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ORIGINAL RESEARCH ARTICLE

A Descriptive Study of Additional Risk Minimization Measures Included in Risk Management Plans Reviewed by the United Kingdom Regulatory Authority

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Abstract
Background Risk management plans (RMPs) describe known and potential safety concerns with medicines, how they will be studied further and how the risks will be minimized. Since 2005, European legislation has required RMPs to be submitted with applications for marketing authorizations for new medicines and they can also be requested if safety concerns arise post-authorization. Currently, there is limited information published on experience with RMPs. This study investigated the application of 'additional' risk minimization measures (ARMMs), which are those beyond routine product information, looking at all RMPs submitted to the UK regulatory authority during a 5-year period.
Objective The aim of this article is to describe when ARMMs are successfully approved by the Medicines and Healthcare products Regulatory Agency (MHRA) according to the type of product, risks and measures included in the plan, and to identify common problems with ARMMs included in RMPs from a regulatory perspective.
Methods In this study, all 225 plans assessed by the MHRA between November 2005 and January 2011 were analysed retrospectively. The RMPs and MHRA assessment reports were reviewed and information was classified using pre-defined categories: type of product, reason for the ARMM, type of safety concern, type of ARMM, type of auditing measure to assess the effectiveness of the ARMM and the MHRA assessment and comments on the plan.
Results Ninety-five (42%) of 225 RMPs assessed by the MHRA included ARMMs. ARMMs were used more frequently for biological than chemical products (47 vs. 40%). The most common forms of ARMMs were educational materials for healthcare professionals (61%). These were commonly used in RMPs for all types of products and more frequently used for high-risk medicines such as biological products. MHRA regulatory review had an important impact on the content of the plans; 75% required amendments. Inadequate auditing measures, which are tools to assess the effectiveness of each additional risk minimization measure, were a common problem with ARMMs and 24% of those submitted did not include any form of auditing measure. A further 23% were refused because the auditing measures included were not appropriate.
Conclusion ARMMs and their related auditing measures are important factors in designing RMPs and achieving regulatory approval. It is usual for an RMP with ARMMs to require revisions prior to approval and this should be factored in to the marketing authorization application process. The type of product, type of risks and target audience should all be considered when designing a successful risk minimization strategy and the RMP needs to be individually customized accordingly.

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1 Introduction

New medicines are authorized based on a limited amount of information about safety and efficacy, which at the stage of marketing authorization comes mainly from clinical trials. The information gained cannot always predict how the drug will be accepted when the product is launched into the general population. Risks may transpire that were not previously identified [1] and there may be specific subsets of patients at higher risk of a harmful effect than the general population [2]. It is therefore extremely important that the safety and efficacy of a medicine is monitored

throughout the product's lifecycle and precautions are taken to limit risks and help ensure that the benefits outweigh the risks by the greatest possible margin for all patients who take the product. The risk management plan (RMP) sets out the pharmacovigilance activities planned to identify, characterize, prevent or minimize risks, including an assessment of the effectiveness of those interventions [3]. Up until July 2012, European legislation required applicants to include RMPs in their marketing applications for innovative medicines or introduce an RMP for a licensed product if safety concerns arise. RMPs are now required for all newly authorized products [4, 5].

The RMP should contain an evaluation of the need for risk minimization activities. Routine risk minimization measures (such as warnings in the product information, careful use of packaging and labelling) may be considered to be sufficient to limit risks, otherwise 'additional' or non-routine risk minimization measures (ARMMs) must be included in the RMP. Examples of ARMMs include communications, (such as direct healthcare professional [DHCP] letters), educational materials, training programmes, patient registries or restricted access schemes [3]. The plan must explain in detail how each of the risks will be addressed using routine and/or additional risk minimization measures. It should also include 'auditing measures', which are tools to assess the effectiveness of each additional risk minimization measure, where they are proposed [3].

The Medicines and Healthcare products Regulatory Agency (MHRA) is the Government Agency responsible for regulating medicines in the UK. It is part of the EU network of regulatory authorities so it is involved in the assessment of European applications and RMPs where UK is the lead assessor (rapporteur) or contributing assessor (co-rapporteur). The MHRA must approve RMPs for new applications before the marketing authorization is granted, and therefore issues with the plans could hold up the grant of a marketing authorization and be costly to the applicant.

As RMPs are a fairly new requirement for industry (since late 2005) there is limited published information on their use. The aim of this study is to describe when ARMMs were successfully approved by the MHRA according to the type of product, risk and measures included in the plan. It sets out to identify common problems with ARMMs included in RMPs from a regulatory perspective. This aims to provide an information base that could help to improve the standard of RMPs and may streamline this part of the regulatory approval process.

