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Identifying and managing ADRs: Qualitative analysis of patient reports to the UK Yellow Card Scheme

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Abstract (250 limit)

Introduction

Adverse drug reactions (ADRs) can have significant negative impact on peoples' daily lives, with physical, economic, social and/or psychological effects. Patient reporting of ADRs has been facilitated by pharmacovigilance systems across Europe. However, capturing data on patients' experiences of ADRs has proved challenging. Existing patient reports to the UK Yellow Card Scheme (YCS) contain free text comments which could be useful sources of information.

Objectives

To investigate patients' experiences of ADRs and their impact on patients as described in free-text data within patient Yellow Card (YC) reports submitted to the Medicines and Healthcare products Regulatory Agency (MHRA).

Methods

A qualitative review of narrative texts was conducted on free text data from 2255 patient YC reports - July to December 2015.

Results

Three key narrative themes emerged from analysis of the free text data in 2255 reports: (1) identification of ADRs, (2) severity and impact of ADRs and (3) management of ADRs. Temporal associations were the most common method of identification followed by differential diagnoses and confirmation with information sources such as healthcare professionals (HCPs). A combination of explicit and implicit impacts were described - physical, psychological, economic and social effects often persisted and caused serious

disruption to many patients' lives. A range of strategies were used to manage ADRs including consultation with HCPs, stopping/reducing the medicine or taking medicines to alleviate symptoms.

Conclusion

Free text data from YC reports has been an underutilised resource to date, however this research has confirmed its potential value to pharmacovigilance and medication safety research.

Keywords: patient reports; adverse drug reactions; pharmacovigilance; Yellow Card; identification; management

1. Introduction

Direct patient reporting of adverse drug reactions (ADRs) has been a key element of effective pharmacovigilance (PV) processes in recent decades. The contribution of patient reports to drug safety was acknowledged and consolidated by European Union (EU) PV legislation in 2012 [1]. Research has determined some of the benefits of patient reporting - identification and investigation of new drug safety signals; more information about the severity and impact of ADRs on quality of life and enhancing dialogue between patients and healthcare professionals (HCPs) [2, 3]. Spontaneous reporting systems (SRSs) have many limitations such as under-reporting, delayed reporting and comparing different systems can be difficult [4]. However, reviews of patient reporting in a variety of countries have recognised both the overall scientific value of patient reports and the importance of facilitating these reports [2, 5].

In the UK, Yellow Card (YC) patient reports of suspected ADRs are submitted to the Medicines and Healthcare products Regulatory Agency (MHRA), through the Yellow Card Scheme (YCS). People who choose to report their ADRs can do so via the internet, telephone or post. Previous research has examined all reports submitted to the YCS between 2005 and 2007 [6]. It found that patient reports could be considered a valuable element of PV with detailed descriptions of ADRs and reports of different drug types and reactions to those submitted by HCPs [6]. Recommendations were made to increase awareness of the YCS among the public which resulted in increased advertising by the MHRA e.g. social media campaign to promote YC reporting in 2017, to increase the usefulness of reports by providing guidance on what to report and inclusion of information on patient reporting in patient information leaflets (PILs).

Recent research into chronic illness has used available narrative resources to explore the personal elements of the illness experience [7, 8, 9]. A narrative approach can facilitate analysis that highlights the variation and complexity of the illness experience as well as its social and cultural context [8]. However, little is known about the thematic content of illness narratives of patients with suspected ADRs. There has been increased interest in using data sources such as social media and social media postings as potential new sources for PV data [10]. Previous research has indicated that combining data from several sources can assist the detection of safety signals [10]. Using social media data or existing data sources in innovative ways can augment PV systems, supplementing established methods of data collection such as YC reports [11]. Current YC reporting forms include free-text comment boxes, which can be used by reporters to provide information on the following: description of their ADR experience including symptoms, use of medicines, details of outcome and other relevant information. While the free-text is used by the MHRA in assessment of the YC report**;** contributing to coding of reaction terms; very limited analysis of free-text data from YC reports has been conducted to date [6]. This study used this novel data source, free-text data within patient YC reports submitted to the MHRA, to investigate patients' experiences ADRs and their impact on patients.

