Drug Safety
https://doi.org/10.1007/s40264-026-01666-6

ORIGINAL RESEARCH ARTICLE

International Medicinal Product Information Documents: A Quantitative Content Analysis of Instructions for Preventing, Mitigating, and Monitoring Adverse Drug Reactions

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Received: 10 October 2025 / Accepted: 3 March 2026

Abstract

Introduction Medicinal product information documents (PIDs) detail clinical characteristics and instructions for monitoring, preventing, and mitigating adverse drug reactions (ADRs). They vary across countries, but there have been no recent international comparisons. We have therefore quantified and compared the completeness of the information given in drug labelling from different countries.

Methods From the websites of 35 regulatory agencies, we retrieved the PIDs of medicinal products that were involved in signals communicated by regulators in 2014–2019. We developed a data extraction framework based on the Dose-relatedness, Time course, Susceptibility (DoTS) clinical classification of ADRs and used its implications for prevention and mitigation to score the completeness of related instructions in PIDs. To extract and classify monitoring instructions, we used a modified Systematic Instructions for Monitoring (SIM) method. PIDs had sufficiently complete instructions for prevention when the DoTS score was ≥ 5/12, and sufficiently complete monitoring instructions when the SIM score was ≥ 3/6. We used proportions of PIDs having a score ≥ 1 to determine the relative availability of clinical characteristics or instructions in a country, compared with all other countries. We quantified their pairwise disagreements using Jaccard's distance and identified clusters with similar patterns of completeness using agglomerative hierarchical clustering.

Results PIDs were available on the websites of 18 of 35 regulatory agencies. They concerned 364 distinct medicinal products, which were involved in 627 signals. Across all countries, the instructions for prevention or mitigation met sufficient completeness for a median of 30% of PIDs (IQR 28–33%), while instructions for monitoring were sufficiently complete for a median of 22% (IQR 19–25%). The information given by the European Union (EU) and Canada had the highest relative availability of clinical characteristics and prevention or mitigation instructions, with a proportion of 0.86. Canadian and EU PIDs also had the highest relative availability of monitoring instructions, with proportions of 0.79 and 0.70. Two clusters of countries showed low disagreements: Malaysia and Singapore; Australia and New Zealand.

Conclusions This study suggests that PIDs often do not contain complete instructions for prevention, mitigation, and monitoring of ADRs. Extending existing regulatory cooperation globally would enable regulators to access clinical characteristics and instructions from different regions.

1 Introduction

The information provided in medicinal product information documents (PIDs) (e.g. Summary of Product Characteristics [SmPCs] in the European Union [EU], Full Prescribing Information in the United States of America [USA], and Data Sheets in New Zealand) should ensure that the therapeutic benefits of medicinal products are maximized and their risks of harms minimized. The structure of these documents is regulated by law in several countries (typically including sections dealing with, for example, warnings, precautions, and contraindications) [1, 2]. In turn, marketing authorization holders are responsible for ensuring that the contents of the PIDs of the products they have launched are clinically relevant [3]. PIDs may contain strategies for preventing or mitigating adverse drug reactions (ADRs) [4]. Mitigation involves reduction of the intensity of a harm, while prevention involves avoidance. Although various

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Published online: 21 March 2026

Key Points

We quantified and compared the completeness of instructions for prevention, mitigation, and monitoring for 627 signals of adverse drug reactions.

According to the frameworks used in the study, instructions were seldom complete for prevention and mitigation (a median of 30% of product information documents) and monitoring (a median of 22%). Product information documents from the European Union and Canada had the highest relative availability of information.

A disagreement analysis showed differences in how adverse reactions are documented internationally, identifying two clusters of two countries each, appearing to exchange information. Global collaboration would improve access to information on prevention, mitigation, and monitoring of adverse drug reactions.

approaches to identifying preventable harms have previously been outlined, there is no ideal definition [5, 6].

Regulatory agencies provide guidelines for updates, specific to therapeutic classes, once evidence of harm accrues—as in the case of signals of ADRs [7]. This notwithstanding, PIDs may lack specific guidance on preventing or mitigating ADRs in specific populations [8–13], or their guidance may be deemed ambiguous [14]. Drug–drug interactions may also be incompletely reported compared with published evidence of harm [8, 12, 15, 16]. In contrast, some warnings sections of PIDs may provide more details on ADRs than other databases of information on harms of medicinal products [17, 18], albeit sometimes missing satisfactory implementation guidelines for clinical recommendations [19]. International comparisons across sections of PIDs, limited to selected countries, suggest quantitative and qualitative differences [20–25]. One broader, 26-country comparison, now over 2 decades old, showed "substantial disagreement" between PIDs and the British National Formulary; incomplete assessments of the worldwide available evidence were thought to have produced international differences [26]. Comparisons of the adequacy of instructions for monitoring of PIDs across countries showed that under 50% were clinically useful [27, 28].

Previous research has focused on sections of PIDs, possibly neglecting clinically relevant contextual information available throughout the whole documents [29]. Furthermore, comparative research on PIDs has been limited to a few countries, and globally focused research is dated, calling for updated studies with a worldwide scope. While instructions for monitoring have been assessed for adequacy, other instructions, where monitoring is unfeasible [30], have been neglected. Lastly, there are limited insights into how signals of ADRs translate into the recommendations available in PIDs [31–33].

2 Aims and Objectives

The aim was to quantify and compare internationally the completeness of the instructions in PIDs for monitoring, preventing, and mitigating ADRs.

3 Methods

3.1 Study Design

This was a quantitative content analysis of instructions available in the PIDs of a set of countries, pertaining to a predefined set of signals of ADRs (including drug–drug interactions). We registered the study protocol at https://doi.org/10.1101/2024.06.14.24308939v1, and have reported any deviations in the electronic supplementary materials.

3.2 Initial Basis of the Study Data

A previously published dataset of signals of ADRs [34, 35] provided (1) the active ingredient(s) of medicinal products (which were coded to WHODrug Global, Uppsala Monitoring Centre's drug dictionary [36] and defined by EU legislation [37]) and their earliest launch dates; (2) ADRs or adverse events involved; (3) the country of communication; (4) the author or stakeholder and year of each communication; and (5) the study design.

