**Hospital Pharmacists’ opinions on a risk prediction tool for medication-related harm in older people**

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**Short title:** Pharmacy opinion on medicine risk tool

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**What is already known about this subject:**

* Risk-prediction tools (RPT) are commonly used in clinical practice.
* The PRIME-RPT is a novel, internally validated tool which predicts older adults’ risk of medication-related harm (MRH) within eight-weeks of hospital discharge.
* It is important to seek opinions of clinicians who will use RPTs before they are integrated into clinical practice.

**What this study adds:**

* The PRIME-RPT was well received by hospital pharmacists and commended for its ability to easily quantify MRH risk.
* The RPT could prioritise pharmacists’ interventions to those at highest risk.
* PRIME-RPT can potentially be integrated into existing clinical pathways.

**Abstract**

**Aim:** Older adults are particularly affected by medication-related harm (MRH) during transitions of care. There are no clinical tools predicting those at highest risk of MRH post-hospital discharge. The PRIME study (prospective study to develop a model to stratify the risk of MRH in hospitalized patients) developed and internally validated a risk-prediction tool (RPT) that provides a percentage score of MRH in adults over 65 in the eight-weeks following hospital discharge. This qualitative study aimed to explore the views of hospital pharmacists around enablers and barriers to clinical implementation of the PRIME-RPT.

**Methods:** Ten hospital pharmacists: (band 6 (n=3); band 7 (n=2); band 8 (n=5)) participated in semi-structured interviews at the Royal Sussex County Hospital (Brighton, UK).The pharmacists were presented with five case-vignettes each with a calculated PRIME-RPT score to help guide discussion.Case-vignettes were designed to be representative of common clinical encounters. Data were thematically analysed using a ‘framework’ approach.

**Results:** Seven themes emerged in relation to the PRIME-RPT: 1. providing a medicine-prioritisation aide; 2. acting as a deprescribing alert; 3. facilitating a holistic review of patient’s medication management; 4. simplifying communication of MRH to patients and the multidisciplinary team; 5. streamlining community follow-up and integration of risk discussion into clinical practice; 6. identifying barriers for the RPTs integration in clinical practice and 7. acknowledging its limitations.

**Conclusion:** Hospital pharmacists found the PRIME-RPT beneficial in identifying older patients at high-risk of MRH following hospital discharge, facilitating prioritising interventions to those at highest risk while still acknowledging its limitations.

**Introduction**

Medication related harm (MRH) including adverse drug reactions (ADRs), non-adherence and medication errors are common during transition points of care. A recent review highlighted that MRH affected between 17-51% of individuals within 30 days of hospital discharge (1). In a UK based observational, multicentred, prospective cohort study 37% of older people suffered MRH in the eight-week period post discharge with an estimated cost of £396 million annually of which £243 million is potentially preventable (2). Strategies to address MRH at transition points of care include medicines’ reconciliation to reduce the number of unintentional medicine discrepancies delivered via, for example, NHS England Discharge Medicines Service (3). However, to allocate resources efficiently a targeted approach, prioritising patients most at risk, is needed.

Future risk can be estimated using risk prediction tools (RPT), many of which are routinely used in clinical practice to inform decisions. For example, the CHA2DS2-VASc score, in conjunction with HASBLED score, helps determine the risk/benefit of anticoagulation to prevent stroke in patients with atrial fibrillation (4). The QRISK score predicts the risk of cardiovascular disease and need for statin therapy (5). MRH risk stratification in older adults could help support clinicians and patients to make informed decisions about treatment plans/decisions and hence deliver safer healthcare (6).

Our research team developed the PRIME risk prediction tool (PRIME-RPT) to identify older patients (>65 years) at risk of MRH in the eight-weeks period after hospital. The PRIME study recruited 1280 patients from 5 hospitals in the UK. The RPT consists of eight routinely collected variables: age, sex, antiplatelet drug, sodium level, antidiabetic drug, past adverse drug reaction, number of medicines, living alone (7). The risk-prediction model equation and an illustrative case example are shown in figure 1. The novelty of the PRIME-RPT is that it provides an individualised numerical score of the possibility of experiencing MRH within eight-weeks of hospital discharge (7). Furthermore, it demonstrated superior accuracy compared to the routine clinical judgement of doctors (8).