2. Methods

In 2015 there were 5439 YC reports to the YCS composed of 4501 patient reports, 712 from parents & 226 from carers [12]. During a six-month period in 2015 – July to December – a total of 3060 YC reports were received by the MHRA. These were 2,457 patient reports, 487 from parents and 116 from carers. Vaccination reports (n=775) were excluded from the 6-month data set as these reports could contain vaccine specific effects such as confounding by

indication, increased symptom reports and healthy vaccine biases [13, 14]. The remaining YC reports (n=2285) were subjected to quantitative and qualitative analysis [15, 16]. Narrative analysis of the free text data was conducted on 2255 reports after exclusion of duplicates (n=4) and blank reports (n=26). The data provided in YC reports included: details of reporter type in three categories – (1) patient/self-reports from those who experienced ADR; (2) reports submitted by carers on behalf of another with ADR and (3) parent reports submitted on behalf of children with ADR; reporting method (internet, telephone, paper, YC leaflet); age and gender of person experiencing ADR; suspect drugs; reaction terms; severity of reaction (severity status classified by MHRA using the Medical Dictionary for Regulatory Affairs (MedDRA) dictionary to assess reaction preferred terms) and outcomes (e.g. life-threatening, hospitalised, disability/incapacity) as well as all free-text comments.

2.1 Ethical approval

This study phase received favourable ethical approval from the Independent Scientific Advisory Committee for MHRA database research (ISAC; Ref GENQ-00097958). The Medway School of Pharmacy Research Ethics Committee was informed of the study and the ISAC approval.

2.2 Data analysis

A qualitative review of the YC narrative reports was conducted using the data management program QSR NVivo 10 to facilitate organisation and analysis of the data. Initially thematic analysis was used to identify recurrent themes across the large dataset. This involves five phases – familiarisation with the dataset; initial coding; identification and organising of themes into hierarchical clusters; reviewing and defining themes to create a comprehensive framework of themes [17]. The initial coding was conducted (BO'D) and then discussed by

members of the research team (JK, RR) with differences resolved by consensus. Once coding was finalised and a thematic framework was created, the remaining free-text data were coded (BO'D). Common themes emerged in this inductive process - varied experiences of ADRs, multidimensional impact of ADRs and coping strategies. Cases with these common thematic elements were selected for narrative analysis to explore the different aspects of ADRs from the patient's point of view (Figure 1). A narrative inquiry approach was selected as it focuses on understanding how people present their personal experiences and offered insight into the variety and complexity of people's experiences of ADRs [18, 19]. Riessman's thematic and structural analyses were used to systematically evaluate the narrative texts – these centre on what was said and how it was said. Narratives were interpreted by examining their content, structure and form and allowing narrative patterns to be considered in a broad environmental and social context [18, 19]. Close reading of these texts identified key narrative aspects in ADR experiences – these focused on how patients decided that they had experienced an ADR; the impact of these reactions on patients' daily lives and the strategies patients used to manage their ADRs. Texts were examined together to identify common patterns or different experiences and to avoid under-analysis [18]. This paper presents a narrative analysis of the free-text data from 2255 YC reports.

3. Results

3.1 Characteristics of the YC reports

A total of 2255 reports were analysed – 'patient' reports (2096; 92%), 99 (4%) 'carer' and 90 (4%) 'parent' reports. The highest proportion were for females (1522; 67%); people aged 21-40 years (675; 31%); severe reactions in 1621 (71%) reports and most reports were submitted via the internet – 1877 'patient'/self-reporters (90%); 83 'carers' (84%) and 81 'parents'

(90%) (See Table 1). Details on the different types of suspect drugs in these reports have been reported elsewhere [16].

Table 1: Report characteristics by reporter type

REPORTED CHARACTERISTICS	REPORTER TYPE F (%) N=2285		
	Patient	*Carer*	*Parent*
Age categories (years)			
Infants < 1	0	0	27(100)
1-20	92(62.6)	2(1.4)	53(36.1)
21-40	649(96.1)	19(2.8)	7(1.0)
41-50	330(97.9)	5(1.5)	2(0.6)
51-60	355(97.5)	9(2.5)	0
61-70	50(95.1)	18(4.9)	0
71-80	162(90.5)	17(9.5)	0
Over 80	44(71.0)	18(29.0)	0
Gender			
Male	656(31.4)	48(50.0)	48(53.9)
Female	1433(68.6)	48(50.0)	41(46.1)
Method of reporting			
Internet (I-net)	1877(89.6)	83(83.8)	81(90)
Telephone	70(3.3)	7(7.1)	3(3.3)
Paper	131(6.3)	8(8.1)	6(6.7)
YC leaflet	13(0.6)	0	0
Other	5(0.2)	1(1.0)	0
SE severity			
Coded as 'severe' by MHRA*	1481(70.7)	72(72.7)	68(75.6)
Not coded as 'severe' by MHRA*	615(29.3)	27(27.3)	22(24.4)