3.2.1 Inclusion Criteria

We restricted the dataset to signals detected from clinical assessments of reports of ADRs. We did so to minimize the possible effect of strength of evidence on the discrepancies in PIDs [38], and to limit the analysis to the most frequent type of evidence in the dataset. We retained only signals communicated by regulatory agencies or authorities, or by national and regional pharmacovigilance centres, between 2014 and 2019. In so doing, we assumed that signals communicated by these stakeholders would be more likely to result in amendments to the PIDs and that 5–10 years would be a sufficient interval for amendments to PIDs to be made.

For details, please see the online resources, supplementary Tables 4 and 5.

We excluded (1) signals communicated by more than one regulator at different times, and retained the earliest communications; (2) signals of adverse reactions to herbal medicinal products, since these products are classified differently across countries and their adverse effects are documented in, e.g. monographs; (3) signals about classes of medicinal products that had been previously communicated for a medicinal product of the same class (we retained the earliest communication); and (4) signals for which no PIDs could be retrieved, or for which a PID could be retrieved from only one website.

3.3 Retrieval of Product Information Documents (PIDs)

We verified that the websites of 35 regulatory agencies or authorities had collections of PIDs and selected those whose PIDs were available in English (see the online resources, supplementary Table 1). The list of countries was adapted from previous systematic reviews [33, 35]. We selected PIDs intended for healthcare providers.

Using the active ingredients obtained in Sect. 3.2 as search terms, we queried the websites and retrieved the most recent versions of PIDs (as of 12/2024) of reference products, the status of which was determined based on the earliest launch date. When searches by active ingredients were unfeasible, we retrieved all available PIDs from a website, and hand searched within the documents by active ingredient. Withdrawn medicinal products were included, as they could still be available on some markets worldwide [33]. We focused on reference products, since information about them may differ from information about their generic or biosimilar counterparts [39, 40]. We also assumed that a longer time on the market would result in more complete documents. Where possible, we retrieved PIDs on the same dose or formulation across all countries. To account for formulation-specific harms, we consulted the records included in the review and determined if there was information on formulations to guide the retrieval of the most appropriate PIDs. Where PIDs were available only for generics or biosimilars, we retrieved the most recent version, irrespective of trade name or brand. For signals of ADRs reported at a pharmaceutical class level, we considered the PID of the reference medicinal product with the earliest launch date, or, if none was available, the most recent version of the documents on the relevant generic or biosimilar, as above. For signals of drug–drug interactions, we retrieved the PIDs of all relevant medicinal products and treated them as a single PID.

3.4 Data Extraction and Scoring

For each included signal, one author (DS) extracted (1) information on the clinical characteristics of the ADRs, (2) instructions for monitoring, and (3) guidance on prevention or mitigation [41]. Extracted data were scored as described in Sects. 3.4.2 and 3.4.3, by the same author. A second author (MF) cross-validated uncertainties, and discrepancies were resolved by discussion.

3.4.1 Extraction of Clinical Characteristics and Instructions for Prevention or Mitigation

To guide extraction and classification of extracted data, we derived domain-based frameworks from two published methods, one to score clinical characteristics and related prevention or mitigation instructions (Dose-relatedness, Time course, Susceptibility [DoTS]), and one to score monitoring instructions (Systematic Instructions for Monitoring [SIM]). In the electronic supplementary materials, we report definitions of concepts, and our reflections on the construction of the frameworks and their use as scoring systems.

3.4.2 Scoring of Extracted Clinical Characteristics and Instructions for Prevention or Mitigation

We used the three domains (Dose-relatedness [Do], Time course [T], and Susceptibility [S]) of the DoTS system to score clinical characteristics and prevention or mitigation instructions [5, 6, 30, 42]. Clinical characteristics could be awarded 1 point at the most. Instructions could receive 3 points when "aligned" (i.e. they shared the same domain as the clinical characteristic) or 1 point when "unaligned" (i.e. they belonged to a different domain or were unaccompanied by a clinical characteristic). Only one aligned instruction, and at most two unaligned instructions, counted towards scoring. If an aligned instruction was present, no additional unaligned instructions contributed to the score. Examples include 1 point for a clinical characteristic + 3 for an aligned instruction (4 points); or 1 point for a clinical characteristic + 2 for two unaligned instructions (3 points); or 1 point for an unaligned instruction, without a clinical characteristic. Therefore, each domain could be awarded 4 points at the most. DoTS scores were assigned to signals per PID. Therefore, the unit of analysis is the signal–PID combination. The same PID could be counted more than once if it concerned more than one signal (see Sect. 3.5). When a PID of a country lacked an instruction or clinical characteristic present in the PID of any other, the relevant domain scored 0 points. For brevity, we illustrate in Fig. 1 how the DoTS scoring framework works in practice. Online resource 1

(supplementary Table 2), as well as the registered protocol, include additional considerations about this framework.

3.4.3 Extraction and Scoring of Instructions for Monitoring

To extract, classify, and score instructions for monitoring, we used six questions from the SIM method as domains [27, 28, 43]: (1) "What to monitor" (e.g. white blood cell counts); (2) "When to start monitoring" (e.g. at the start of treatment); (3) "How frequently to monitor" (e.g. every 4 weeks); (4) "When to stop monitoring" (e.g. after 3 months); (5) "Critical value" (e.g. white blood cell counts < 4000/µL); and (6) "How to respond" (e.g. withdraw). We assigned 1 point per domain (for a maximum of 6 points). Instructions unavailable in the PID of a country received 0 points if they were available in the PID of at least another country.

3.4.4 Thresholds of Completeness for DoTS and SIM Total Scores

We described individual DoTS domains that reached the maximal score of 4 as "complete". Conservatively, we deemed PIDs to have sufficiently complete prevention or mitigation instructions when their total DoTS score was at least 5 (of 12; ~ 42%). Instructions for monitoring were sufficient when their SIM score was at least 3 (of 6; 50%) [45].

3.5 Data Analysis

3.5.1 Summary Statistics

We quantified the availability of any clinical characteristics or instructions for prevention, mitigation, and monitoring by calculating the percentage of PIDs within a country whose total DoTS or SIM score was ≥ 1. Similarly, we quantified the completeness of instructions for prevention, mitigation, and monitoring, using the DoTS or SIM thresholds in Sect. 3.4.4. Beyond availability of instructions, we quantified the prevalence of specific instructions by DoTS and SIM domains (e.g. "withdraw medicinal product", "use reduced doses"; see also Fig. 1).

