



City Research Online

City, University of London Institutional Repository

Citation: Flood, C., Matthew, L., Marsh, R., Patel, B., Mansaray, M. & Lamont, T. (2014). Reducing risk of overdose with midazolam injection in adults: an evaluation of change in clinical practice to improve patient safety in England. *Journal of Evaluation in Clinical Practice*, 21(1), pp. 57-66. doi: 10.1111/jep.12228

This is the accepted version of the paper.

This version of the publication may differ from the final published version.

Permanent repository link: <https://openaccess.city.ac.uk/id/eprint/4515/>

Link to published version: <https://doi.org/10.1111/jep.12228>

Copyright: City Research Online aims to make research outputs of City, University of London available to a wider audience. Copyright and Moral Rights remain with the author(s) and/or copyright holders. URLs from City Research Online may be freely distributed and linked to.

Reuse: Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

City Research Online:

<http://openaccess.city.ac.uk/>

publications@city.ac.uk

Title

Reducing risk of overdose with midazolam injection in adults: An evaluation of change in clinical practice to improve patient safety in England.

Authors

Flood, C.1 Matthew, L. 2 Marsh, R. 3 Patel, B. 4 Mansaray, M.5 Lamont, T.6

Journal

Journal of Evaluation and Clinical Practice.

(This is the final author version and readers are recommended to read the final print or on line version via the Journal of Evaluation in Clinical Practice for possible minor updates or corrections).

1. Senior Lecturer in Mental Health Nursing, RGN, RN (MH), BSc, MSc, PhD, National Patient Safety Agency, 4-8 Maple Street, London W1T 5HD.
2. Assistant Director, BSc, MRPharmS, National Patient Safety Agency, 4-8 Maple Street, London W1T 5HD.
3. Clinical Psychologist Trainee, BSc, MSc, National Patient Safety Agency, 4-8 Maple Street, London W1T 5HD.
4. Senior Analyst BSc, MSc, National Patient Safety Agency, 4-8 Maple Street, London W1T 5HD.
5. Business Manager, National Patient Safety Agency, 4-8 Maple Street, London W1T 5HD.
6. Scientific Advisor, BA, MSc, NIHR Health Service & Delivery Research Programme, National Patient Safety Agency, 4-8 Maple Street, London W1T 5HD.

Corresponding author

Dr Chris Flood, Myddelton Street Building, City University London, Northampton Square, EC1V 0HB, London, c.flood@city.ac.uk, 0207 040 5989.

Current organisations and addresses of authors

- 1) City University London, Myddelton Street Building, City University London, Northampton Square, EC1V 0HB, London.
- 2) Aintree hospitals NHS Foundation Trust, Aintree University Hospital, Longmoor Lane, Liverpool, L9 7AL.
- 3) University of Bath, 1 West North, University of Bath, Bath, BA2 7AY, UK.
- 4) Care Quality Commission, Finsbury Tower 103–105, Bunhill Row, London, EC1Y 8TG, United Kingdom.
- 5) NHS East London and City,
- 6) University of Southampton, Alpha House, Enterprise Road, Southampton SO16 7NS.

Word count including title, short summary and references 6,197

Short summary

Rationale aims and objectives. This study sought to evaluate potential reductions in risk associated with midazolam injection, a sedating medication, following a United Kingdom National Patient Safety Alert. This alert, '*Reducing risk of overdose with midazolam injection in adults*', was sent to all National Health Service organisations as a Rapid Response Report detailing actions services should take to minimise risks.

Method. To evaluate any potential changes arising from this alert, a number of data sources were explored including reported incidents to a national reporting system for health care error, clinician survey and audit data, pharmaceutical purchasing patterns and feedback from NHS managers.

Results. Prior to the Rapid Response Report, 498 incidents were received by the National Patient Safety Agency including 3 deaths. Post implementation of the Rapid Response Report (June 2009), no incidents resulting in death or severe harm had been received. All organisations reported having completed the Rapid Response Report actions. Purchase and use of risk-prone, high-strength sedating midazolam by health care organisations decreased significantly as did the increased use of safer, lower strength doses (as recommended in the Rapid Response Report).

Conclusions. Organisations can achieve safer medication practices, better knowledge, awareness and implementation of national safer practice recommendations. Risks from inadvertent overdose of midazolam injection was reduced post implementation of national recommendations. Ongoing monitoring of this particular adverse event will be required with a sustained patient safety message to health services to maintain awareness of the issue and reduction in the number of midazolam related errors.

Introduction

The risks associated with midazolam overdose are well known and relevant to clinicians, with international evidence from the United Kingdom, America and New Zealand (1), demonstrating that drug related errors are a major factor associated with iatrogenic injury in hospitalised patients. These same authors cite Midazolam as being one of the most common drugs involved in ampoule labelling errors. The discussion around attempts to reduce Midazolam related error and overdose is an important international question beyond the findings of the NPSA in the United Kingdom and this UK based research report will be of interest to international health policy makers wishing to evidence that safety alert systems can reduce adverse incidents and make practice safer. Other international reports already emphasise the scale of medication error globally (2,3) with estimates for example of between 40,000 and 98,000 deaths occurring a year in the US which are attributable to medical error (4), making it the eighth leading cause of death (5). The Lazarou et al study (3) specifically highlights the incidence of serious and fatal adverse drug reactions in hospitalized patients with research suggesting 6.7% of the hospital patient population having serious drug reactions in hospitalized patients and 0.32% having a fatal drug reaction. Given that medication error accounts for 28% of all medical mistakes in the US (2) these studies combined give an idea of the scale of the problem and the importance of attempting to design policies and systems that reduce error.

In 2008 The National Patient Safety Agency (NPSA) issued a Rapid Response Report (RRR): ‘Reducing risk of overdose with midazolam injection for adults’ (6). This paper outlines an evaluation to assess the implementation and impact of this RRR on clinical practice, purchasing for safety and reporting of midazolam incidents.