2 Methods

In this study, all 225 plans assessed by the MHRA between November 2005 and January 2011 were retrospectively analysed and each product was categorized according to the type of product (biological or chemical and orphan or non-orphan) and the indication. Biological products were defined using the European Medicines Agency's (EMAs) definition of a biological medicine, a medicine containing an active substance that comes from a biological source [6]. Orphan products were defined using the European definition as medicines intended for a condition affecting no more than 5 in 10,000 people in the EU that is unlikely to be able to receive revenues to cover the investment in its development without incentives [7]. The therapeutic indication was recorded for each product and they were categorized into Anatomical Therapeutic Chemical (ATC) categories using the WHO 2nd level classification system to show the pharmacological/therapeutic subgroup [8]. If the drug substance was not listed in the index, the ATC category was based on the MHRA assessment report or review of the summary of product characteristics (SPCs).

For the 95 RMPs with ARMMs the safety concerns with risk minimization measures agreed or proposed, with MHRA comments, were described.

Risks were categorized for analysis into ten groups:

1. Adverse drug reactions (ADRs): Harmful effects caused by the medicine.
2. Contraindications: Harmful effects in specific situations.
3. Effects on test results or monitoring: These risks could disrupt the monitoring or diagnosis of the patient and result in harm.
4. Interactions: Risks when combined with other medicines, food or drink.
5. Medication errors: Mistakes with the product, administration or dosing causing adverse events.
6. Product quality risks: Risks from the manufacture or administration that may affect the product's quality.
7. Risk of transmission: Effects from the spread of viruses or other infective agents.
8. Off-label use: Risks of abuse or use in unlicensed indications.
9. Reduced efficacy: Risk that the product's benefit will fail in certain situations.
10. Teratogenicity: Harmful effects in pregnancy.

The measures proposed to mitigate each risk were described from analysing the draft versions of the RMP submitted to the MHRA. The MHRA's assessment of each ARMM was recorded and the comments were summarized and categorized as; approved, minor comments or rejected. Minor comments were defined as small comments on the wording used in the risk minimization materials or requests to review the educational materials before use. The MHRA's view on the final version of the plan was recorded as; application withdrawn, under assessment, approved or refused.

The ARMMs in the initial and approved version of the RMP were recorded. A wide range of measures was described and it was common for a plan to list more than one type of measure. To aid analysis the measures were categorized into 15 groups as follows:

1. Educational materials for healthcare professionals (HCPs).
2. Educational materials for patients.
3. HCP communications.
4. Training for HCPs.
5. Training for patients.
6. Pregnancy prevention programme.
7. Controlled distribution/restricted access – to control which patients receive the product.
8. Monitoring of product.
9. Monitoring of patient.
10. Monitoring of HCP – tools to monitor if HCP is using the product correctly.
11. Registry – a list of the patients who are taking the product to follow up on any adverse events.
12. Patient alert card – a card summarizing all the warnings and precautions for the patient.
13. Tools for patient records – tools to flag up to other prescribers that the patient has taken the product.
14. Labelling tools – tools to help identify products.
15. Switch-over strategy – to ensure that patients are prescribed the correct product when a new product has been launched.

The presence of an auditing measure in the first and subsequent versions of the RMP and a description summary was recorded. They were categorized into the following four categories defined as follows:

1. Spontaneous reporting – monitoring of ADR reports of cases of particular adverse effects as they occur.
2. Communication – assessing whether risks have been communicated successfully.
3. Prescribing – analysing the effect on prescribing.
4. Hard outcomes – conducting a formal study to assess the effect of the measure on hard outcomes. These could be ecological studies of secular trends.

The MHRA comments on the proposed measures were summarized and categorized as:

1. refused – major amendments required;
2. approved with minor amendments;
3. approved – no changes required.

All of the information above was collated into an Excel spreadsheet for analysis. Numbers and percentages were calculated for each category to enable comparisons to be made.

3 Results

Between November 2005 and January 2011, 95 of 225 (42%) RMPs assessed by the MHRA included ARMMs in the proposed or final version. Of the 171 approved RMPs, 72 included ARMMs (42%) (Fig. 1).

Comparison between the numbers of RMPs with routine measures and the numbers with ARMMs showed that ARMMs were more common than routine measures (in two or more plans) for: contrast media, drugs for obstructive airway diseases, ophthalmologicals, immunosuppressants, muscle relaxants, antibacterials for systemic use and other nervous system drugs (such as drugs for addictive disorders) (Fig. 2). Routine measures were more common (in two or more plans) for: drugs classed in the ATC category for all other therapies, cough and cold preparations, analgesics, drugs for bone diseases, vaccines, diabetes drugs, antithrombotics, antihaemorrhagics, cardiac therapy, pituitary and hypothalamic hormones, antivirals, immunostimulants, psycholeptics, psychoanaleptics (Fig. 2).