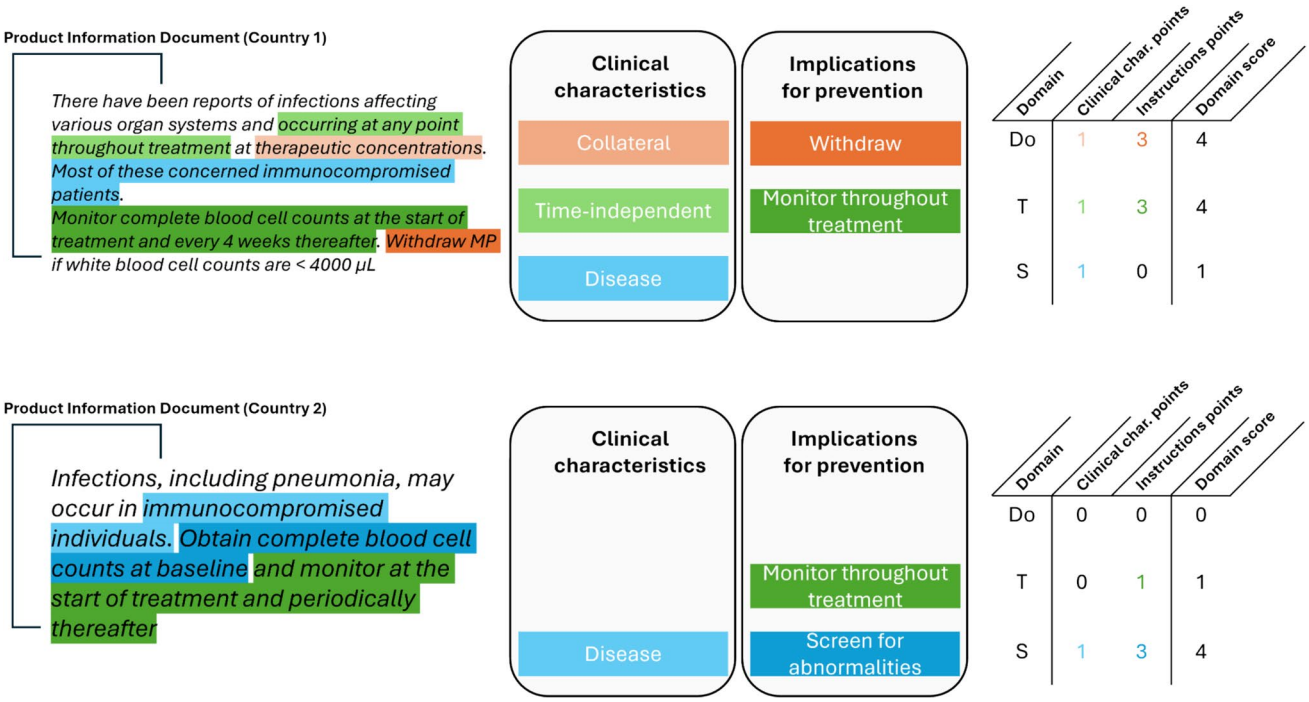

Fig. 1 Schematic illustration of the application of the DoTS framework to two fictitious PIDs. Suppose a signal of *Pneumocystis jirovecii* pneumonia to an MP for multiple sclerosis. The PID from the first country includes clinical characteristics of the adverse drug reaction on Dose-relatedness (Do; *bright red*), Time course (T; *light green*), and Susceptibility (S; *light blue*) domains and related instructions (*darker shades*) for Do and T. The PID from the second country instead has no information on Do, contains clinical characteristics and instructions relevant to S, and instructions relevant to T, but no information on this clinical characteristic. The PID from country 1 is awarded 4 points to T, 1 to S, and 4 to Do. The other is awarded 1 point to T, 4 to S, and 0 to Do. Only clinical characteristics and implications for prevention or mitigation relevant to the example are depicted here. *DoTS* Dose-relatedness, Time course, Susceptibility, *MP* medicinal product, *PID* product information document

3.5.2 Cross-Country Comparisons

We calculated the relative availability of clinical characteristics or instructions by dividing (1) the number of PIDs whose total DoTS or SIM scores were at least 1 by (2) the number of PIDs whose total DoTS or SIM scores were at least 1 in any country.

We assessed the level of pairwise disagreement in availability of instructions between countries using the Jaccard distance, a statistic used to measure the distance between binary vectors that ignores shared absences [44]. For each PID in a specific country, we assigned three binary values for the presence or absence of clinical characteristics and aligned or unaligned instructions. For each pair of countries, we counted the number of positions where binary vectors disagreed. We then computed the Jaccard distance as the number of disagreements over the total number of positions where at least one country had a non-missing value, assuming that any absence was random. For reference, we have included the formula for calculating the Jaccard distance in the electronic supplementary materials.

To evaluate patterns of similarity across multiple countries, we performed a cluster analysis. Based on pairwise distances, as described above, we used agglomerative hierarchical clustering. This method iteratively groups (i.e. clusters) the two countries (or, at a later stage, clusters) with the shortest pairwise distance. In our study, the distance between clusters is calculated as the average of distances between each pair of individual countries within the clusters.

3.5.3 Tools for Data Analysis, and Data Presentation

We have tabulated results, or presented them in bar plots of percentages of PIDs by country of origin and DoTS or SIM domain, together with the median proportions across countries and interquartile ranges (IQRs).We analysed all data using R Statistical Software (v.4.3.2), with "proxy" to compute the Jaccard distance, "stats" for hierarchical clustering, and "ggplot2" to create figures [45]. For heatmaps, and apposed dendrograms, we used "ComplexHeatmap" [46, 47].

4 Results

The research data are available in Electronic Supplementary Materials 2. Copies of the PIDs are available on request.