Evaluating complex and national policy interventions at a national level can be a formidable process, with methods of review that understandably focus on measuring and reporting on programme effectiveness. However these evaluations can often find evidence that is mixed or conflicting. (7). The safer use of

Midazolam policy intervention and evaluation has sought to use a broad range of methods to capture any potential evidence of safer practice and changes towards a less error prone system linked to the use of Midazolam.

Background

The potential for over sedating patients using midazolam for conscious sedation is well documented (8,9). A fatal patient safety incident involving the use of midazolam was reported to the NPSA in 2008 (2). The death occurred following the administration of two consecutive doses of 5mg midazolam to an adult for sedation. The patient deteriorated and subsequently failed to resuscitate. The NPSA thereafter decided to review the risks associated with midazolam overdose. This involved a search of the National Reporting and Learning System (NRLS) (a centralised NPSA reporting system designed to capture patient safety incidents occurring in National Health Service in England and Wales). A search of the NRLS was undertaken for incidents reported between October 2003 and November 2008, containing the words ‘midazolam’ or ‘flumazenil’ (the reversing agent used for midazolam), or associated terms (3). Four-hundred and ninety-eight (498) incidents resulted from an inappropriate dose of midazolam being prescribed or administered to patients. Three incidents had resulted in death (8).

The NPSA review of these 498 incidents (8) indicated that adult patients were being overdosed with high strength midazolam injection when used for conscious sedation. Data showed risks of the entire contents of high strength ampoules being administered when only a fraction of this dose is required for most patients. Incidents occurred when the dose prescribed exceeded the dose required, doses were not titrated to individual patient need, concurrent medications were not taken into account and where high risk patients were involved. Data also suggests that flumazenil is frequently used to reverse over sedation and on occasion, no account is taken for its shorter half-life (compared to midazolam) leading to residual sedation.

The response

The NPSA was created in 2001 to collect information about patient safety incidents in healthcare, to identify national learning and to publish recommendations to improve safety in clinical practice. The NRLS database was created to collect incidents reported voluntarily from NHS organisations in England and Wales. Running since 2003, this database is the largest of its kind in the world, already having received over 6 million reports of incidents that caused or had the potential to cause harm. Voluntary incident reporting does not reveal the true incidence or prevalence of errors. Furthermore at the time of conducting this research there was no legal obligation for organisations to report general adverse events with non-severe events only requiring voluntary reporting. However, the overall volume of incidents or reports gathered can provide important insights into reported errors, their frequency and their causes offering opportunities for national learning and identification of possible solutions. The reported baseline figure of the overall harms of 498 gave the NPSA a 5 year retrospective context to help identify the scale of the problem associated with Midazolam administration overall. There is a methodological problem with using data from the overall reporting of adverse events over time to make a judgement on whether the health system is becoming more error prone or safer. Paradoxically reported overall (all) harm can appear to be increasing as a result of raising awareness of a particular patient safety risk through the release of a patient safety alert. In turn this can lead to increased reporting. Whilst increased reporting from a patient safety perspective is in itself welcome, it needs to be recognised that this can thereafter give the impression that a patient safety ‘event’, related to a given risk is increasing in frequency, when in fact it is more a reflection of increased awareness and reporting in the health care system. Because of this the NPSA always prioritised the reporting of ‘severe’ incidents or ‘deaths’ arising from certain events. This was felt to be a more meaningful interpretation of any data and this approach is reflected in this study, with a particular focus on the most harmful practices and errors, categorised by the NPSA as reported ‘severe’ or ‘deaths’. These offer a more rigorous statistic and a more meaningful before and after analysis as a result.

Rapid Response Reports have been used by the NPSA to raise awareness in the health service of serious risks to patient safety. The one-page alerts contain a brief explanation of the issue and clearly defined actions for NHS organisations in England and Wales to reduce the potential for harm, recommended personnel

appropriate to lead implementation and deadlines for completion to ensure actions are implemented as rapidly as possible. Risks associated with midazolam injection overdose, when used for conscious sedation in adults, was an issue deemed appropriate to take forward as an RRR on the basis of the number of incident reports received and following discussions with clinical practitioners at the front line of healthcare.

The RRR - NPSA/2008/RRR011: Reducing risk of overdose with midazolam injection in adults was released to NHS organisations in England (via the Central Alerting System, CAS) and direct to organisations in Wales on the 9th December 2008. The deadline for actions to be completed was the 6th June 2009. The full set of actions can be seen at http://www.bsg.org.uk/attachments/811_midazolam_rrr_08.pdf

In summary, actions related to the restriction, storage and use of high strength midazolam and flumazenil, audit and local development of policy.

Objectives of this evaluation

The objectives of the RRR were to reduce the risks associated with midazolam injection overdose in adults, when used for conscious sedation. The evaluation therefore aimed to measure any changes in; the number of incidents reported to the NPSA after release of the RRR (over 15 months); clinical practice linked to the use of Midazolam, Flumazenil and dosing regimens used; purchasing changes as well as knowledge or improved awareness resulting from implementation and reading of the recommended actions. This study attempted to measure actual change in clinical practice by a multi-modal approach which included survey of clinicians, audit of clinical areas and evidence of change in purchasing behaviour.

Measurements identified as potential markers of success for the RRR were:

- A reduction in incidents involving serious harm or death reported to the NRLS post implementation of the RRR compared with pre issue.
- A self-reported compliance rate of over 90% for NHS organisations implementing the recommendations where the RRR is deemed relevant.

- A change in purchasing patterns for high strength and low strength midazolam injection ampoules where use of high strength midazolam decreases and low strength increases post implementation compared with pre issue.
- Feedback in the form of survey returns from clinicians and implementation leads (who use midazolam for conscious sedation) on awareness of the issue and RRR, compliance and a change in local practice as a result of implementation.