The most common types of risk requiring an ARMM were ADRs (39%). Medication errors were the second most common type of risk, (23%) (Table 1).

Educational materials for healthcare professionals were the most common measure approved (104 for 172 safety concerns [60%]). The majority of plans approved contained some educational materials for healthcare professionals (44 of 72 approved RMPs with ARMMs [61%]). Educational materials for patients were the second most common measure approved (59 for 34 safety concerns [34%]). Training for HCPs, registries, HCP communications, controlled distribution or restricted access schemes and patient alert cards were also frequently used (Table 2).

A total of 75 RMPs with ARMMs were for biological products. Considerably more of the RMPs for biological products included ARMMs; 35 (47%) compared with 60 (40%) for non-biologicals. Of the 72 overall approved RMPs with ARMMs, 23 (32%) were for biological

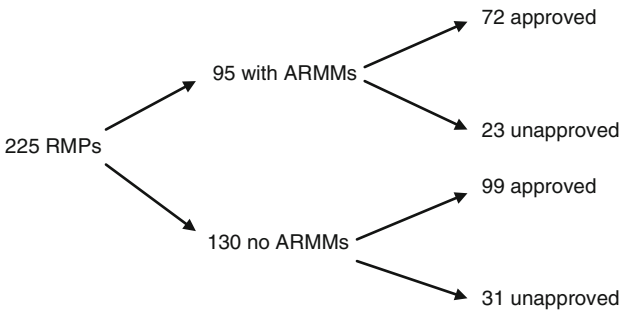

Fig. 1 Risk management plans included in the study population. *ARMM* additional risk minimization measures, *RMP* risk management plan