***SE = side effects;** *MHRA 'in-house' classification of severity status – assessment of reaction preferred terms within the Medical Dictionary for Regulatory Affairs (MedDRA) dictionary*

Analysis indicated distinct narratives of the ADR experience – three key narrative patterns included (1) identification of ADRs, (2) severity and impact of ADRs and (3) management of ADRs.

Results are presented below according to each of the core themes with illustrative quotes by reporter type (patient, carer, or parent) and drug type. Additional quotes are included in the appendices (Appendix 1).

3.2 Identification of ADRs

Information on methods of ADR identification was provided in 679 (30%) of reports. These methods included the timing sequence of side effects (SE) (14%); differential diagnosis (5%), confirmation with HCPs (6%), patient information leaflets (PILs) (2%) and/or other information sources.

While some information on timing of the SE is available elsewhere in YC reports the free text data describes the use of temporal associations to identify the ADR – these included de-challenge, re-challenge as well as changes in dose:

> *"Within an hour of taking the medication I have extremely uncomfortably sweating which lasts for about 4 hours which I never had in the past. I have tried varying the times I take it to no available [sic]. I have even tried not taking it for one day and found that I did not get the sweating. And as soon as I started it again the next day the sweating came back."*
>
> *Patient, female, 63 years, propranolol, I-Net.*

Some patients made a differential diagnosis by assessing the factors that could be causing their ADR:

"..hives / rash on palm of left hand, wrist and between fingers. No exposure to anything new which might cause this."

Patient, male, 27 years, citalopram, I-Net.

ADRs were also confirmed with HCPs and pharmacists were often used as an initial point of contact:

"Within hours of applying the gel, the skin on my scalp blistered and subsequently developed crusts. After seeing the pharmacist I made an appointment to see my GP the following day who prescribed an antibiotic cream and confirmed that I should not reapply the gel.""

Patient, male, 78 years, Picato, I-Net.

Only a small number of patients used patient information leaflets (PILs) as a method of identifying their ADR:

"Although I am somewhat prone to mouth ulcers, this is usually after a specific event such as abrasion. After the third ulcer without obvious cause, I checked the patient information leaflet (PIL) for naproxen, which I had been taking for about a week, and noted it was a possible side effect."

Patient, male, 64 years, naproxen, I-Net.

Many reporters used multiple information sources – the internet, HCPs, family/friends – to assist them in identifying their ADRs:

"Dizziness, drowsiness, hallucinations, headache, rapid heart rate, shaking, sleep disturbance, vertigo, vomiting. After speaking to a nurse and basic searches on the internet, the patient was told they should never have been given such a high dose.."

Carer, female, 49 years, Zamadol SR, I-Net.

3.3 Severity and impact of ADRs

Elaborate narratives were provided on ADR severity with a range of mild, moderate and severe effects. Information on the severity of ADR effects was explicitly provided in 1371 reports (44%); mild effects were described by 290 (21%); moderate by 532 (39%) and severe effects by 559 reports (41%). Some reports

described effects as ‘severe’ which would be commonly labelled by HCPs as ‘mild’ e.g. rash, muscle pain, diarrhoea:

> *“Side effects – just like a bad flare up of irritable bowel disease/ irritable bowel syndrome – stomach pain/cramps and severe diarrhoea.. one day I was in tears at work after being stuck in the restrooms for nearly 2 hours.”*
>
> *Patient, female, 30 years, Xeristar, I-Net.*

Self-assessment of ADRs was not linked to HCP consultation or with negative outcomes – many effects which did not result in hospitalisation or incapacity were still described by reporters as ‘severe’.