Before implementing the PRIME-RPT into clinical practice, engaging stakeholders is an essential pre-requisite for the successful translation of research findings into clinically meaningful impact (9). The practicality of the RPT needs to be considered within a clinical setting through seeking the opinion of the relevant healthcare professionals who will be applying it, primarily hospital pharmacists. This qualitative study explores hospital pharmacists’ opinions about the PRIME-RPT. Specifically, we aimed to understand the enablers and barriers of implementing the PRIME-RPT at the point of hospital discharge.

**Methods**

Design and participants

This qualitative study was conducted at the Royal Sussex County Hospital (RSCH), Brighton, UK between September to November 2020. Pharmacists providing discharge services to medical patients were observed by AH (research-fellow) to observe their engagement in hospitalised patients’ discharge process and guide content of the subsequent semi-structured interviews with five hypothetical case-vignettes. Junior band 6 (n=3) and band 7 (n=2) pharmacists as well as specialist band 8a (n=3) and band 8c (n=2) pharmacists were included.

Hypothetical case-vignettes (appendix 1), guided by the research aim, were developed by AH and KA (chief-investigator). Based on patients discharged from the medical wards at the RSCH, they were representative of the common clinical encounters and the spectrum of MRH observed in practice. Application of the PRIME-RPT to the case vignettes produced a risk range of 4-48%.

Each case-vignette featured patient demographic data including age, gender, hospital length of stay and discharge diagnosis. A clinical summary including co-morbidities, social history, medications issued, available blood tests and MRH risk score calculated by the PRIME-RPT formula were included. These hypothetical case-vignettes were discussed with and agreed by all co-authors.

Data collection

Face-to face interviews with pharmacists were conducted by AH. The case vignettes were presented to participating pharmacists along with the calculated PRIME-RPT score to help guide discussion. Interviews lasted 20 minutes to 1 hour. All interviews were digitally recorded and transcribed with accompanying field notes. Data were analysed using the Framework approach, a method developed for social policy research (10). The following key stages were included: verbatim transcription of recorded interviews, familiarisation, identifying a thematic framework, indexing, charting, mapping, and interpretation.

AH and KA independently read the interview transcripts to identify potential themes, followed by discussion of identified themes. They considered how to retain the diversity of the initial codes and areas of overlap to produce overarching thematic headings and higher-level sub-themes. The research question and impact of using the PRIME-RPT in clinical practice informed this process. Suitable quotes congruent with overarching themes were identified.

Standard techniques were used to ensure systematic, verifiable approaches to analysis and ensure procedural clarity. These included consistent availability of verbatim transcripts and digital audio recording. Data collection took place until data saturation (defined as no new themes being elicited) (11). Data were analysed thematically using a Framework approach, developed by the National Centre for Social Research, particularly suited to multidisciplinary research teams (12,13). This approach involves five processes: data familiarisation, coding, indexing, charting, and interpretation.

Data analysis was iterative, in which issues raised by participants were fed into subsequent interviews. This was further assisted by weekly discussions of the interview findings between AH and KA and additional regular discussion of findings with the broader multidisciplinary research team who all have relevant expertise in geriatric and pharmaceutical care.

Ethical considerations

The study was presented and registered with the local Pharmacy Research and Audit Group at RSCH (reference: PRAGSEP20/01). It was deemed to be part of service evaluation of current pharmacy discharge processes and therefore not classified as ‘clinical research that required ethical approval.’ Voluntary semi-structured interviews with pharmacists included only discussion of hypothetical scenarios; there was no requirement for ethical approval.

**Results**

Thematic analysis of the pharmacists’ interviews produced seven distinct themes around the PRIME-RPT (table 1).

1. Prioritisation aide
2. Medicine deprescribing alerts
3. Biopsychosocial model of medication management
4. Communication/presentation of risk to patients, hospital staff and community teams
5. Streamlining community follow-up and integrating MRH risk discussion into clinical practice
6. Barriers towards clinical integration
7. Limitations of the risk predictions tool

Data extracts illustrating each of the seven themes are presented in table 2.

Prioritisation aide

The PRIME-RPT provides stratification of patient’s MRH risk in the eight-weeks following hospital discharge. The tool could be used to prioritise high-risk patients for targeted interventions such as medication counselling, close community follow-up or use of compliance aids to reduce risk. Pharmacists highlighted that their workload is substantial and welcomed a prioritisation aide.