Methods

This study was approved by the Department of Health's External Gateway principals that ensure that no excessive burden is placed on the NHS, social care organisations and public health audiences. The NPSA as an Arms Length Body was authorised to self regulate and assess their national communications (which included surveys and audits) against standard criteria in accordance with these gateway principles. As an additional measure all NPSA released surveys and communications were reviewed by a Department of Health Gateway team before they were issued, against a set of standard criteria informed by Department of Health policy and approved by Ministers. All 333 Health care trusts that provide acute care were asked to participate in the elements of the evaluation that required the completion of surveys and audits. This involved an email inviting participation in the evaluation going to the patient safety lead for each Trust.

1) Analysis of NRLS data

The NRLS was searched for patient safety incidents resulting in death or severe harm related to midazolam use. Included in the analysis were incidents reported before the release of the RRR, (between October 2003 and November 2008) compared with NRLS data post implementation (between June 2009 and August 2010). Incidents were reported with the NPSA official degrees of harm: 'no harm', 'low', 'moderate', 'severe harm' and 'death'. Two clinical reviewers independently reviewed incidents to ascertain whether they were valid midazolam related incidents. Search criteria included all incidents in the NRLS where text fields contained various midazolam terms (see appendix).

2) Analysis of Central Alerting System (CAS) data

The Central Alerting System (CAS)(10) is a web-based system for issuing patient safety alerts and other safety guidance to the NHS. CAS has a feedback mechanism which requires all NHS Organisations to report on actions taken in respect of issued patient safety alerts in England, thus enabling issued alerts to be assessed for organisational compliance.

3) Analysis of purchasing data

Data on purchasing of midazolam and flumazenil medication for injection was provided by the NHS Purchasing and Supply Agency (PASA)(11) which, until the 31st March 2010, was a Department of Health agency providing expertise, knowledge and excellence in purchasing and supply matters for the health service (National Health Service Purchasing and Supply Agency, 2008).

The Agency advised on policy and the strategic direction of procurement and its impact on developing healthcare, across the NHS. At the time of the evaluation, data was available from 12 months prior to the release of the RRR and for 8 months after the implementation deadline.

4) Feedback from clinicians and from NHS Organisation leads

Gastroenterology clinicians responded (100 from a United Kingdom total of 903) to an online survey emailed by the British Society of Gastroenterology in November 2009. Respondents were given 2 months to complete the short Select Survey online (NPSA, 2005). Gastroenterologists were selected in the survey as they were a discrete cohort of clinicians who, in previous scoping work with the NPSA, had shown a keen interest in the risks and issues related to over sedation in Midazolam usage.

Questions covered the use of midazolam, awareness of the RRR, risks and perceptions of change in practice as a result of the RRR. Additionally clinicians were asked if they knew who the local implementation leads were in their Trust to ascertain the impact of efforts to communicate the national alert.

Also, in November (2009) implementation leads in 167 acute trusts were contacted via the Patient Safety Action Teams located in each of the ten Strategic Health Authorities in England. The leads were asked to

complete an online survey asking about the local implementation of the RRR, including barriers and enabling factors.

5) Audit results from local Trusts using NPSA Audit Tool

Using the same approach and time period, audits were distributed which identified the actions in the original RRR and were distributed to all acute organisation Chief Pharmacists. These RRR actions included; 1) Ensuring that the storage and use of high strength midazolam (5mg/ml in 2ml and 10 ml ampoules; or 2mg/ml in 5ml ampoules) is restricted to general anaesthesia, intensive care, palliative medicine and clinical areas/situations where its use has been formally risk assessed, for example, where syringe drivers are used. 2) Ensuring that in other clinical areas, storage and use of high strength midazolam, is replaced with low strength midazolam (1mg/ml in 2ml or 5ml ampoules). 3) Reviewing therapeutic protocols to ensure that guidance on use of midazolam is clear and that the risks, particularly for the elderly or frail, are fully assessed. 4) Ensuring that all healthcare practitioners involved directly or participating in sedation techniques have the necessary knowledge, skills and competences required. 5) Ensuring that stocks of flumazenil are available where midazolam is used and that the use of flumazenil is regularly audited as a marker of excessive dosing of midazolam. 6) Ensuring that sedation is covered by organisational policy and that overall responsibility is assigned to a senior clinician which, in most cases, will be an anaesthetist.

Results

Reporting and Learning System incident review:

Prior to the release of the RRR (December 2008) : 498 incidents were received by the NPSA including 3 deaths. Post implementation of the RRR (June 2009), no incidents resulting in death or severe harm had been received by the NPSA.

CAS results

By December 2010, 96% (321) of the 333 NHS Organisations that deemed the RRR relevant to them had reported completing all actions arising from the RRR. In December 2011, CAS was re-checked and all organisations had reported having completing all actions arising from the RRR.

Changes in purchasing patterns within the National Health Service in England

Figure 1 shows the trend of midazolam and flumazenil purchasing, comparing 12 months data prior to the release of the RRR with 8 months data post this date.

A two sample t-test was performed using Microsoft Excel to test if there was a significant difference in the number of ampoules purchased for the different strengths of Midazolam and Flumazenil pre and post-implementation of the RRR. The mean difference between the pre and post RRR purchasing quantities along with the standard deviations, 95% confidence intervals, and two tailed p-values are shown in Table 1.

A trend analysis of Flumazenil purchases from January 2008 to November 2010 was carried out. This is shown in Figure 2 which also indicates the RRR release date and deadline date. A polynomial trend line of order 6 gave the best fit line with an R-squared value of 0.27.

<insert figure 1 here>

Table 1 illustrates that the purchase and use of risk-prone, high-strength midazolam decreased significantly for one strength of the product. The use of safer, lower strength product (as recommended in the RRR) increased significantly ($p=0.05$) for both strengths.

<Insert table 1 here>

Figure 2 shows an overall unchanged trend in the purchase of flumazenil, with an R squared statistic (0.27) to represent a line of best fit.