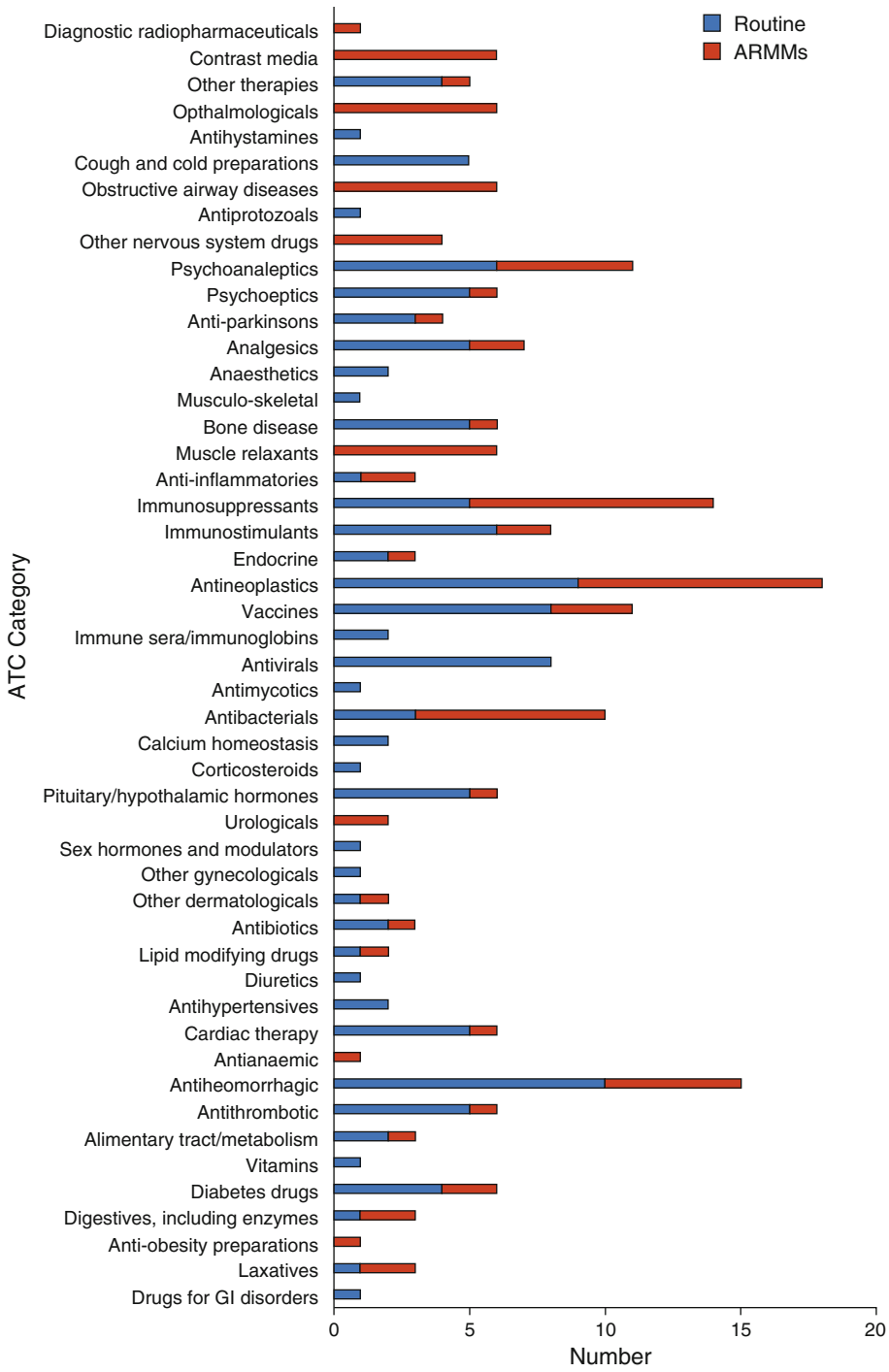

Fig. 2 Anatomical Therapeutic Chemical categories of the risk management plans in the study population and the proportion of routine measures and additional risk minimization measures. *ARMM* additional risk minimization measures, *ATC* Anatomical Therapeutic Chemical, *GI* gastrointestinal, *RMP* risk management plan

products. This was higher than the proportion of approved RMPs for biological products without ARMMs, of these, 26 (26%) of 99 were for biological products. The RMPs for biological products contained a higher frequency of risks requiring minimization measures than non-biological products. In total there were 115 risk minimization measures for the 35 biological product RMPs, averaging at 3.29 risks per RMP, which was more than for non-biological RMPs (1.55). The proportion of risks from missing information was also higher for biological products (10 vs. 6%) (Table 3).

A total of 36 RMPs for orphan products with ARMMs were included in the study population. There were equal proportions of RMPs for orphan products that included ARMMs to minimize safety concerns and non-biological products (42%). There were identical proportions of orphan products in the group of RMPs with ARMMs and RMPs without ARMMs (15%). The number of risks with ARMMs

Table 1 Number and percentage of additional risk minimization measures approved for each category of safety concern in risk management plans

Category of safety concern	Safety concerns with ARMMs approved in the RMP [n (%)][a]	Product plans with ARMMs [n (%)][b]
ADR	67 (39)	33 (46)
Medication errors	39 (23)	28 (39)
Contraindication	18 (10)	8 (11)
Off-label use	15 (9)	14 (19)
Teratogenicity	12 (7)	12 (17)
Interactions	8 (5)	6 (8)
Effect on test results/monitoring	6 (3)	6 (8)
Product quality risks	4 (2)	4 (6)
Reduced efficacy	2 (1)	2 (3)
Risk of transmission	1 (1)	1 (1)

ADR adverse drug reaction, *ARMMs* additional risk minimization measures, *RMP* risk management plan

[a] Given as a percentage of the total number of safety concerns identified in RMP with ARMMs approved (172)

[b] Given as a percentage of the total number of approved RMP with ARMMs (72)

Table 2 Types of additional risk minimization measures in approved risk management plans according to the number of safety concerns and number of approved risk management plans

Measures	Safety concerns within approved plans [n (%)][a]	RMP approved containing ARMMs [n (%)][b]
Educational – HCP	104 (60)	44 (61)
Educational – patients	59 (34)	27 (38)
Training – HCP	24 (14)	12 (17)
Registry	14 (8)	7 (10)
HCP communication	13 (8)	11 (15)
Controlled distribution/ restricted access	11 (6)	7 (10)
Patient alert card	7 (4)	7 (10)
Training – patient	1 (1)	1 (1)
Monitoring – product	3 (2)	3 (4)
Pregnancy prevention programme	2 (1)	2 (3)
Tools for patient records	4 (2)	2 (3)
Monitoring – patient	1 (1)	1 (1)
Monitoring HCP	1 (1)	1 (1)
Labelling tools	3 (2)	3 (4)
Switch-over strategy	1 (1)	1 (1)

ARRM additional risk minimization measures, *HCP* healthcare professional, *RMP* risk management plan

[a] Given as a percentage of the total number of risks with ARMMs approved (172)

[b] Given as a percentage of the total number of approved RMPs with ARMMs (72)

in each RMP was much higher than for non-orphans products (3.40 vs. 1.96 risks with ARMMs per RMP) (Table 3).