Pharmacist 1: *“The tool can help prioritise patients. The positive is that you can focus on the really high-risk patients.”*

Whilst there is no formal definition for the cut off for ‘high-risk’ provided for the PRIME-RPT, the absolute risk presented as a numerical score allows referral for follow-up based on the value of the risk score.

Medicine deprescribing alerts

The total number of drugs a patient is prescribed is an important determinant of MRH risk according to the PRIME-RPT. ‘The number of drugs alert’ within the PRIME-RPT reminded ward pharmacists to target discharged patients with polypharmacy and potential medication interactions. The RPT could act as an aide memoire for junior pharmacists to review indications for medications and reduce potential MRH risk by deprescribing.

Pharmacist 10: *“This lady has got low sodium. What is she on amitriptyline for? It isn’t clear and she is a classic case of polypharmacy, essentially. We could deprescribe some of these medications after investigating the indications and if they are still essential.”*

Biopsychosocial model of medication management

People who live alone are more likely to experience MRH and this is reflected in the PRIME-RPT (7). The relationship between living alone and risk of MRH is complex but partially driven by poor medication adherence (14). Knowledge of patients’ living conditions can be a trigger for pharmacists to more holistically explore how patients manage medications and reduce barriers to improve medication adherence. This can include consideration of whether medication timings can coincide with care calls or using assistive devices, for example.

Pharmacist 5: *“Knowing that patients score higher because they live alone is useful prompting and to think about how patients manage if they are by themselves…how are they going to get their medications?”*

However, scoring patients for simply living alone could hide potential nuances and engender false sense of security. For instance, family member or carers may not be well versed in patient’s medications and therefore, the risk of suffering MRH is not necessarily mitigated just because the patient is not living alone. In patients who rely on others to get their medications, carer/family education is equally as important as patient education.

Pharmacist 4: “*You can’t assume just because the patient is living with the family, they’ll get their medications on time or correctly or follow sick day rules.”*

Communication/presentation of risk to patients, hospital staff and community teams

The PRIME-RPT provides an objective score of MRH risk and is an effective way of communicating this risk to important stakeholders including patients, families, hospital, and community teams. It facilitates a patient-centred approach to appropriate prescribing and deprescribing by actively involving them in discussions relating to potential benefit and harm from medications. The RPT can also highlight high-risk patients that need close follow-up and medication review to clinicians.

The way risk is presented to clinicians can impact on their decision making. In our interviews, what pharmacists considered high versus low risk varied widely between interviewed participants. Pharmacist 3 highlighted they thought 8% risk of MRH is low risk “*but it’s still almost 1 in 10 chance. Putting the risk as a 1 in something would probably make me take the 8% more seriously.”* Presentation and communication of risk is especially important when considering there is no formal definition for the cut off for low, medium, or high-risk.

Similarly, poor communication with patients can cause undue stress and alarm to patients which might lead to non-adherence and subsequent harm.

Pharmacist 3: *“When telling patients, the risk of harm from their drugs, it needs to be presented with tact so that they aren’t scared of the side-effects, especially if the benefits outweigh the risks.”*

Streamlining community follow-up and integrating MRH risk discussion into clinical practice

For the PRIME-RPT to be successfully implemented into routine clinical practice, it must be easy to use and interpret, results must be appropriately followed up and the tool should be integrated into existing clinical pathways. PRIME-RPT uses variables that are routinely collected and available in patients’ hospital records, making it easy to use. It produces a percentage value which represents the risk of experiencing MRH in the eight-weeks following discharge, making it simple to interpret. Documenting the MRH risk score on discharge summaries and electronic patient records were cited as simple ways of communicating risk with community pharmacists and GPs to arrange appropriate follow-up. PRIME-RPT could also be integrated into planned national UK initiatives such as the Discharge Medicines Service (DMS) (3), which aims to reduce the number of patients suffering MRH following hospital discharge. Consequently, knowledge of MRH following hospital discharge can facilitate efficacious use of community resources by highlighting those at the greatest risk of harm and those needing close community follow-up.