<Insert figure 2 here>

Gastroenterologist post implementation survey results

A total of one hundred responses were received from an unknown population of gastroenterologists in England (Table 2). 20% of respondents reported that low strength midazolam was not routinely available on the wards before the alert was issued. Four of fifteen qualitative free text responses to the survey suggested that the availability of 1mg/1ml was a widespread recent change. Almost two thirds (63%) of respondents said they were aware that the NPSA had issued a Rapid Response Report (RRR) but less than half (49%) knew the lead person responsible for implementing it in their organisation. Four of the clinicians expressed concern around the potential adverse effects of the new policy on midazolam, relating to possible inadequate sedation with more junior staff fearing using higher doses even if clinically appropriate. For example one clinician commented ‘I am concerned that this has resulted in more patients having inadequate sedation for what can be very unpleasant and even distressing procedures. We need to learn how to use sedation safely, not just to reduce it. The major

recent issue with midazolam is that SpRs (equivalent to a Consultant in training) are now terrified of using more than minimal doses of midazolam, leading, in many cases to under-sedation of patients for procedures such as colonoscopy.’ Another clinician also commented on the risk of using insufficient dosing – ‘I have had very experienced patients who have had repeated procedures over many years recently complaining that their latest procedures have been the most unpleasant they have ever experienced, and when I have reviewed the sedation doses, they are much lower than they used to be. An incomplete examination due to patient discomfort is important. When endoscopists are learning, they inevitably need greater doses of sedation than when they are experienced, sometimes just to top-up a sedation that is wearing off, and this needs to be taken account of.’

<insert table 2 here>

Local implementation leads survey results

One hundred and thirty three separate survey returns were completed from thirty-seven NHS organisations in England. The results from this survey were consistent with the purchasing data findings; 65% of the implementation leads stated that they had deliberately changed their midazolam purchasing habits. Survey questions showed that 86% of respondents said a communication plan had been developed to ensure robust communication of arrangements. More than half of the respondents (51%) said they had developed an evaluation plan and a date to complete an evaluation. Implementation leads indicated that key facilitators in implementation were the background information in the Alert providing the rationale for the recommendations, existing policies, processes and multidisciplinary team working within organisations. Key barriers to implementation were identified as time, difficulty auditing flumazenil and the lack of clinical engagement. Additional feedback from 30% of respondents stated that the implementation timeframe was not appropriate with the most common reason being a need for additional time for training.

<insert table 3 here>

Audit results from local Trusts

Organisations were also asked to inspect clinical areas and use an organisational audit tool to measure specific actions from the original RRR. The highest compliance rates (>99%) were for actions 1 and 2 of the RRR in relation to restricting access to high strength midazolam (78 and 75 cases respectively). Lower compliance rates (58%) were observed for action 5 of the RRR linked to auditing of flumazenil (36 cases) to check for over-use of the antidote (Table 3).

Discussion

The evaluation of the midazolam RRR from the NPSA guidelines in the UK NHS, saw a significant level of self-reported compliance; especially with actions 1 & 2 (on the restriction, replacement and risk assessment of high dose midazolam) having been implemented most successfully within the deadline. Further severe harm and death incidents appear to have been avoided following the issuing of the RRR. There has been a significant change towards the purchasing of less risk-prone strengths of midazolam ampoules, as recommended by the RRR and some significant change in the downward purchasing of error prone higher doses. From the recent purchasing patterns for flumazenil it may suggest that clinicians are using it less as a means of countering midazolam overdose, (a possible indicator of safer use of midazolam) though change between before and after purchasing is not shown as statistically significant.

What is the wider learning around how best to evaluate national policies to improve health care?

This evaluation of a national policy to promote safer practice raises wider questions on how best to deploy strategies to effect healthcare improvement. One systematic review (12) has demonstrated that current

available evidence does not identify any effective, generalisable strategies for specifically changing organisational culture to improve healthcare. Others (13) have pointed to the limitations of using clinical guidelines and that the development of good guidelines does not always ensure that they are then used in practice. These authors assert that systematic reviews of strategies for changing professional behaviour show that relatively passive methods of disseminating and implementing guidelines such as publications in professional journals or mailing targeted healthcare professionals, rarely leads to changes in professional behaviour. Other authors (14) have cited successful examples of where one page summaries have been provided around the principles of antibiotic use, but that overall the development of any clinical practice guidelines must be supported by other educational activities, as multifaceted interventions tend to be more effective than single interventions. However in a systematic review of 235 studies (15) of guideline dissemination and implementation strategies it was shown that multifaceted interventions did not appear more effective than single interventions. Across these studies there was just a median 10% healthcare improvement, suggesting that it is possible to change healthcare provider behaviour and improve quality of care, but with most dissemination and implementation strategies only resulting in small to moderate improvements in care.

This paper focuses on the results of an evaluation of one single alert and national policy initiative, from the NPSA, to improve practice and knowledge and ultimately safety in relation to the administration of Midazolam. A valid question arises as to the overall value of the process and system for other alerts and Rapid Responses released by the NPSA. Prior to its closure the NPSA was intending to conduct similar evaluations on all of its main policy initiatives and alerts as standard. Due to the demise of the NPSA this did not happen. However in an attempt to partially answer the question regarding the value of alerts we can retrospectively look back at some other key NPSA alerts that were evaluated and the potential effect they had on making the health system safer. For example Flood et al (2013) (16) evaluated the Rapid Response Report (RRR) that promoted better practices around the management of resuscitation in mental health inpatient environments. The RRR included guidelines for the provision for life support and resuscitation for mental health service users and the evaluation examined how effectively the guidelines were implemented across

health-care providers in England. Similar to the Mizalolam evaluation, serious incident data were also compared prior to the release of the national guidelines and after the guideline release dates. This included looking at events around choking and cardiac/respiratory arrest in inpatient areas. There were five deaths post-implementation of the guidelines that were considered to have serious enough error associated with the resuscitation process. This was down from 18 prior to the release of the guidelines. There is evidence of a reduction in the worst types of error resulting in death, albeit with small numbers.