4.1 Retrievable PIDs Across the 35 Countries Considered

We found available PIDs in English on the websites of regulators of 18 of 35 countries or groups thereof: Australia, Bhutan, Canada, the EU, Ethiopia, Ghana, Kenya, Malaysia, New Zealand, Nigeria, the Philippines, Rwanda, Saudi Arabia, Singapore, South Africa, Tanzania, the USA, and Zimbabwe. Following consultation with the Kenyan Pharmacy and Poisons Board, we obtained the URL that listed PIDs from Kenya. Of the other 17 websites, we found no available PIDs in 11, PIDs in languages other than English in four, and outdated or too few PIDs in two.

4.2 Signals Included in the Analysis

The previously published datasets included 835 signals based solely on clinical assessments of case reports communicated in 2014–2019 by regulatory agencies or national pharmacovigilance centres. A total of 116 (14%) signals were excluded because they were communicated by multiple regulators at different times, 82 (10%) because only one country had at least one relevant PID, and ten (1%) because they concerned herbal medicinal products. In total, 627 (75%) signals remained for analysis. These concerned 364 distinct medicinal products coded to WHODrug Global, for which there were PIDs available for at least two of the countries considered. Five of these had been withdrawn in at least one country.

4.3 PIDs with Available Clinical Characteristics or Instructions

We found, in at least one PID, clinical characteristics or instructions for prevention or mitigation for 472 of 627 signals (75%), and instructions for monitoring for 129 of 627 signals (21%).

A total of 5737 of 8282 PIDs (69%) had a DoTS score ≥ 1, of which 1937 had a positive Dose-relatedness score, 1639 had a positive Time course score, and 2161 had a positive Susceptibility score.

4.4 Domain-Level Completeness Across Countries

With regards to instructions for prevention or mitigation, the median proportion of PIDs with a maximal Dose-relatedness score = 4 was 20% (IQR 17–24%); for Time course it was 22% (IQR 21–25%) and for Susceptibility 56% (IQR 53–58%). The percentages of PIDs having such a score were below the medians of all domains for Bhutan, the Philippines, Rwanda, and South Africa, and above the

medians for Australia, Canada, and the EU. See Table 1 and online resource supplementary Figure 2.

For monitoring instructions, "Critical value" scored 1 in a median proportion of 63% of PIDs (IQR 47–67%), "How to respond" in a median of 61% (IQR 58–70%), followed by "What to monitor" (57%; IQR 50–62%), "When to start monitoring" (51%; IQR 45–59%), "How frequently to monitor" (54%; IQR 42–60%), and "When to stop monitoring" (37%; IQR 21–62%). The PIDs from Australia, Canada, the EU, and Singapore had consistently positive deviations from the median across all domains (Table 2 and online resource supplementary Figure 2).

4.5 Sufficient Completeness of PIDs Across Countries

The median proportion of PIDs with a total DoTS score ≥ 1 was 68% (IQR 59–76%; online resource, supplementary Figure 3 and Table 6), and the median proportion of PIDs with a total DoTS score ≥ 5 was 30% (IQR 28–33%, online resource, supplementary Figure 4 and Table 7). The median proportion of PIDs with a sufficiently complete SIM score (i.e. ≥ 3) was 22% (IQR 19–25%; online resource, supplementary Figure 5 and Table 8).

Table 1 Percentage of PIDs having a domain score = 4, grouped by country of origin of PIDs, and Dose-relatedness (Do), Time course (T), and Susceptibility (S) domains

Country	Do Median 20% IQR 17–24%	T Median 22% IQR 21–25%	S Median 56% IQR 53–58%
Australia	26% (68/260)	26% (57/223)	58% (137/237)
Bhutan	1% (1/69)	0% (0/67)	9% (7/82)
Canada	26% (70/272)	27% (64/237)	60% (146/245)
Ethiopia	17% (16/94)	26% (23/90)	56% (58/104)
European Union	25% (73/287)	25% (63/250)	62% (165/266)
Ghana	10% (6/63)	22% (13/58)	54% (40/74)
Kenya	20% (12/60)	19% (10/52)	55% (30/55)
Malaysia	20% (49/240)	22% (46/207)	57% (122/214)
New Zealand	23% (54/231)	23% (44/192)	53% (107/202)
Nigeria	17% (15/86)	21% (16/75)	62% (53/85)
Philippines	15% (18/118)	21% (23/112)	45% (49/108)
Rwanda	14% (13/95)	20% (16/80)	53% (52/99)
Saudi Arabia	23% (56/240)	22% (42/195)	58% (119/204)
Singapore	21% (51/240)	24% (49/207)	56% (119/211)
South Africa	18% (38/211)	13% (22/165)	51% (89/176)
Tanzania	17% (14/82)	21% (17/81)	62% (52/84)
United States	24% (67/279)	25% (61/243)	53% (133/251)
Zimbabwe	24% (11/46)	23% (9/39)	56% (22/39)

Medians and IQRs calculated across all countries. For each domain, the denominator included all PIDs corresponding to signals with information in that domain in at least one country; when information for a given signal was present in other countries but absent in a specific country, this absence was scored as 0 and retained in the denominator

IQR interquartile range, *PID* product information document

4.6 Relative Frequencies of Instructions

Of the 1639 PIDs that had Time course domain scores ≥ 1, 1482 (90%) included corresponding instructions; of the 2161 with Susceptibility ≥ 1, 1564 (72%) included instructions; and of the 1937 with Dose-relatedness ≥ 1, 677 (35%) included instructions.

Out of 3723 instructions for prevention or mitigation, 1564 (42%) concerned the Susceptibility domain; 882 of these related to immunological reactions, for which avoidance was recommended 877 times. Disease was the second most common susceptibility factor, totalling 477 instances, with 288 recommendations for avoidance. Time-relatedness featured in 1482 instructions (40%): 318 instances pertained to time-independent reactions, for which monitoring was recommended 217 times. Time-dependent reactions ($n = 290$) were mostly early sustained ($n = 99$), followed by late ($n = 71$), delayed ($n = 47$), first dose ($n = 18$), early tolerant ($n = 9$), withdrawal ($n = 8$), rapid ($n = 8$), and intermediate ($n = 6$). Most of these were accompanied by recommendations to withdraw ($n = 89$) or monitor ($n = 83$). Dose-relatedness instructions ($n = 677$, 18%) largely comprised collateral effects ($n = 574$) and instructions to withdraw ($n = 484$). Of all 3723 instructions, 948 (25%) were unaccompanied by clinical characteristics or accompanied by clinical characteristics to which they were not clearly relevant. Most of such instructions ($n = 505$) recommended either monitoring or forewarning the patient ($n = 227$).