Pharmacist 4: *“We used to use several AKI and antimicrobial tools before, but they failed to catch-on because there was no community integration…Why am I going to do all the work of calculating risk for these patients and making changes if nothing is being followed up?”*

Barriers towards integration of the PRIME RPT into routine clinical use

The study pharmacists highlighted important barriers, which would hinder the use of the PRIME-RPT in routine clinical practice. These barriers included:

* The tool can trigger stress and anxiety for both patients, carers, and pharmacists,
* The fact that the tool is not accompanied with built-in interventions/solutions,
* The tool gives a numerical score without categorisation.

Junior pharmacists, who represented five of the ten interviewees, stated extra knowledge of MRH risk could potentially affect their confidence. Key concerns were a lack of guidance on specific interventions for patients at a given risk.

Pharmacist 1: “*With the tool on its own, it's kind of left your own devices and what you think is sensible for the patient. I would like a bit of extra guidance.”*

All interviewed pharmacists noted that being given the percentage risk of MRH without guidance could be overwhelming for less experienced colleagues without additional guidance. Six of the ten interviewees agreed formalising definitions of low, medium, and high-risk with development of a decision support tool would help provide guidance for pharmacists.

Pharmacist 7: “*I think you need some sort of guidance on what to do once you work out the risk otherwise it would just be left to person looking at the medications and it won’t be very systematic and will likely vary from pharmacist to pharmacist.”*

Limitations of the PRIME-RPT

Nine pharmacists highlighted important limitations of the tool itself including:

* Medicine interactions not highlighted,
* Risk of starting new medicines not picked up by tool,
* Underestimation of risk in non-adherent patients.

Polypharmacy features as an important predictor of harm however, the tool does not highlight potential drug interactions. In case study 3, the patient was on nine medications including apixaban for atrial fibrillation and aspirin for previous transient ischaemic attacks. Calculated MRH risk as per the PRIME-RPT was 29%. Four pharmacists highlighted this was a potential underestimation of risk because of the risk of significant bleeding. Consequently, the PRIME-RPT could potentially underestimate MRH risk in patients with potentially dangerous medicine interactions.

Pharmacist 3: *“Why is she on both antiplatelet and DOAC? I would want to check if this is intentional or not because that is a potentially harmful drug interaction.”*

Pharmacist 9 expressed concern that the tool *“focuses more on the chronic medication risk rather than the acute medicine risk.”* In case study 1, the patient was prescribed co-amoxiclav for raised inflammatory markers but no overt signs of infection. The acute risk of starting new medications is not explicitly considered when calculating MRH risk using the PRIME RPT.

Pharmacist 9:*“In the short term it can increase the risk of harm from Closterium difficile infection...That risk isn’t picked up by the tool.”*

The PRIME-RPT may underestimate MRH risk in patients who are non-adherent with medications. The PRIME-RPT assumes, all patients take their medications as instructed. In case study 5 a 67-year-old female with advanced dementia and on six medications had a calculated 8% MRH risk. Pharmacist 10 highlighted that although she is of low risk from suffering from MRH according to the PRIME-RPT, she is still at risk of MRH if she is not taking her medications as instructed. Nine pharmacists agreed that the tool could potentially divert the attention away from patients with low MRH risk scores, but those patients may still benefit from pharmacy input.

Pharmacist 10: *“She would still benefit from pharmacy interventions like a compliance check to see if she is taking her medicines even if the calculated risk if low*.”

**Discussion**

The PRIME-RPT is an internally validated RPT for assessing MRH in the eight-weeks following hospital discharge. Prior to integration in practice, we sought to engage key stakeholders who will be applying the tool, namely hospital pharmacists. This qualitative analysis of semi-structured interviews with ten hospital pharmacists explores their opinions on the PRIME-RPT and addresses key challenges associated with its implementation into clinical practice.

Overall, the PRIME-RPT was well received; commended for being easy to use and as a useful prioritisation aide. Specifically, pharmacists highlighted that using an objective numerical score, promptly highlights high-risk patients who would benefit from pharmacist interventions such as medication review, medication counselling and deprescribing in accordance with patients care goals. Pharmacists found the RPT to be a useful communication aide when counselling patients facilitating a patient-centred approach. It also allows focused discussions with healthcare professionals and ensures appropriate community follow-up.