3.1 Medicines and Healthcare products Regulatory Agency Assessment of Additional Risk Minimization Measures (ARMMs)

Of the 95 RMPs that included ARMMs, 24 (25%) plans were approved by the MHRA first time with no comments or amendments, while 34 (36%) needed minor amendments. If minor comments were provided by the MHRA, further review of the RMP was not required (Table 4).

The MHRA reasons for refusing risk minimization measures were grouped into five categories as follows (out of 37):

1. Risks not addressed appropriately or risks omitted – 17 RMPs (46%). For example, ARMMs omitted for serious safety concerns from incorrect administration when training and educational materials could be useful for reducing such administration errors.
2. Concerns about type of measures proposed – 10 RMPs (27%). ARMMs proposed in these plans were not appropriate for the type of safety concern. For example, serious concerns such as serious ADRs often required more than one ARMM.
3. Auditing measures not sufficient or lacking – 4 RMPs (11%). These were either omitted from the plan or not appropriate for the type of ARMM and likely to be ineffective.
4. Concerns that educational materials were promotional – 3 RMPs (8%). Promotional language about the benefits of the product included.
5. Lack of information on ARMMs/auditing measures – 3 RMPs (8%). The MHRA could not assess the RMPs without comprehensive information on the measures proposed such as details of how the ARMMs would be distributed.

3.2 Auditing Measures

Of the 95 RMPs submitted with risk minimization measures, 72 (76%) included some form of auditing measure to assess the effectiveness of the measures. Sixty-seven (71%) plans submitted this in their first version and five (5%) in the second version after a request from the MHRA. It was common for RMPs to include several auditing measures; however, 23 (24%) of the plans did not include any.

Monitoring the effects of measures on spontaneous ADR reporting was the most common type of approved auditing measure in 37 product plans (40%). Monitoring the

Table 3 Risk management plan characteristics according to type of product

Type of product	All [n (%)]	Biological [n (%)]	Non-biological [n (%)]	Orphan [n (%)]	Non-orphan [n (%)]
ARMMs included	95/225 (42)	35/75 (47)	60/150 (40)	15/36 (42)	80/189 (42)
Routine measures only	130/225 (58)	40/75 (53)	90/150 (60)	21/36 (58)	109/189 (58)
Risks with ARMMs included	208	115	93	51	157
Approved RMPs with ARMMs	72/171[a] (42)	23/72[b] (32)	49/72[b] (68)	11/72[b] (15)	55/72[b] (77)
Routine measures only and RMP approved	99/225 (44)	26/99 (26)	73/99 (74)	15/99 (15)	84/99 (85)
Risks with ARMMs (approved)	172	58	114	28	121
Risks with ARMMs per approved RMPs (mean)[c]	2.39	2.52	2.33	2.55	2.20
Risks with ARMMs per all RMPs (mean)[d]	2.19	3.29	1.55	3.40	1.96
Missing information (as a proportion of all types of risk with ARMMs approved)	10/172 (6)	6/58 (10)	4/114 (3)	1/28 (3)	7/121 (4)

ARMM additional risk minimization measure, *RMP* risk management plan

[a] Given as proportion of all approved RMPs (171)

[b] Given as proportion of the approved plans with ARMMs (72)

[c] Number of risks with ARMMs/approved RMPs (72)

[d] Total number of risks with ARMMs/RMPs with ARMMs (95)

Table 4 Medicines and Healthcare products Regulatory Agency's assessment decision of risk management plans with additional risk minimization measures

MHRA decision (first submission)	Number (%)
Approved	24 (25)
Minor amendments required	34 (36)
Refused	37 (38)

MHRA Medicines and Healthcare products Regulatory Agency

Table 5 The category of auditing measure

Type of auditing measure	Auditing measures [n]	RMPs including each auditing measure [n (% of all approved RMPs with ARMMs)]
Spontaneous reporting	119	37 (40)
Communication	63	19 (22)
Prescribing	40	15 (17)
Hard outcomes	2	1 (1)
None	18	13 (15)

effectiveness of communications was also common, (19 [22%]). Effects on prescribing were included as a measure in 15 plans (17%). Formal hard outcome studies, used to assess the effect of the minimization measure on outcomes such as mortality or morbidity in the patient population, were uncommonly proposed; only one plan was approved with this type of auditing measure (Table 5).

Nearly one-quarter of plans (17 of 72 [23%]) with auditing measures were refused partly or wholly due to insufficient auditing measures. The reasons for refusal could be categorized as follows:

- auditing measure was not appropriate – 11 RMPs (65%);
- more information was required – five RMPs (29%);
- amendments to planned protocol or measures were required – 1 RMP (6%).