Of the 1906 monitoring instructions, 743 (39%) belonged to the domains "What to monitor"; 423 (22%) belonged to "How to respond"; 317 (17%) to "When to start monitoring"; 171 (9%) to "Critical value"; 149 (8%) to "How frequently to monitor"; and 103 (5%) to "When to stop monitoring".

See the electronic supplementary material online resources, supplementary Tables 9–12, for the full breakdown of the counts of clinical characteristics and instructions.

4.7 Cross-Country Comparisons

4.7.1 Relative Availability of DoTS Clinical Characteristics and Instructions by Country of Origin of PIDs

The PIDs from the EU and Canada had the highest relative availability of clinical characteristics or instructions for prevention and mitigation, with a ratio of 0.86. This shows that 86% of the signals with a total DoTS score ≥ 1 in any

Table 2 Percentage of PIDs having a domain score ≥ 1, grouped by country of origin of PIDs and the domains of the SIM

Country	What to monitor Median 57% IQR 50–62%	When to start monitoring Median 51% IQR 45–59%	When to stop monitoring Median 37% IQR 21–62%	How frequently to monitor Median 54% IQR 42–60%	Critical value Median 63% IQR 47–67%	How to respond Median 61% IQR 58–70%
Australia	67% (76/114)	64% (32/50)	42% (8/19)	55% (12/22)	68% (17/25)	63% (40/63)
Bhutan	0% (0/21)	0% (0/10)	0% (0/3)	0% (0/3)	0% (0/4)	0% (0/9)
Canada	78% (94/120)	82% (49/60)	77% (17/22)	75% (21/28)	93% (27/29)	72% (49/68)
Ethiopia	55% (22/40)	56% (9/16)	20% (1/5)	33% (3/9)	44% (4/9)	71% (12/17)
European Union	67% (84/126)	60% (37/62)	77% (17/22)	64% (18/28)	66% (19/29)	74% (50/68)
Ghana	57% (12/21)	71% (5/7)	33% (1/3)	40% (2/5)	100% (2/2)	60% (6/10)
Kenya	52% (13/25)	44% (4/9)	100% (2/2)	100% (2/2)	67% (2/3)	62% (8/13)
Malaysia	61% (62/101)	51% (25/49)	61% (11/18)	52% (11/21)	57% (13/23)	68% (39/57)
New Zealand	62% (59/95)	64% (25/39)	58% (11/19)	60% (12/20)	67% (14/21)	60% (30/50)
Nigeria	50% (16/32)	50% (7/14)	25% (1/4)	50% (4/8)	88% (7/8)	53% (10/19)
Philippines	57% (32/56)	43% (13/30)	63% (5/8)	53% (8/15)	47% (7/15)	59% (19/32)
Rwanda	42% (15/36)	31% (4/13)	0% (0/5)	38% (3/8)	38% (3/8)	56% (10/18)
Saudi Arabia	57% (56/98)	51% (23/45)	19% (3/16)	63% (12/19)	52% (11/21)	60% (34/57)
Singapore	59% (61/103)	56% (27/48)	72% (13/18)	57% (12/21)	67% (16/24)	68% (40/59)
South Africa	48% (38/79)	45% (17/38)	33% (3/9)	59% (10/17)	60% (9/15)	48% (20/42)
Tanzania	44% (16/36)	38% (5/13)	33% (1/3)	29% (2/7)	33% (2/6)	71% (10/14)
United States	64% (77/120)	52% (31/60)	41% (9/22)	50% (14/28)	48% (14/29)	57% (39/68)
Zimbabwe	63% (10/16)	57% (4/7)	0% (0/0)	60% (3/5)	67% (4/6)	70% (7/10)

Medians and IQRs calculated across all countries. For each domain, the denominator included all PIDs corresponding to signals with information in that domain in at least one country; when information for a given signal was present in other countries but absent in a specific country, this absence was scored as 0 and retained in the denominator

IQR interquartile range, *PID* product information document, *SIM* Systematic Instructions for Monitoring

country also scored ≥ 1 in the EU or Canada. Conversely, Bhutan had the lowest ratio, at 0.16. No country had a ratio of 1, meaning that no PID of a single country fully included clinical characteristics or prevention or mitigation instructions relevant to a signal that were otherwise available in other countries. See Table 3.

4.7.2 Relative Availability of SIM Items by Country of Origin of Product Information

The Canadian PIDs had the highest availability of instructions for monitoring and those of Bhutan the lowest (proportions of 0.79 and 0.00, respectively), relative to all other countries (Table 4).

4.7.3 Disagreement Analysis

By average linkage, there were two clusters of countries: (1) Singapore and Malaysia; (2) Australia and New Zealand. One country, Bhutan, was in an independent cluster from all others (Fig. 2).

5 Discussion

5.1 Main Findings

We found at least one clinical characteristic, or instruction for prevention or mitigation, in the PIDs of 18 countries relevant to 472 of 627 signals. Monitoring instructions were identified for 129 of these signals. Instructions belonging to the Susceptibility domain were the most complete across all countries (DoTS score = 4; median 56%; IQR 53–58%). However, only a median of 30% of PIDs contained sufficiently complete prevention or mitigation instructions (DoTS score ≥ 5; IQR 28–33%) across countries. Similarly, complete monitoring instructions were present in a median of 22% of PIDs (SIM score = 3; IQR 19–25%). The results also showed that the PID of a country never consistently included all possible information on prevention, mitigation, and monitoring available in that of other countries (i.e. the relative availability of information never reached 1). Finally, we identified two clusters of countries: Malaysia and Singapore; Australia and New Zealand.