The PRIME-RPT places particular emphasis on polypharmacy by scoring patients for the total number of drugs they are prescribed. Polypharmacy is a recognised cause of iatrogenic harm. ‘The number of drugs alert’ within the tool reminded ward pharmacists to target polypharmacy.

Other tools to predict MRH risk in older people include the risk model proposed by McElnay et al. (15), Geriatric ADE risk score (IMEPAG Study) (16), GerontoNet ADR Risk Score (17), and BADRI Score (18). However, unlike the PRIME-RPT, none focus on MRH risk at transition points of care, where up to 51% of patients experience MRH (1,2,6). Whilst there is no formal definition for the cut off for ‘high-risk’ provided for the PRIME-RPT, the absolute risk allows referral for follow-up based on highest risk score. The PRIME-RPT could be integrated into proposed national UK initiatives such as the Discharge Medicine Service (DMS) which aims to reduce MRH following hospital discharge (19). DMS uses electronic referral platforms through which patient discharge summaries and medication information are sent to community pharmacists responsible for providing post-discharge patient support (19). The PRIME-RPT can be used to identify patients who require extra medication support in the community, which may reduce MRH.

We acknowledge that our findings are only based on a sample of ten hospital pharmacists. Patients and other key stakeholders such as hospital doctors, GPs and community pharmacists were not included. Similarly, using case vignettes may not capture the full range of clinical encounters where pharmacists regularly manage in clinical practice. The hospital setting of all the case vignettes discussed with pharmacists only may not capture the full range of opinions that could be generated from other members of the clinical team such as doctors and nurses. However, our preliminary findings could inform a tailored discussion with additional groups. Practical limitations to widespread adoption of the PRIME-RPT include the need for impact studies to assess the effect of using such a tool on clinician behaviour, patient outcomes, and cost-effectiveness of care(20). Future impact studies can inform the development of a decision support tool/implementation pathway around medicines during transitions of care. This may include signposting to existing resources such as the Scottish Polypharmacy Guidance (21), STOPP START Toolkit (22) or the development of an entirely new toolkit. These studies should ensure that MRH risk information shared between patients and healthcare professionals is statistically accurate, clinically meaningful, relevant and actionable (23).

**Conclusion**

Our qualitative study demonstrated that the PRIME-RPT has several advantages from a hospital pharmacists’ perspective such as targeting high-risk patients and prioritising interventions. However, more work is required to assess the effect of using such a tool on clinician behaviour, patient outcomes, presentation of medicines risk, and cost-effectiveness of risk-stratification.

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**Figures**

Figure 1: Model equation and with an illustrative case example.

Table

Description automatically generated

**Tables**

Table 1: Themes identified in each of the ten interviews with study pharmacists.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Interviews | | | | | | | | | |
| Themes | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Prioritisation aide | X | X | X | X | X | X | X | X | X | X |
| Medical deprescribing alerts | X | X | X | X | X | X | X | X | X | X |
| Biopsychosocial model of medication management |  | X | X | X | X | X |  | X |  | X |
| Communication/presentation of risk to patients, hospital staff and community teams | X | X | X |  | X | X |  |  | X | X |
| Streamlining community follow-up and integrating MRH risk discussion into clinical practice |  | X | X | X | X | X | X | X | X | X |
| Barriers towards clinical integration | X | X |  |  | X |  | X |  | X | X |
| Limitations of the risk predictions tool |  | X | X | X | X | X | X | X | X | X |

Table 2: Illustrative data extracts by themes.