However, the survey evaluation of health trusts showed that despite organisations reporting 100% compliance with the implementation of the guidelines, around half of frontline clinical staff were not aware of them. Although the survey responses showed a contradiction between organisational and clinical staff awareness, the analysis suggested a reduction in moderate and severe harm cases and of deaths. There was evidence of a reduction in the worst types of error resulting in death, albeit with small numbers.

Similarly an evaluation by Lanskear et al (2005)(17) sought to assess the effectiveness of the response of NHS hospital trusts to an alert issued by the National Patient Safety Agency designed to limit the availability of concentrated potassium chloride in hospitals in England and Wales. 207 clinical areas in 20 randomly selected acute NHS trusts in England and Wales were selected between 31 October 2002 and 31 January 2003. Staff awareness of and compliance with the requirements of the national alert, including the withdrawal of concentrated potassium chloride solutions from non-critical areas, provision of pre-diluted alternatives and storage and recording in accordance with controlled drug legislation was reviewed. Of those interviewed, 78% of nurses and 30% of junior doctors were aware of the alert and there was a high rate of compliance with the alert guidelines – including that concentrated potassium chloride be stored in a separate locked cupboard from the common injectable diluents. The authors concluded that the NPSA alert was effective and resulted in the rapid development and implementation of local policies to reduce the availability of concentrated potassium chloride solutions.

These two other examples taken with the Midazolam evaluation, may suggest that the principal of attempting

to remove or reduce the error prone risk is a key way of approaching patient safety and potentially improving practice and reducing the number of serious incidents. It may be that some transferable learning overall can be gleaned from all three of the above described NPSA Rapid Response Reports that have been implemented and evaluated. Common themes across the three RRRs were 1) the reviewing of systems and local policies, 2) identifying of national actions for reducing health care related risk, 3) instructions for the reducing and removing from the system of known error prone elements/activities identified from retrospective data sets, such that it was easier for health care operators to do the right thing. In practice this included 1) the redesign of systems where necessary, 2) the education and training of staff and 3) continued awareness raising of the issue under scrutiny amongst key health care staff.

There is currently a lack of clarity in the literature regarding what methods to choose to implement successful change, though some tentative observations may be arrived at. Firstly that in some respects the results reported in this paper are consistent with the earlier literature's modest expectations for health improvements. The improvements may be accounted for given the weight of influence a body like the National Patient Safety Agency had to influence change in the United Kingdom. Secondly that given the experience of the Midazolam and other RRR policy evaluations discussed in the paper, this approach to making health care systems safer may well be transferable across to any policy initiative. However we cannot say this conclusively and each patient safety initiative, with its own specific aims and objectives will benefit from its own evaluation designed accordingly to assess whether it has been effective.

When re-visiting nationally reported midazolam errors between September 2010 and September 2013, a further two cases of overdose that were classified as serious harm have been highlighted. This presents potentially a mixed picture. On the one hand this highlights the potential for errors to once more creep back into the health care system if an on-going patient safety message is not sustained. Conversely the fact that no deaths had occurred in this additional time frame may suggest a more sustained change has taken place and that the original RRR safety measures implemented throughout the UK health care system has proven

successful.

There are also known weaknesses associated with before and after studies that need to be considered, with the potential for sensitization and awareness raising of those taking part in the studies. Thereafter, effects may be mistaken for the intervention when this may not be the case (18). It cannot be said that from the results of the gastroenterologist survey that clinical practice changed as a direct result of RRR, given their responses to the questions, which suggest their awareness and knowledge levels were already high.

Other limitations to this study include individual clinicians self selecting in responding to surveys (as well as gastroenterologists already being a self selected professional group that had already shown an interest in the clinical problem). Additionally the Central Alert System requires a self reported organisational compliance with RRRs which may be susceptible to biased reported with an incentive for organisations to overstate compliance. Currently the overall compliance rate for all alerts for health care Trusts in the UK is 99% (CAS, December 2011). CAS is a web-based system for issuing patient safety alerts and other safety guidance to the NHS. It was introduced in 2008, and intended as a means to help trusts be more accountable in recording the safety and quality of the care they provide. NHS trusts in England are required to respond to any safety alerts that are issued using CAS, such that when they have completed actions required in any alert, they confirm via CAS. However the system relies on self-certification and Trusts are responsible entirely for the accuracy of the reporting. Assessing the efficacy of implementation using compliance was supplemented therefore with other methods for testing the implementation of the RRR policy guidance. Future research may lend itself well to examining these issues in the private sector which was not evaluated as part of this evaluation as well as evaluating national purchasing data patterns alongside safety interventions for other types of medications in addition to midazolam. An examination of the Welsh data would also be a valuable future project given the RRR was originally designed as a national alert for both England and Wales. Unfortunately at the time of the evaluation the Welsh data was not available.

Conclusion

There have been improvements around the safer use of midazolam and a reduction in harm to patients in the UK evidenced with high organisational RRR compliance rates, encouraging clinician and implementation lead survey findings, a lower number of NRLS incident reporting and changes in PASA purchasing patterns. The most encouraging result is the purchasing data for which the changes are compelling due to the widespread substitution of high strength products for lower risk midazolam injections. Of note is that this is evidence of positive organisational behaviour change that is not limited by self-report bias.

Feedback from clinical areas suggests that more work needs to be done to identify the leads for implementing recommendations from the Rapid Response Report and for better engagement between clinicians. Further assessment of embedded and sustained compliance in the recommended use of flumazenil injection, may be necessary to ensure full implementation of the NPSA guidelines. Organisations should review purchasing patterns, review where midazolam is stored, audit their use of flumazenil and monitor training especially for juniors undertaking sedation procedures. Previously the National Patient Safety Agency, was responsible for patient safety in England and Wales. However, as part of the Arms Length Body Review the NPSA was being abolished (Department of Health, 2010). From 1st April 2010 the NHS Commissioning Board was identified as the responsible interim body for patient safety.