Although 72 of the 95 plans included an auditing plan, only 55 of the 95 plans (58%) with ARMMs included auditing measures that were of an acceptable standard to the MHRA. Forty of the 95 plans (42%) did not include any approvable auditing measures.

4 Discussion

This study is the first of its kind to describe ARMMs in RMPs. It has produced a wealth of information on the type of measures proposed in RMPs, the types of risks, the types of products and the MHRA assessment. The key findings are explained as follows:

Routine measures were considered by the MHRA to be sufficient to minimize a product's risks in just over half of RMPs submitted (58%). For a considerable proportion of RMPs (42%), routine measures alone were not considered to be sufficient to minimize risks (Fig. 1). This shows the number of ARMMs in the initial submission to the MHRA; considering the significant investments involved in implementing ARMMs, this proportion is high. This suggests that companies consider ARMMs to be important pharmacovigilance tools to maintain a positive benefit risk profile for the medicine, to meet regulatory requirements and to try to ensure the MA grant is not delayed due to the RMP.

ARMMs were more commonly used for higher risk products such as biologicals and orphans and generally more common for products in ATC categories for serious illnesses and less commonly for products associated with lower risks, such as cough and cold preparations. All of the RMPs submitted for muscle relaxants were approved with ARMMs. This group mostly consisted of botulinum toxin-containing products that have risks associated with their biological nature such as ADRs of local or systemic toxin spread that could cause toxin reactions. Other factors may influence the use of ARMMs such as, length of use of the product, familiarity of the class of product and method of administration (Fig. 2).

Biological medicines are known to be higher-risk molecules than synthetic molecules. They have complex and difficult manufacturing procedures and unpredictable stabilities [9], and there is a higher potential for serious safety concerns such as immunogenicity and tumorigenicity [10] compared with non-biologicals. The safety concerns associated with biological products are likely to be more complex and challenging to minimize, such as risk of transmission of infectious agents, hypersensitivity, immune complex formation, autoimmunity and toxicity risks [10]. Risks for biological products are difficult to predict and characterize in preclinical studies and clinical trials [11]. In this study, a larger proportion of RMPs for biologicals (47%) than for non-biologicals (40%) used ARMMs (Table 3). Strategies to minimize risks in the RMPs for these products need to be carefully considered and the results show that ARMMs are commonly used. The findings of this study are consistent with another study, which found that RMPs for biologicals contained a higher frequency of risks concerning missing information than for non-biological products, and safety studies were proposed more frequently in RMPs for biological products [12] (Table 3).

Experience of orphan products is limited by the size and design of the clinical trials that can be performed and the diseases they treat may be less well characterized, as they are used to treat diseases and conditions with small patient populations [13]. These molecules are therefore higher risk and would require more ARMMs and a more complex minimization plan. This is reflected by this study's findings, which show that the number of risks with ARMMs in each RMP was much higher than for other products (3.40 vs. 1.55 risks with ARMMs per RMP) (Table 3).

4.1 How ARMMs Were Used

ARMMs were used for all ten categories of safety concerns in the approved RMPs. The two most common types of safety concerns and ARMMs are discussed below and teratogenic risks, which are also a common and interesting area.

ADRs have a considerable impact on patients and the healthcare system [14]. It has been suggested that 51% of ADRs can be prevented, by ensuring the drug is taken appropriately and correctly [15] and ARMMs can help to minimize ADR risks [16]. In this study, ADRs were the most common type of risk to require an ARMM, accounting for 39% of risks with ARMMs (Table 1). For serious adverse events, such as serious infections or hypersensitivity reactions, training, patient alert cards and patient registries were used to try to ensure that symptoms were recognized as soon as possible to reduce harm to the patient. For more general ADRs such as transient gastrointestinal effects that could cause patients to stop taking their medication, communication tools, such as patient educational materials, were commonly used. Where medicines affect laboratory results or require patient monitoring, patient alert cards and tools for patient records were used to convey to other healthcare professionals and laboratory technicians that a patient was taking the medicine.

Medication errors were the second most common type of risk to require an ARMM (Table 1). Medication errors can lead to ADRs which are otherwise preventable [15] so it is important to address these risks, and ARMMs can be important tools. Educational materials, training programmes and HCP communications were used to communicate about risks of medication errors from incorrect strengths and doses and administration techniques. Controlled distribution and restricted access tools were used to minimize risks from inadequately trained prescribers administering the product.