|  |  |
| --- | --- |
| Themes | Illustrative example quotes |
| Prioritisation aide | **Pharmacist 2:** Knowing the risk means that you can concentrate on patients that are of high-risk. You're more likely to go back and review them and make sure that you screen their discharge summaries with a bit more time and a bit more care. |
| **Pharmacist 5:** On a busy day this tool could help you. Sometimes we have fifteen discharge summaries to do in one day. If I have a younger patient who is 65, they’ve come in because of constipation and the PRIME tool says there is only a 4% [MRH] risk then it would give me reassurance. So, it won't just help prioritise clinical screening and medication review but also discharge prioritisation. |
| **Pharmacist 10:** I think the tool can help prioritise patients but not solely based on the tool. You still need a pharmacist to assess the patient and use their own clinical judgement. |
| Medicine deprescribing alerts | **Pharmacist 1:** This person is on so many medications. We can rationalise some of these medications, surely. |
| **Pharmacist 6:** The tool does highlight the dangers of polypharmacy because it scores for the total number of medications a person is on. I would want to rationalise medicine whenever possible based on this tool. |
| Biopsychosocial model of medication management | **Pharmacist 2:** I think one of the interesting things is the fact that patients score for living alone. It does make you kind of think a bit more holistically about the patient. So, you could think about whether the patient gets help with their medications either from family friends or from their carers. If patients have twice-daily carers, is it possible to change the timing of the medications so that they can get help from their carers in taking their medications? This would be a good way especially in cases where patients live alone, and they may have some sort of cognitive impairment to make sure that they are compliant with their medication. |
| **Pharmacist 4:** I see that the tool scores patients if they are living alone. I think it hides some of the nuances. Just because somebody is living with family means they will get the help taking their medications they need. There may be conflict within the family, they themselves may not be medically well versed or understand what the medications are. I think the tool may be overly simplifying in this case. |
| Communication/presentation of risk to patients, hospital staff and community teams | **Pharmacist 5:** The way that you present the risk can really alter patients and pharmacist perception of the risk. Say for example you take somebody who doesn't work on the ward very often and you tell them that the patient has a 30% risk of suffering from harm, they might think that that’s not too bad: it's only 30%. However, when you think about it that is almost one in three chance and I'm pretty sure if you were to tell someone that they have a 1-in 3 chance of suffering from some sort of adverse drug event they are likely to be quite alarmed by this and be more questioning of why they're on the medications, what is the benefit, what is the harm, how did you come to the decision that I need to be on the drug, for example. |
| **Pharmacist 9:** The PRIME risk along with my clinical knowledge of the patient would make me suggest a GP review for this patient post-discharge. The 40% helps consolidate and reassure me that, yes, GP review is needed. |
| Streamlining community follow-up and integrating MRH risk discussion into clinical practice | **Pharmacist 2:** I think the tool will either succeed or fail based on the community follow-up. I can see a lot of people thinking to themselves, why am I using this tool and flagging up who is at high risk if these patients do not get followed up properly. I do think it is a good tool that has the potential to help pharmacists do their job but we would need to ensure proper follow-up to stop it from falling by the wayside. |
| **Pharmacist 8:** You can probably put the PRIME risk in the discharge summary or integrate it into our new medication discharge platforms and DMS [Discharge Medicines Service] so you can easily flag someone’s medications up for community review. At the moment we are so reliant on GPs and involving the community pharmacists would be good. Some of the medication reviews and other things could easily be done by the community pharmacist. |
| Barriers towards clinical integration | **Pharmacist 2:** One of the disadvantages of the tool is the fact that you can only change so many things to reduce the risk as per the tool. you can't change age or gender. You can try to reduce the number of medications they are on but if they need to be on those medications then your limited in terms of your interventions that reduce the risk of medication related harm following discharge. In this sense the tool would just highlight to you who is at risk of suffering from harm but in terms of solutions you are limited to a bit more counselling and making sure that they are appropriately followed up in the community. I can see this eventually leading to some anxiety within the team and the pharmacist who is doing the discharge summary for the patient because they may well feel like they've done an inadequate job. |
| **Pharmacist 7:** I think the tools needs clear risk categories like low, medium, or high risk and some guidance on what to do next. For example, we have set things we do when patients come in like work out creatinine clearance. Based on the creatine clearance we know we must adjust medications to renal dosing. Some instruction like that for the PRIME tool would be useful; risk categories and guidance/recommendations on next steps. |
| Limitations of the risk predictions tool | **Pharmacist 2:** One of the limitations of the PRIME tool is that is does not consider medication interactions which could be potentially harmful.It is a bit strange the patient [referring to case study 3] is on apixaban and aspirin. That’s a potentially bad drug interaction there and the PRIME tool doesn’t score for that. I mean based on that alone I would say that the risk of this patient is higher than suggested by the PRIME tool. |
| **Pharmacist 10:** In many ways the [PRIME] tool will help prioritise patients. The positive is that you can focus on the high-risk patients, but the downside is that even if the risk from medications is low, you pull attention away from people who may benefit from pharmacy input to optimize their medications. |