Table 3 Number of PIDs by country, and across any country, with a DoTS score ≥ 1, sorted by descending relative availability of clinical characteristics or instructions for prevention or mitigation by country (proportions)

Country	Retrieved unique PIDs	PIDs with a DoTS score ≥ 1 (per country)	PIDs with a DoTS score ≥ 1 (any country)	Proportions
Canada	322	368	427	0.86
European Union	352	396	460	0.86
Australia	310	330	412	0.80
United States	335	350	439	0.80
Singapore	271	294	374	0.79
New Zealand	261	276	356	0.78
Zimbabwe	42	51	65	0.78
Saudi Arabia	268	286	371	0.77
Tanzania	98	101	132	0.77
Malaysia	278	286	378	0.76
South Africa	241	230	316	0.73
Ethiopia	133	118	162	0.73
Kenya	63	66	91	0.73
Nigeria	112	103	142	0.73
Ghana	75	76	109	0.70
Rwanda	121	102	152	0.67
Philippines	137	113	182	0.62
Bhutan	99	19	117	0.16

For each country, the number of retrieved PIDs is given (over a total possible of 364 unique medicinal products). At most, 352 of 364 medicinal PIDs were retrievable from a single country, the European Union, and as few as 42 of 364 for Zimbabwe. So, the number of signals to which we could attribute a DoTS score, including zero, varied; e.g. for the European Union, it was 460, and for Zimbabwe 64. PIDs could refer to several signals, so the number of PIDs with DoTS scores ≥ 1 exceeds the number of retrieved PIDs

DoTS Dose-relatedness, Time course, Susceptibility, *PID* product information document

Table 4 Number of PIDs by country, and across any country, with an SIM score ≥ 1, sorted by descending relative availability of instructions for monitoring by country (proportions)

Country	Retrieved unique PIDs	PIDs with an SIM score ≥ 1 (per country)	PIDs with an SIM score ≥ 1 (any country)	Proportions
Canada	322	95	121	0.79
European Union	352	89	127	0.70
Australia	310	76	115	0.66
USA	335	77	121	0.64
Malaysia	278	66	103	0.64
Singapore	271	65	104	0.62
Zimbabwe	42	10	16	0.62
New Zealand	261	59	96	0.61
Philippines	137	33	57	0.58
Saudi Arabia	268	57	100	0.57
Ghana	75	12	21	0.57
Ethiopia	133	22	40	0.55
Kenya	63	13	25	0.52
Nigeria	112	16	32	0.50
South Africa	241	38	79	0.48
Tanzania	98	17	36	0.47
Rwanda	121	15	36	0.42
Bhutan	99	0	21	0.00

For each country, the number of retrieved PIDs is given (over a total possible of 364 unique medicinal products). PIDs could refer to several signals, so the number of PIDs with SIM scores ≥ 1 exceeds the number of retrieved PIDs

PID product information document, *SIM* Systematic Instructions for Monitoring

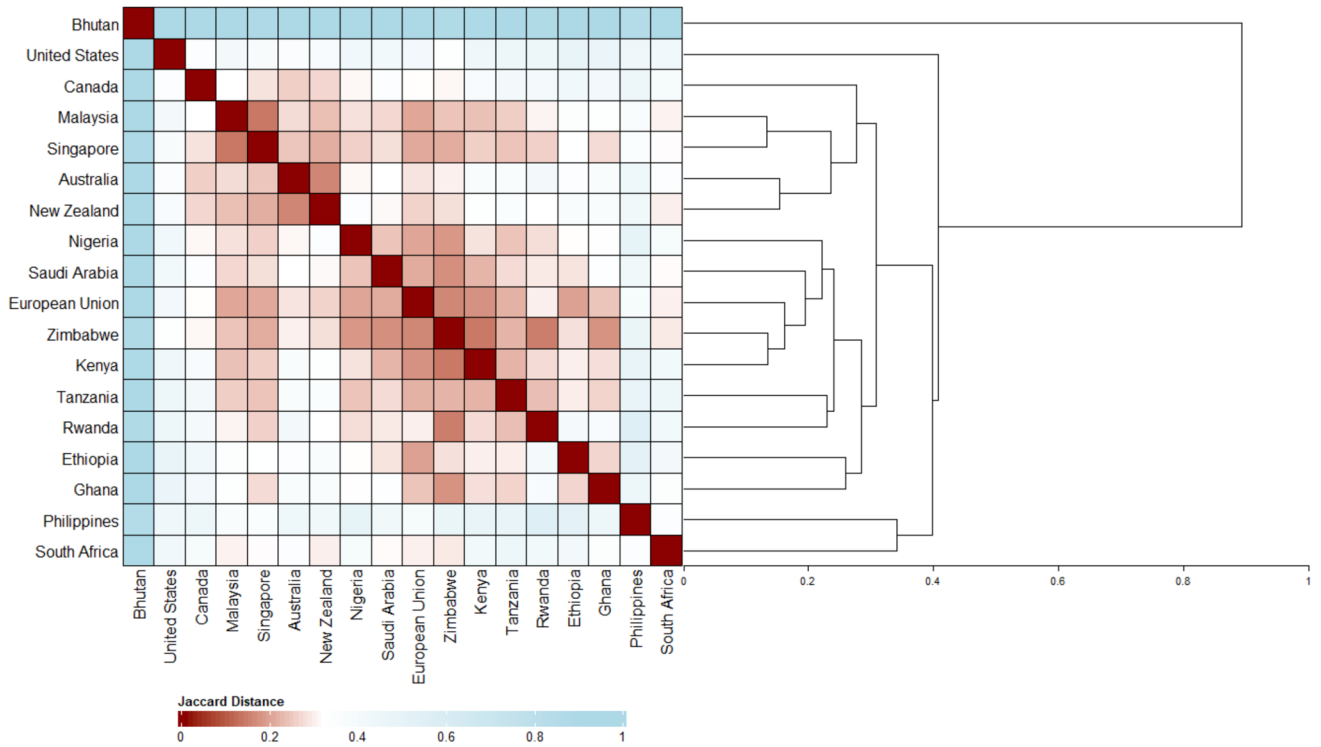

Fig. 2 Left side: Heatmap of the Jaccard distance for all countries in the study. Colours were assigned based on trimmed quantiles of Jaccard distance (5th percentile, 50th, and 95th), to compress outlier distances. Shorter distances are towards the red end of the spectrum. Right side: Dendrogram, showing clusters of countries based on average linkage distance. Clusters that join at lower average linkage distances are closer, such as Singapore and Malaysia. Bhutan belonged to an outlier cluster (average linkage distance = 0.90)