There is scope for further evaluations of policy initiatives and the implementation of national guidelines based on the model of evaluation described in this paper and its processes. Lessons learnt from this and from the evaluations of other RRRs regarding how best to implement safer health care policy include the reviewing of existing systems and local policies, the identifying of national actions for reducing health care related risk and offering instructions for how best to avoid those known error prone elements/activities, redesigning systems where necessary, and the education, training and awareness raising of health care staff closest to the issues under scrutiny.

References

1. Abeysekera A, Bergman IJ, Kluger MT, Short TG. (2005). *Drug error in anaesthetic practice: a review of 896 reports from the Australian Incident Monitoring Study database*. Anaesthesia. Volume 60, pages 220–227, March.
2. Patel I, Balkrishnan R. Medication Error Management around the Globe: (2010). An Overview. Indian J Pharm Sci. Sep-Oct; 72(5): 539–545.
3. Lazarou J, Pomeranz BH, Corey PN. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 279:1200–05.
4. Kohn LT, Corrigan JM, Donaldson MS. (2000). Institute of Medicine. *To Err is Human: Building a Safer Health System*. Washington DC: National Academy Press.
5. Altman DE, Clancy C, Blendon RJ. (2004). Improving patient safety--five years after the IOM report. N Engl J Med; 351:2041.
6. *Reducing risk of overdose with midazolam injection in adults*. NPSA/2009/RRR011. 9th December 2008. Last accessed 21st February 2013
http://www.bsg.org.uk/attachments/811_midazolam_rrr_08.pdf
7. Pawson R, Greenhalgh T, Harvey G, Walshe K. (2005). *Realist review--a new method of systematic review designed for complex policy interventions*. J Health Serv Res Policy Volume: 10 Suppl 1, Pages: 21-34.
8. National Patient Safety Agency. *Reducing risk of overdose with midazolam injection in adults*. Rapid Response Report: NPSA/2008/RRR011: National Patient Safety Agency. 2008.
9. Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A. (1995) *Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods*. Gut; 36:462-7.

10. Central Alerting System. <https://www.cas.dh.gov.uk/Home.aspx>. Last accessed 21st February 2013.
11. National Health Service Purchasing and Supply Agency (2008). Last accessed 28th August 2012 <http://www.nhsidentity.nhs.uk/tools-and-resources/national-suppliers/nhs-purchasing-and-supply-agency>.
12. Parmelli, E Flodgren, G. Beyer, F. Baillie, N. Schaafsma, ME. Eccles. MP. (2011)._The effectiveness of strategies to change organisational culture to improve healthcare performance: a systematic review. Implementation Science. 6:33.
13. Feder G, Eccles M, Grol R, Griffiths C, Grimshaw J. Using clinical guidelines. (1999) BMJ. March 13; 318(7185): 728–730.
14. Belongia, EA. Schwartz B. (1998) Strategies for promoting judicious use of antibiotics by doctors and patients. BMJ; 317:668.
15. Grimshaw, M. Eccles. MP Med J Aust (2004). Is evidence-based implementation of evidence-based care possible? 180 (6): 50.
16. Flood, C. Gull, N. Thomas, B. Gordon, V. Cleary, K. (2013). Is knowledge and practice safer in England after the release of national guidance on the resuscitation of patients in mental health and learning disabilities? Journal of Psychiatric and Mental Health Nursing. DOI: 10.1111/jpm.12126.
17. Lankshear, A. J. Sheldon, T.A. Lowson, K.V. Watt, I. S. Wright, J. (2005) Evaluation of the implementation of the alert issued by the UK National Patient Safety Agency on the storage and handling of potassium chloride concentrate solution. Qual Saf Health Care;14:196-201
doi:10.1136/qshc.2004.011874.
18. Robson C. Real World Research. (2002) *A Resource for Social Scientists and Practitioner-Researchers*. Blackwell Publishers. Oxford.
19. Department of Health. *Liberating the NHS: Report of the arms-length bodies review*. 26 July 2010. Last accessed 28th August 2012.

| Summary | Mean Difference between pre and post RRR | Standard Deviation Pre | Standard Deviation Post | Months | | 95% CI around mean difference | | | P value | |
|---|--|------------------------------|-------------------------------|--------|------|-------------------------------|----------|----------|----------|----------|
| Injection strength | (post-Pre) | | | Pre | Post | Lower CI | Upper CI | 2 tailed | | |
| Flumazenil | | | | | | | | | | |
| 500micrograms/5ml | 43 | 510.4 | 1024.7 | 12 | 8 | - | 723.4 | 809.7 | 0.9016 | |
| Midazolam 10mg/2ml (HS) ^a | - | 12,061 | 13300.8 | 12 | 8 | - | 23,793.1 | - | 327.9 | 0.0603 |
| Midazolam 10mg/5ml (HS) | - | 31,681 | 12692.8 | 12 | 8 | - | 45,934.4 | - | 17,428.1 | 0.0002 |
| Midazolam 2mg/2ml (LS) ^b | | 10,021 | 2199.2 | 12 | 8 | | 6,625.9 | | 13,415.7 | 3.32E-06 |
| Midazolam 5mg/5ml (LS) | | 43,179 | 6152.7 | 12 | 8 | | 24,878.7 | | 61,478.8 | 2.54E-05 |

Table 1. Mean difference in purchasing data for midazolam and flumazenil comparing pre and post RRR release periods

^a HS = high strength. ^b LS = low strength.

