶⁻²⁰. This stresses even more that the implementation of PRO-ADRs in clinical practice can be very valuable. However, it can be challenging to implement PRO-ADRs on a national scale, given the diversity of software systems and policies between hospitals. Tailored implementation plans, accompanied by high efforts, will be needed to successfully implement PRO-ADRs in electronic health records.

Some methodological issues must be addressed concerning this study. Firstly, the outcomes might be biased due to the use of the convenience sampling method. Nine out of 19 participants were member of the expert or supervisory committee of the Dutch Biologic Monitor, and 9 stakeholders worked in a hospital that participated in the pilot. Moreover, only half of the invited stakeholders (54.3%) were willing and available to participate in the stakeholder analysis, and marketing authorization holders were not selected in the analysis and therefore not represented. A second limitation is that the interviews were summarized and not transcribed verbatim. Due to this, details might have been lost and intonations could not be characterized. However, to safeguard the quality of the summaries, the texts were sent to the respective interviewees for verification.

4.1 Implications for clinical practice

PROMs are regarded as a valuable tool to capture subjective components of a patient's health, including the symptoms, course and burden of ADRs. In line with increasing emphasis on patient centeredness, the Dutch Biologic Monitor was developed as a framework for a CEM system that can be used to collect detailed information on the patient perspective on ADRs. The outcomes of this stakeholder analysis encourage other research initiatives to also incorporate PROMs in CEM studies. The value of PRO-ADRs is expected to increase when they are structurally integrated in clinical practice, preferably in electronic health records. This will stimulate and activate healthcare providers to incorporate the experiences of their patients in (shared) decision-making processes, and will allow them to tailor treatments to individual patients. Given these points, PROMs should be widely applied in clinical practice, as this contributes to timely and effective treatment strategies, patient centeredness, patient satisfaction and shared decision making.

4.2 Future research

The outcomes of this stakeholder analysis encourage other research initiatives to incorporate PROMs in drug safety studies and to share the PROs with clinical practice. However, to obtain a better impression of the patient-reported safety of a drug or drug group, it is recommended to monitor all pharmacological options for specific indications. This will give more insight in the spectrum of potential ADRs and discrepancies between drugs and patient groups.

5.0 Conclusions

From a multi-stakeholder perspective, it is recommended to transform the pilot Dutch Biologic Monitor into a PROM-based drug safety monitoring system focused on ADRs that preferably monitors all pharmacologic options for IMIDs. Moreover, PRO-ADRs should be implemented in routine

medical care, since this will allow healthcare providers to discuss and evaluate the experiences of patients during consultations.

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Author contributions

All authors were involved in the conception and design of the study. LJ Kosse and NT Jessurun collected, researched, analyzed and interpreted the data. LJ Kosse, NT Jessurun and M de Vries were involved in the drafting of this manuscript. All authors critically 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 interests

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*** of considerable interest*

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Figure1 Flow chart of the study design.

Figure 2 Map of stakeholders' positions towards the establishment of a PROM-based national drug safety monitoring system focused on ADRs that is based on the Dutch Biologic Monitor.

Figure 3 Multi-stakeholder perspective on the added value of a PROM-based national drug safety monitoring system for ADRs with respect to good healthcare quality, health benefits and the facilitation of efficient care.

Group	Profession	No. interviewed	No. of participants in Dutch Biologic Monitor	No. of expert or supervisory committee members
<i>Patient (organizations)</i>	Head of patient interests of patient association	1		1
	Policy advisor of patient association	1		1
<i>Medical specialists</i>	Dermatologist	2	1	2
	Gastroenterologist	1	1	1
	Rheumatologist	3	2	2
<i>Pharmacist (associations)</i>	Pharmacist	2	2	1
	Hospital pharmacist	3	3	1
	Policy advisor of national pharmacists association	1		
	Policy advisor of national hospital pharmacists association	1		
<i>Governmental organizations</i>	Pharmacovigilance assessor of Dutch Medicines Evaluation Board	1		
	Coordinator of Horizon Scan Pharmaceuticals ^a (National Health Care Institute)	1		
<i>PROM-using research institutes</i>	Cancer researcher	1		
	Policy advisor oncology of national cancer association	1		
Total		19	9	9

^aTranslated from Dutch [Horizonscan Geneesmiddelen]. PROM indicates patient-reported outcome measure.

Table 1

A. Dutch Biologic Monitor

Familiarity with the pilot
Strengths and weaknesses of the pilot

B. Preferred methodology of a national drug safety monitoring system for ADRs

View on the use of PROMs
View on the combination of PROs on ADRs with clinical information in health systems
View on the sharing of PROs on ADRs with treating healthcare professionals
Selection criteria for drugs that need to be monitored
Drugs that need to be monitored
Patient groups that need to be followed
Suggestions on the methodology

C. Position towards a national drug safety monitoring system for ADRs

Position
View on the feasibility of a national system

D. Added value of a national drug safety monitoring system for ADRs

What new knowledge can result from a national system
Added value with respect to good healthcare quality
Added value with respect to health improvements
Added value with respect to the facilitation of efficient care

ADRs indicates adverse drug reactions; PROs, patient-reported outcomes; PROMs, patient-reported outcome measures.

Table 2

	Dutch Biologic Monitor	<i>National drug safety monitoring system</i>
<i>Indications</i>	IMIDs	IMIDs, (oncology)
<i>Monitored drugs</i>	Biologics	Biologics, small molecules, new drugs
<i>Age group</i>	≥18 years	All ages
<i>Data source</i>	PROMs	PROMs
<i>Questionnaires</i>	<ul style="list-style-type: none"> • Elaborate • No connection to clinical parameters • Concise medical history • No focus on drug effectiveness 	<ul style="list-style-type: none"> • Short • Connected to clinical parameters • Elaborate medical history • Focus on drug effectiveness
<i>Use of questionnaires in clinical practice</i>	Limited	Integration of questionnaires in medical records

IMIDs indicates immune-mediated inflammatory diseases; PROMs, patient-reported outcome measures.

Table 3

Supplementary Table 1: Proposed definitions of good healthcare quality, health improvement and efficient care.

Parameter	Definition
<i>Good healthcare quality</i>	Care that is patient-centered, effective, safe and in time, adjusted to the needs of individual patients
<i>Health improvement</i>	The delivered care results in relevant health improvements, such as less health problems, increased quality of life or better functioning
<i>Efficient care</i>	Care that is more effective against lower or equal costs, or care with the same effectivity at lower costs

Supplementary Table 2: Overview of the drugs indicated for IMIDs that were most

Inflammatory bowel diseases	Inflammatory rheumatic diseases	Inflammatory skin diseases
Stem cell therapies	All pharmacologic options	Apremilast
Tofacitinib	Baricitinib	Baricitinib
Upadacitinib	Sarilumab	Tofacitinib
	Tofacitinib	Tildrakizumab
	Upadacitinib	

frequently recommended for a PROM-based national safety monitoring system focused on ADRs.