5.2 Low Overall Completeness of the PIDs

We have extended previous research characterizing possible deficiencies in PIDs to multiple countries and have found that instructions for prevention, mitigation, and monitoring, therein, are incomplete—as others have previously shown in part [27]. The thresholds used to define "sufficient completeness" may be viewed as strict, but we used published thresholds for the SIM method, and a conservative one (5/12, or ~42%) for the DoTS classification. An explanation for the low total DoTS scores may be that signals based on case reports provide insufficient evidence to formulate complete instructions for prevention, mitigation, and monitoring. Specifically, the time required to accrue evidence to characterize ADRs and formulate relevant, actionable instructions for prevention, mitigation, and monitoring may be longer than the 5–10 years we have allowed for. Indeed, previous reviews have shown that only a third of communicated signals had been corroborated by observational studies within 5 years from the amendments to PIDs that they prompted [48]. In principle, the deficiencies of the instructions in the PIDs that relate to signals of ADRs may be compensated by additional written media, such as Direct Healthcare Professional Communications (DHPCs). However, in practice, DHPCs communicated between 2007 and 2018 have also been found to have inadequate instructions for monitoring, 47% of the EU's DHPCs having an SIM score ≥ 3 [28]. To remedy the lack of implementation guidance, some have suggested that the warnings in PIDs should include shared decision-making guides or risk calculators to assist healthcare providers, accompanied by tools to assess the uncertainty of evidence (such as GRADE) [19]. In all, our judgment is that PIDs may not always provide healthcare providers with complete guidance for prevention, mitigation, and monitoring of ADRs whose possible causal relationship has been determined based on reports of ADRs. We advocate clarity, consistency, and transparency in presenting information in PIDs through, for example, tabulated lists of ADRs categorized by degree of potential harm, with accompanying level of evidence, and implications for practice [49]. The EIDOS (Extrinsic species, Intrinsic species, Distribution, Outcome, Sequelae)/DoTS classifications have previously been used in risk management planning [50], so coherent use of this framework from planning of risk management throughout the compilation of PIDs may further increase the consistency with which the domains were complete. Finally, more mixed-methods research is required to ascertain

whether amendments to PIDs impart knowledge to and attain intended behavioural changes in healthcare providers and patients [51].

5.3 Low Domain-Level Completeness

The individual domains had different degrees of completeness (i.e. their scores reached 4), where Susceptibility scores tended to be higher and Time course and Dose-relatedness lower.

Susceptibility may have been more complete because of "immunological" ADRs, which include Gell and Coombs types I–IV, such as Stevens-Johnson's syndrome or autoimmune haemolytic anaemia. For the Susceptibility domain, we accepted that mandatory, sometimes nonspecific, contraindications in the case of "hypersensitivity" [1, 3] counted towards, or implied, recommendations of avoidance. When specific instructions were given, recommendations for avoidance were sometimes ambiguous and could have merited stricter judgment. For example, we made no distinction between instructions to "permanently discontinue" and "discontinue", or between "withdraw" and "withdraw permanently", for immunological ADRs, since their suspicion or diagnosis typically call for permanent discontinuation and avoidance of subsequent use [52, 53]. Nevertheless, only prior knowledge of susceptibility enables avoidance. So, the completeness of the Susceptibility domain can be adduced to mitigating strategies too, rather than preventive ones alone.

Collateral effects, the most frequent in the Dose-relatedness domain, i.e. harms that occur in the same dosage range as expected benefits, are generally unavoidable, and so it is understandable that the median domain score was lower, as instructions for mitigation may require knowledge of efficacious treatments of drug-induced harms. Simultaneously, the frequency of collateral ADRs may indicate that effects classified as collateral were merely listed in tables in PIDs, and that their clinical characteristics were omitted. While PIDs may contain descriptions of selected, tabulated ADRs, e.g. if they are serious or severe or have a delayed time course [1], the clinical usefulness of these sections remains to be evaluated.

Time course also scored low. Contextually, information on time to onset was among the least complete data in databases of reports of suspected ADRs [54]. Paradoxically, temporality was the second most frequently occurring feature of case reports that supported clinical assessments [35]. This may indicate that, albeit rarely, available information on the time course of an ADR is accounted for in clinical assessments but may not be made available to healthcare providers as often. For example, the EU signal of uveitis with topiramate was supported by "reports of bilateral uveitis developing shortly after the initiation of topiramate treatment with no confounding disease and relatively rapid resolution of uveitis after cessation of topiramate treatment", but no information on temporality of this early (sustained) ADR reached any of the PIDs we consulted. Others have found that information on the duration of adverse effects was scarcely available in PIDs of the EU and USA [55]. Time-dependent or time-independent ADRs may sometimes be mitigated by monitoring. The Canadian PIDs had the most complete instructions for monitoring; this may be because they often contained a specific section dedicated to monitoring instructions. Other countries could improve the completeness of such instructions by introducing a similar section.

5.4 International Differences in PIDs

Like others, we have shown that there are international differences in PIDs. An intuitive explanation for these discrepancies may be the variation HLA polymorphisms across populations, which may inform the clinical relevance of certain pieces of information. For example, Stevens-Johnson's syndrome caused by carbamazepine has been associated with HLA-B*1502 in Han Chinese, and with HLA-B*3101 in Europeans [56, 57]. However, we also observed instances where PIDs included information on genetic susceptibility relevant to minority populations. For instance, the Nigerian, Rwandan, South African, and Tanzanian PIDs for clopidogrel all reported that insulin autoimmune syndrome may occur more frequently in patients carrying the HLA-DRA-4 subtype and that this is more frequent in the Japanese population. Despite such instances, genetic susceptibilities were rarely available in the PIDs (see electronic supplementary materials, supplementary Table 11), and so, population-level differences are unlikely to account for broader international differences we observed.