A considerable component of YC reports described the impact of ADRs. Overall, the impact of adverse effects was described in 2140 reports (70%): the majority of reports described explicit physical impacts (2099; 93%) but reports also provided information on psychological (532; 24%) and social impacts (760; 34%). Patients provided vivid accounts of increased anxiety, depression and/or irrational thoughts which caused serious disruption to their everyday lives:

> *“Tiredness, rash and itchiness. I would like to stop taking these tablets. I feel bad taking them, headaches, severe aches in my legs and very sore hips, swollen fingers and the feeling of being constantly depressed.”*
>
> *Patient, male, 58 years, Ramipril, I-Net.*

In many cases these debilitating impacts could persist over time and overlap across physical, psychological and social domains. Many carers reported a combination of negative effects across these domains:

> *“Her body began to inflate like a balloon. Her body became numb...Such changes in her body and face made her very distressed. She could not bear her physical changes and numbness. She became disabled from her distress and lost her independence.”*
>
> *Carer, female, age not supplied, Seroxat, paper.*

The convergence of these effects often had adverse implications for patients in their emotional and social functioning. It was clear that numerous aspects of patients’

lives were negatively affected including their social/work life with attendant impact on their quality of life (QoL):

> *"Couldn't run, sleeping 18 hours, change of personality, no motivation to do anything, apathy, loss of friends. Loss of jobs. The antipsychotics have nearly completely destroyed my life. I am no longer able to function like I once did. My mind is now in a total mess."*
>
> *Patient, male, 20 years, Risperdal Consta, I-Net.*

Many of the narratives also focused on the negative effects of ADRs on family life. Patients' distress was often further compounded by strained relationships and disruptions to established roles within familial structures. These particular concerns were consistently highlighted with evocative descriptions of the negative effects on the family environment:

> *"My father was on this medication for 6 months before his death and day to day life for himself and his wife and my sisters was awful. He became aggressive, violent and suffered severe anxiety and paranoid thought. He mentioned suicide on more than one occasion."*
>
> *Carer, male, 50 years, Champix, I-Net*

3.4 Management of ADRs

Overall 990 (41%) reports provided details of how patients managed their ADRs – these included HCP consultation, self-directed interventions (medical/non-medical), accepting the effects and taking steps to prevent a further event. Generally reports linked to older age categories were more likely to consult with HCPs. Some patients were prescribed medicines to counteract their symptoms:

> *"Nausea, severe migraine, pain in legs and pelvic area, anxiety, persistent vomiting unable to stop for 3 days...a practice nurse made a home visit and prescribed prochlorperazine 3mg to stop the vomiting and paracetamol suppositories for the pain."*
>
> *Patient, female, 48 years, Esmya, I-Net.*

Patients consulted with a range of HCPs including GPs, pharmacists, hospital doctors, nurses etc. GPs were the first point of contact for most patients and many had multiple HCP contacts:

"I was prescribed the clarithromycin and metronidazole to be taken together by the A and E doctor…Later, I woke up with a very sore mouth and throat. I contacted my general practitioner (GP) to see if I should stop taking them. I saw the GP in the evening taking the medication with me, by this time my mouth lips and throat were blistered."

Patient, female, 71 years, I-Net.

However some patients described negative experiences with HCPs with the perception their symptoms were dismissed as minor/insignificant:

"Reduced sexual drive. Inability to maintain erection. I spoke to a General Practitioner (GP) at my local practice. She said that as I was in my fifties it was probably not something to worry about – whilst inconvenient, she said, it was better than being depressed."

Patient, male, 50 years, fluoxetine, I-Net.

Many patients' decided not to adhere to the medicine themselves once the symptoms presented:

"The consequences of stopping the statin were immediately noticeable. I lost most of my aches and pains that I suffer overnight and the pain in my elbows cleared up…I have stayed off atorvastatin for 5 weeks...and I have no more aches or pains."

Patient, male, 60 years, atorvastatin, I-Net.

These self-directed behaviours also included reducing the dose or using over the counter (OTC) remedies to treat the effects. Patients also lessened the effects with simple non-medical methods e.g. drinking milk to counteract heartburn or complimentary alternative medicines (CAMs). While patients described a variety of methods of managing ADRs some considered that the benefits of their medicines outweighed its side effects:

"The mouth ulcers occur every time I have the injection about on to three weeks after. Sometimes they last for a few days but they have lasted for three weeks. Each time I take the medicine which I've been on for two years I get one of the side effects. The mouth ulcers have been seen by my dermatologist but I had plaque psoriasis covering 85% of my body including my hair and face so I am more than happy to suffer with the occasional side effect."