Teratogenic risks accounted for 7% of the risks with ARMMs (Table 1). These plans commonly used controlled distribution and restricted access tools to ensure that pregnancy precautions were taken prior to prescribing the drug. Patient registries were used to track patients prescribed a medicine to ensure that teratogenic effects did not occur and to follow up on any cases of pregnancy. Pregnancy prevention plans used combinations of tools with the objective of preventing any cases of pregnancy, and some included patient informed consent forms to ensure that patients have understood the risks of treatment and the precautions. Compliance with the programme is important and it was raised by the MHRA that, where possible, related products should use similar strategies to avoid confusion and aid compliance.

The most common types of ARMM approved in RMPs were educational materials for HCPs (used for 104 [60%] of risks) and patients (used for 59 [34%] of risks) (Table 2). From a company perspective, educational materials may be less resource intensive to implement than training tools and can be easily distributed to recipients. They are useful to convey important safety messages and can be very effective in changing prescribing behaviours

[17, 18]. Pharmaceutical companies may use company representative visits to simultaneously distribute educational materials and stimulate interest in the medicine by providing information on the benefits of the product [19]. This is not always acceptable from the perspective of the regulator. A common reason for the MHRA to refuse materials was where educational materials were not clearly separate from promotional activities, and concerns were raised when the sales force was used as the only way to communicate messages about the safe use of the product. There could be a conflict of interest if company sales representatives are relied upon to communicate risks that may limit product sales.

Educational materials offer advantages over other forms of ARMMs, as they tend to be paper based and contain written information that can be stored and kept as a reminder. This is preferable to spoken information that cannot always provide the level of detail required and cannot be accessed after the visit [20]. Prescribers are limited in how much time they can spend with each patient and so written materials that explain the key messages and can be taken home can be extremely useful for patients.

The MHRA requested educational materials to be added to nine RMPs suggesting educational materials are viewed by the MHRA, as a useful tool in minimizing risks. This may be because the materials are a way for the regulator to ensure that correct messages are written down and can therefore be conveyed to the target audience. It may also be that written documents can be straightforward to assess and changes to the content can easily be requested by the regulator and implemented by the applicant.

4.2 Impact of Assessment Process

This study suggests that the MHRA regulatory review had a considerable impact on the content of the plans. Amendments were requested in 75% of the plans and a large number of RMPs were refused by the MHRA with major amendments required (38%) (Table 4).

The MHRA frequently requested justification for the inclusion of patient educational materials, particularly when the additional benefits for having educational materials, as well as routine risk minimization measures (SPC, technical leaflet, patient information leaflet), were not clear. One plan was rejected for this reason. The MHRA commented with concerns that the educational materials were mixed with marketing initiatives particularly if the educational information was disseminated using the company sales staff or the content was promotional. MHRA commonly requested companies to submit the educational materials to the MHRA for review prior to issue.

Insufficient information in the RMP was a common reason for refusal. RMPs can only be approved if enough information is provided to allow full assessment. If educational materials were proposed as ARMMs, the content of the materials and information on how the materials would be distributed was required by the MHRA. For example, if the product was to be used by paramedics, the plan should propose methods to ensure that the communication does reach the target audience.

The MHRA review frequently requested changes to the content and presentation of RMP materials. Previous studies looking at the effectiveness of pharmaceutical communications have highlighted that the presentation and wording of communication materials can have a significant influence on how prescribers respond, and this can lead to changes in practice [21]. This suggests that the MHRA critical input on the content and presentation of materials could have a significant impact on how the medicine is used.

4.3 Measuring the Effectiveness of ARMMs (Auditing Measures)

Of the 95 RMPs including ARMMs, 23 (24%) did not include any auditing measure suggesting that compliance with this regulatory requirement is relatively low. It was not clear from the MHRA assessments why this was the case. It could be due to difficulties in implementing or designing these measures or a lack of understanding of the legislation.

The most common type of auditing measure was monitoring the effect on spontaneous ADR reporting (37 [40%]). It is a regulatory requirement to monitor reports of adverse events, [22] so this method can be readily implemented but spontaneous reporting rates fluctuate due to confounding factors and under-reporting can be a significant limitation [23] (Table 5).

An innovative way of collecting ADR information was suggested in an approved RMP that used HCP communications to inform prescribers how to minimize the effects of ADRs and reduce the chance of ADRs occurring. The HCP communication included a coupon designed for HCPs to return to the company with details of any adverse events. The MHRA agreed with this plan but requested for the protocols to be submitted for how the data would be collected and analysed.