Table 2. Results from midazolam survey to clinicians

| | | |
|--|------------------|-------------------|
| 1) Have you administered high strength midazolam in the last 3 years for conscious sedation (outside of palliative care or intensive care)? | Responses | Percentage |
| Yes | 66 | 66 |
| No | 30 | 30 |
| Don't know | 1 | 1 |
| [No Answer Entered] | 3 | 3 |
| Total | 100 | 100 |
| 2) Is low strength midazolam routinely available on the wards of your organisation? | Responses | Percentage |
| Yes | 80 | 80 |
| No | 11 | 11 |
| Don't know | 6 | 6 |
| [No Answer Entered] | 3 | 3 |
| Total | 100 | 100 |
| 3) Have you been involved in a midazolam overdose incident in the past three years? | Responses | Percentage |
| Yes | 12 | 12 |
| No | 83 | 83 |
| Don't know | 2 | 2 |
| [No Answer Entered] | 3 | 3 |
| Total | 100 | 100 |
| 4) If you answered yes to the previous question, did this incident result in death or long term harm to the patient? | Responses | Percentage |
| Yes | 1 | 8 |
| No | 11 | 92 |
| Total | 12 | 100 |
| 5) Prior to the NPSA's RRR and this survey were you aware of the potential risks to patients of midazolam overdose when used for conscious sedation? | Responses | Percentage |
| Yes | 93 | 93 |
| No | 2 | 2 |
| [No Answer Entered] | 5 | 5 |
| Total | 100 | 100 |
| 6) Prior to the NPSA's RRR and this survey were you aware of the potential risks to patients of routinely relying on flumazenil as a reversing agent for midazolam? | Responses | Percentage |
| Yes | 89 | 89 |
| No | 6 | 6 |
| [No Answer Entered] | 5 | 5 |
| Total | 100 | 100 |
| 7) Prior to this survey, were you aware the NPSA had issued an RRR on the risks of midazolam overdose? | Responses | Percentage |
| Yes | 63 | 63 |
| No | 32 | 32 |
| [No Answer Entered] | 5 | 5 |
| Total | 100 | 100 |
| 8) Do you know who the lead for implementing this RRR is in your organisation? | Responses | Percentage |
| Yes | 49 | 49 |
| No | 46 | 46 |
| [No Answer Entered] | 5 | 5 |
| Total | 100 | 100 |

| Action | Total responses | Applicable responses from total ^a | Of those applicable numbers compliant with action | Percentage compliant with actions |
|---|-----------------|--|---|-----------------------------------|
| A risk assessment has been undertaken in clinical areas/situations where high strength midazolam is used for syringe drivers, to identify and reduce the risks associated with using high strength midazolam in clinical practice. | 90 | 74 | 71 | 96 |
| An assessment of current utilisation and indications for use of flumazenil has been undertaken. | 90 | 72 | 58 | 81 |
| Indications for use of flumazenil are present in therapeutic protocols | 83 | 65 | 52 | 80 |
| Local policy has been updated to reflect this | 81 | 58 | 45 | 78 |
| Organisational responsibility for conscious sedation has been assigned to a senior clinician | 93 | 65 | 57 | 88 |
| Reference to existing guidance on standards agreed by relevant professional bodies has been made and a training plan developed to ensure that all relevant practitioners have the necessary skills and competences required by professional bodies. | 93 | 68 | 53 | 78 |
| Stocks in areas other than anaesthesia and intensive care have been reviewed and replaced with 1mg/ml (2ml, 5ml ampoules as appropriate for the intended use). ACTION 2 in RRR | 92 | 75 | 75 | 100 |
| Stocks of high strength midazolam injection (5mg/ml as 2ml and 10ml ampoules and 2mg/ml as 5ml ampoules) have been removed from areas except where used for anaesthesia or intensive care sedation. ACTION 1 in RRR | 91 | 79 | 78 | 99 |
| The organisation is able to demonstrate on-going action and improvement in relation to achieving training milestones and maintenance of competence of healthcare practitioners. | 78 | 54 | 39 | 72 |
| The plan is reviewed regularly by the clinical governance group. | 79 | 53 | 36 | 68 |
| The use of flumazenil has been audited against therapeutic protocols. ACTION 5 in RRR | 83 | 62 | 36 | 58 |
| Therapeutic protocols reviewed and updated. | 90 | 75 | 62 | 83 |
| Grand Total | 1043 | 800 | 662 | 82 ^b |

Table 3. Result of organisational audit of actions specified in the Rapid Response Report

^a Responses to the Rapid Response Report actions that trusts regarded to be relevant and applicable to them.

^b Average percentage compliance with NPSA actions

Comparison of means of usage of Flumanzenil and Midazolam before (Jan08-Dec08) and after (Jan09-Aug09) issue of Midazolam RRR