Instead, we identified clusters of countries that may operate similarly, indicating the influence of international regulatory cooperation. For instance, the Trans-Tasman Mutual Recognition Arrangement [58] may explain the cluster of Australia and New Zealand. Other clusters may be driven by practices of reliance, as defined by Good Reliance Practices (GRelP), that is, the possibility of a country's regulatory agency to partly or fully adopt assessments made by a reference agency that are relevant to their local context, including those that relate to amendments of PIDs [59]. Regulatory agencies of Ethiopia, Ghana, Kenya, Rwanda, Saudi Arabia, South Africa, Tanzania, and Zimbabwe adopt GRelP for matters of pharmacovigilance, and list as reference agencies those in the EU, Canada, the USA, and Australia, among others [60–67]. Despite the

provisions of the GRelP, their effectiveness at harmonizing PIDs remains to be fully understood [68]. Furthermore, previous research on patterns of worldwide withdrawals of marketing authorizations have suggested that strengthened regulatory cooperation is needed to improve harmonization in pharmacovigilance [33, 69]. We reiterate and extend this suggestion to better the consistency of PIDs across countries too, particularly those that are visible outliers. A global repository of PIDs may help identify discrepancies and foster harmonization where necessary. Partial work only has been completed towards this milestone [70, 71], while an initiative by the European Medicines Agency (EMA) for medicinal products in the EU is underway [72].

6 Strengths and Limitations

In this descriptive study, we have accounted for the types of evidence that may have contributed to amendments of the PIDs and have investigated their variability across one of the largest sets of countries studied in recent years. Furthermore, we have adapted or used published methods to ascertain the completeness of PIDs and selected statistical approaches suitable to the nature of the data. To our knowledge, studies on prevention or monitoring instructions have been done on selected classes of medicinal products, while we based our research question on a wide set of medicinal products that have received regulatory attention.

Our choice of interval in the years of communication (2014–2019) may have allowed additional evidence to accrue before any instructions were added to the PIDs. As such, clinical assessments of case reports may not have been the only contributors to amendments to the PIDs, although follow-up observational studies tend to be infrequent [48]. We did not extract information on the evidence supporting instructions, so we could not distinguish between precautionary and preventive strategies. Similarly, we have not recorded the date of the latest updates of PIDs, and some differences may have been brought about by delays in updates. Update delays may have also affected the PID of reference products that we have chosen to focus on, similar to those known to affect generic products.

We used a prespecified list of regulatory agencies to obtain PIDs, some of which were not publicly available. While this may suggest obstacles for healthcare providers in finding information relating to harms in some countries, it is possible that PIDs in such countries are available in paper format, which we did not retrieve or request. In addition, we only considered PIDs in English and therefore omitted otherwise relevant PIDs. In reviewing the websites of regulators, we recorded 17 with insufficient PIDs or those without them, only four of which provided PIDs in languages other than English. We recognise that PIDs available in other languages may contain information that is unavailable in English. Subsequent research should therefore procure paper-based PIDs and involve a group of researchers fluent in multiple languages, particularly where PIDs are available in English but where the official language may differ.

The DoTS classification has not been validated as a normative method of extracting instructions from PIDs, and so some recommendations may have been unfairly scored. Moreover, the threshold for defining sufficient completeness of instructions for prevention or mitigation was chosen arbitrarily, albeit conservatively and with some consideration of the nature of the evidence that may have underpinned amendments to PIDs. In view of the subjectivity that accompanies content analyses, our framework and research data have been made transparent and publicly available. Nevertheless, future research could validate scoring systems that ensure simplicity and retain construct validity.

We did not penalize PIDs that merely listed ADRs in dedicated tables and attributed the collateral determinants of ADRs to the tabulated ones. In so doing, we may have artificially increased the scores of the Dose-relatedness domain, and a different scoring method might account for lack of information. However, it is possible that regulatory agencies may not have deemed the clinical significance of ADRs in dedicated tables to be sufficient to warrant inclusion of recommendations for prevention, mitigation, or monitoring [1, 3]. We did, however, penalize the scores of PIDs that did not indicate clinical characteristics or instructions relating to an ADR when that of at least another country did; we did that by assigning zero points to the relevant domain. In only a small set of 44 out of 627 signals for DoTS instructions (about 7% of the data) and 20 signals for monitoring instructions (or 3%) did we penalize PIDs based on the PID of only one country.

Lastly, we have not formally evaluated the clusters' stability, and by scaling distances, we assumed that PIDs missed at random. If similar research were carried out, other techniques, bootstrapping, for example, might be used to assess stability [73]. Furthermore, the clustering was carried out on distances in scores, and so disagreement reflects dissimilarity of scores rather than dissimilarity of instructions. To err on the side of caution, we have only highlighted clusters at lower levels of the hierarchy.

7 Conclusions

Across 18 countries, instructions for prevention, mitigation, and monitoring that concerned signals detected by assessing case reports were seldom deemed complete. To ensure international harmonization of product information, existing agreements of regulatory cooperation between countries, or groups thereof, may require global extension. A unified

repository of documents that include product information may obviate the lack of some product information online and reduce the extent of discrepancies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-026-01666-6.

Funding This work is part of Daniele Sartori's DPhil in Evidence-Based Medicine at the University of Oxford (Nuffield Department of Primary Care Health Sciences and the Department of Continuing Education), UK. The DPhil is fully funded by the UMC. No undue influence or coercion was exerted on DS by the funder throughout the design and conceptualization of the study, the writing of this manuscript, or its associated protocol.

Declarations

Conflict of Interest JKA has written papers on adverse drug reactions in peer-reviewed journals and has received royalties from textbooks that he has edited or co-edited; he has often acted as an expert witness in cases involving adverse drug reactions, most often in coroners' courts. DS has communicated signals of adverse drug reactions, some of which may have also been included in product information of one or more countries. GNN is an Editorial Board member of *Drug Safety*; GNN was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. MF and IJO have no relevant competing interests.

Disclosures The views expressed are those of the authors and not necessarily those of the Uppsala Monitoring Centre or the University of Oxford.

Availability of Data and Material The original research data are part of the electronic supplementary materials. The product information documents we retrieved are available on request.

Code Availability The R code is publicly available at https://github.com/PVverse/paper.PI.

Authors' Contributions DS conceptualized and designed the study with support from IJO, JKA, and GNN. MF joined the research team after registration of the protocol on MedrXiv, took part in cross-validation of scores, designed the scripts for data analysis, and provided suggestions on data presentation and analysis. DS wrote the manuscript with support from all co-authors, who also reviewed and approved drafts and the final version.

Ethical Approval This research did not involve human participants, tissues, and/or personal data. As such, ethics approval was not required.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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