Market research approaches to assess the effectiveness of communications were commonly employed in RMPs (22% of plans with ARMMs) to assess whether the communication was received, understood and resulted in a change of behaviour, for example patient questionnaires to monitor the effectiveness of patient educational materials (Table 5). However, actual changes in behaviour can be difficult to assess. The population responding to market research tools may not reflect the whole user or prescriber population and this could introduce bias. The MHRA

commented a number of times that the companies needed to include information on which sampling methods would be used to avoid bias and validate the data obtained from the surveys.

Measures to assess the effect of ARMMs on healthcare professionals' prescribing habits were used as an auditing measure in 15 (17%) of the plans (Table 5). Drug utilization studies can provide information on levels of usage, how the product was used and the characteristics of users and use of interacting drugs. They can be used with drug registries to collect information on a wide range of risks and can be particularly useful in studying subgroups of the population. For established products, studies can be used to show the change in usage in the population after ARMMs were introduced. The MHRA frequently requested to review the protocols for drug utilization studies. Monitoring changes in prescribing is relatively resource intensive and this may explain why they are not commonly used by companies. The main disadvantages are that they may not reflect the use of the minimization measures as many factors can influence prescribing [24]. Studies of hard outcomes and qualitative rather than quantitative drug utilization studies may be more useful for studying the impact of ARMMs on clinical outcomes [25].

Of the RMPs with ARMMs, only one included a study of hard outcomes (Table 5). These studies can be difficult to implement and can be resource intensive. The potential for using studies of hard outcomes to measure the effectiveness of ARMMs has so far not been explored or utilized by companies.

Auditing measures were generally of a low standard, and nearly one-quarter (23%) of plans submitted with auditing measures was refused by the MHRA partly or wholly due to insufficient auditing measures. The most common problems were that the auditing measures proposed were viewed by the MHRA to be inappropriate and likely to be ineffective, did not include enough information on the measures or enough information on study protocols and further information was required by the MHRA. When studies are planned, sufficient information on the study protocol should be included in the RMP to allow assessment, and selection bias should be carefully considered. A previous study also found similar issues with post-authorization safety studies (PASS), around 40% of the study proposals did not contain sufficient information to allow assessment by the regulators [12]. This suggests that the quality and detail of information submitted on study protocols in RMPs could be improved to facilitate regulatory assessment.

4.4 Limitations and Areas of Further Study

This study did not assess what occurs after the RMP is agreed or whether the auditing measures were carried out and what the findings were. Whether as a result of the measures, HCPs or patients comply with the safety messages and whether this directly impacts on clinical outcomes is the crucial test. This has not been assessed by this study and is something that is particularly difficult to measure. Previous studies have attempted to assess the effectiveness of specific aspects of an RMP in altering prescribing behaviours and these have shown mixed results [18, 19, 21, 26, 27].

The categorization process for some of the groups was subjective so there may have been inaccuracies. To minimize this potential bias, a dual assessment system could have been used. However, this was not practical in terms of time and resources. To minimise categorization inaccuracies, clear definitions were used for each category and care was taken to be consistent in making decisions on the categorizations.

Statistical tests to determine whether comparative results were of statistical significance have not been performed. This is a descriptive study so this was not considered necessary. An area of further study could be to perform statistical tests using the data collected to determine whether the findings are of statistical significance.

5 Conclusions

It is well recognised that RMPs are extremely important pharmacovigilance requirements to ensure that medicines continue to show a positive benefit risk profile when they are used in the general population. This is crucial to protecting public health and vital to the commercial success of the molecule. ARMMs are useful pharmacovigilance tools for communicating safety information, restricting and controlling the use of medicines to enable safe use and they have an important role to play in the success of the RMP.

This is the first study to systematically describe regulatory experience of assessing RMPs and ARMMs. It included review of all RMPs assessed by the MHRA for over 5 years from when the legal requirements were introduced and provided a wealth of valuable information on ARMMs. It shows that ARMMs are used frequently to minimize risks in RMPs. They are used more frequently for higher-risk products and educational materials are the most common type of measure approved. The regulatory review had an important impact on the content of the plan and inadequate auditing measures were a common problem.

The findings of this study add to limited existing knowledge of how to successfully utilize ARMMs in RMPs and to achieve regulatory approval. The information collected could help to improve the standard of RMPs, as it describes the use of ARMMs in approved RMPs according to the type of product and type of risk and highlights potential problems from the UK regulator's perspective.

New pharmacovigilance legislation came into force in 2012 [4, 5] and aims to improve the standard of drug safety and allow greater transparency of pharmacovigilance information. One of the planned requirements is for summaries of approved RMPs to be published on the internet [4, 5]. This will allow information on ARMMs to be shared widely and this will help to further improve the standard of RMPs across Europe.

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