RRR Release - 9th December 2008
RRR Deadline - 6th June 2009

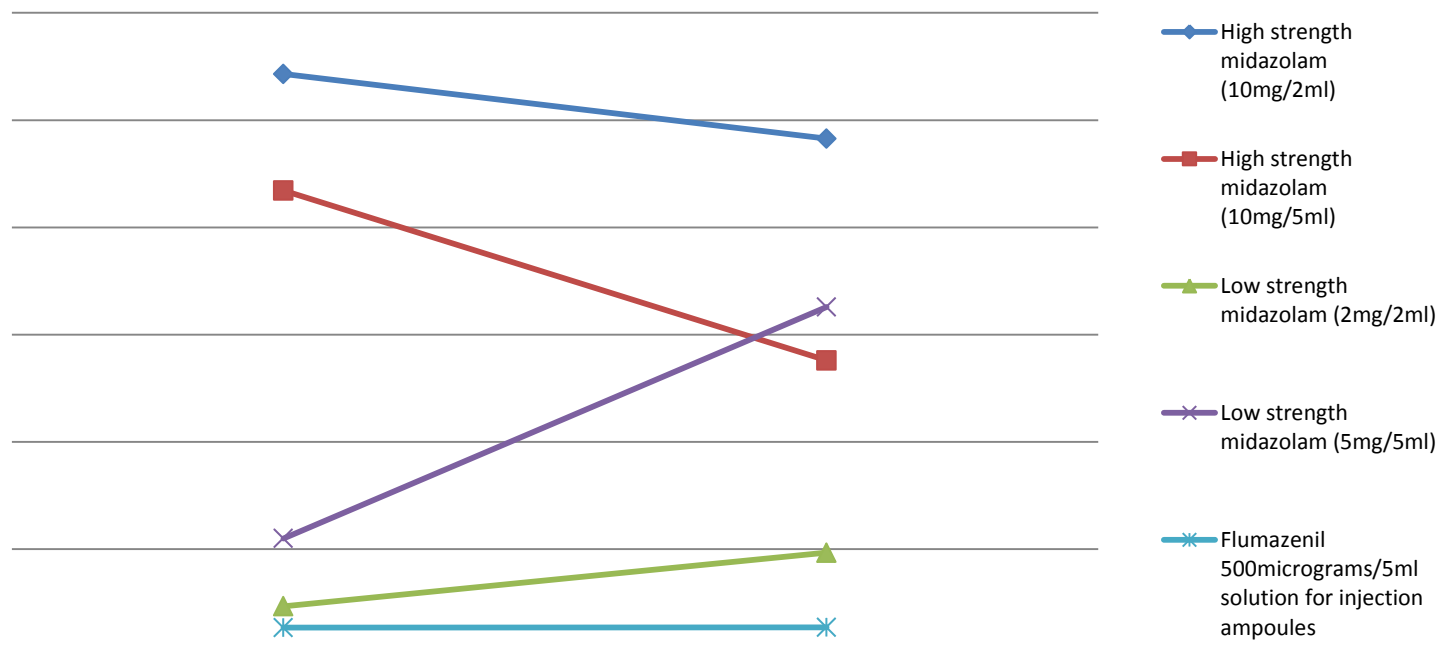
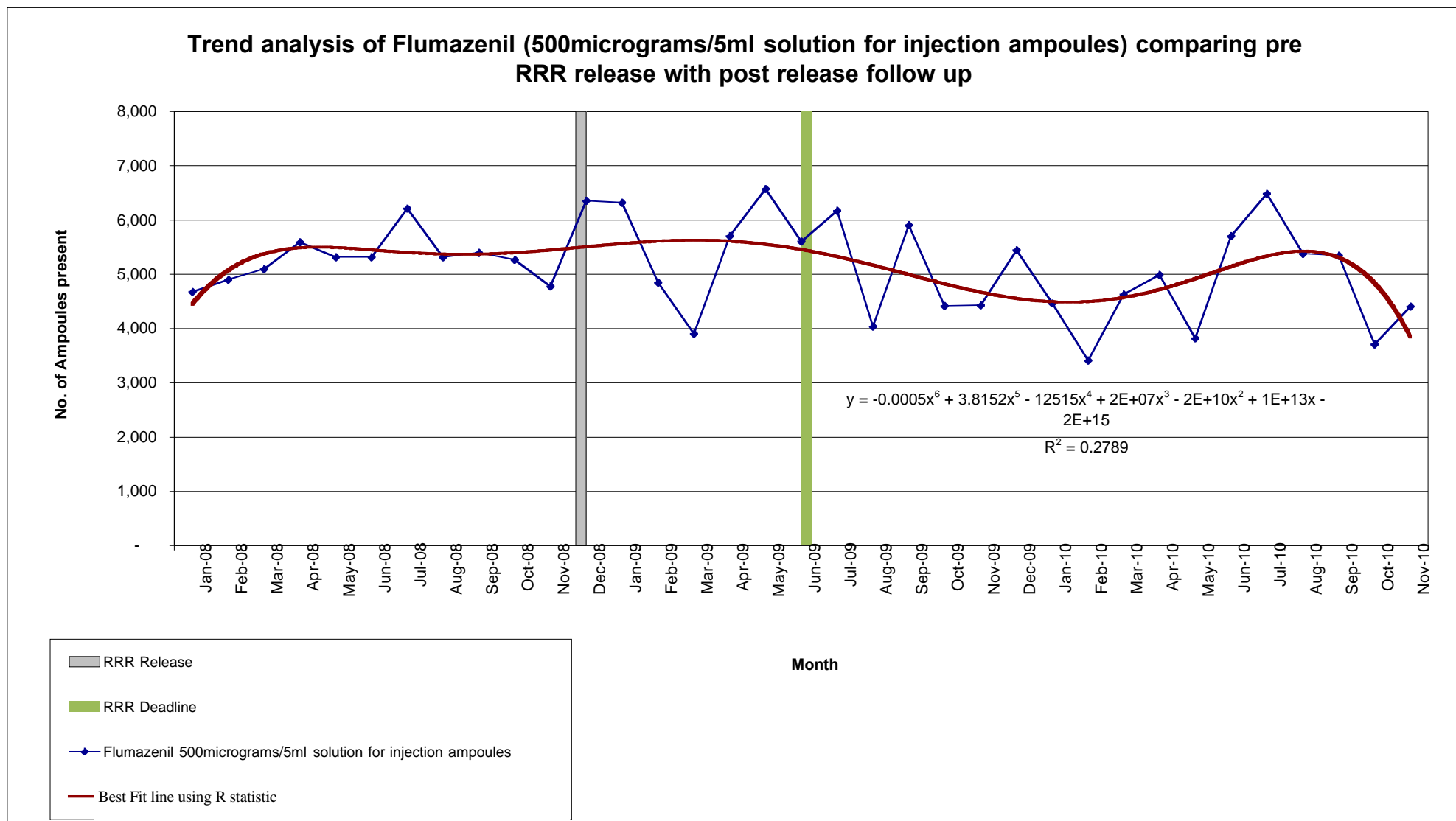


Figure 1.

Fig 2. Trend of Flumazenil purchasing



Appendix

Terms used in NRLS search for midazolam related incidents

MIDAZALOM, MIDAZELAM, MIDAZILEM, MIDAZOLAM, MIDIZOLAM, MIDOZALAM, MIDOZOLAM, HYPNOVAL, HYPNOVEL, FLUMAZENIL, FLUMAZIMIL, ANEXATE, ANNEXATE