Patient, female, 36 years, Stelara, I-Net

Some patients explicitly stated their intention to take preventative steps by recording the ADR in their medical records:

"I have also written to my doctor to add to my notes that I need to have the Jenson Product to keep my blood pressure and pain at bay."

Patient, female, 67 years, omeprazole, I-Net.

Some information on the motivation for reporting ADRs was evident – YC reporters wished to share their experiences, increase patient awareness of debilitating effects and prevent others from suffering similar reactions:

> *"Needless to say l am stopping taking the Nefopam immediately as its hard enough coping with the problems l have without these extra problems. I hope my experience may help others not go through the same."*
>
> *Patient, female, age not supplied, nefopam hydrochloride, paper.*

Discussion

This research used an existing resource – free text data from YC reports – to increase insight into patients' experiences of ADRs. The qualitative analysis of free text comments in a large UK-wide sample resulted in three key narrative themes: (1) identification of ADRs, (2) severity and impact of ADRs and (3) management of ADRs.

Analysis of YC data indicated that patients mostly use temporal associations to link symptoms to medication which reflects previous research [20, 21]. Other methods of identification were differential diagnosis and a variety of information sources to confirm ADRs. While HCPs and PILs were the most commonly cited sources, the overall use of HCPs, PILs and the internet was low. This may be a simple result of under-reporting – HCPs/PILs might have been used but as YC reports do not seek information on how people identified their ADR their use may not have been explicitly reported. It is noteworthy that many YC reporters used multiple sources which can increase the possibility of contradictory information as well as information overload [22]. Effective patient-centred heath information about ADRs should consider the implications of multiple information sources and factors such as information overload. Our study used patient reports, which ensures the patient has already made a causal link. It is important to note that some patients do not make such casual links and may have a different experience [23].

Detailed information on the severity and impact of ADRs was supplied by reporters. These findings further illustrate the serious disruption to many patients' lives which can be a feature of ADRs [24]. A striking finding was the prolonged impact of such effects for many YC patients – persistent negative physical, psychological and social consequences for patients. Similar patterns of impaired emotional and social functioning were found in previous YC research [6], internet forums, and qualitative research with survivors of serious ADRs [25, 26]. The addition of a section to YC reports on the impact/disruption to daily life of ADRs could increase their usefulness and provide information on persistent negative physical, psychological and social consequences of ADRs. Another important finding concerned the self-assessment of ADRs by patients – many described effects as 'severe' which included effects commonly labelled by HCPs as mild such as rash, muscle pain. Individual perceptions and attentional biases in health behaviours may explain elevated perceptions of severity [27, 28]. However, rather than dismissing these patients' assessments as heightened health anxieties or symptom amplification, they should be taken as evidence of divergent opinions on symptom severity between patients and HCPs. Regardless of HCP perception, if a patient perceives an ADR as severe they may stop taking the medicine. Awareness of the differences that can exist between patients' perceptions of symptom severity and those of HCPs could inform effective HCP-patient risk communication and shared decision making about medicines.

Many reports provided details of how patients managed their ADRs – these included HCP consultation, non-adherence, and counteracting effects with additional medicines. Previous research with patients with a chronic condition has identified higher use of HCP consultation and use of additional medicines to alleviate the effects, along with lower non-adherence [29]. Specific health concerns in patients with chronic conditions might use different managing behaviours than YC reporters.

Many YC reporters who described HCP consultations also stopped their medicine, contrasting with previous non-adherence studies where patients who sought information from non-HCPs were more likely to be non-adherent [30, 31]. Higher levels for non-adherence were evident among YC reporters than was found in a UK-wide Omnibus survey conducted in 2009 [32].

It is noteworthy that many reports described interactions across a range of HCPs – GPs, pharmacists, hospital doctors and nurses etc. – and that engaging with HCPs is a key aspect of managing ADRs. However, as with previous YC research, dismissive attitudes to ADRs amongst HCPs were evident in the free text comments of our study [6]. The importance of listening to the patient's experience of ADRs should be emphasised in healthcare professional education.

As with previous YC research [6] many YC reporters were motivated to share their experiences for altruistic reasons such as preventing harm to others, improving patient safety. However only a small number of YC reports described an intention to record ADRs in medical records. An accurate medical record, including ADRs, is important to the risk assessment of future prescribing decisions. While time constraints, accessibility to HCPs, and attitudes of HCPs, may prevent this recording, spontaneous reporting systems should emphasise the benefits of informing healthcare professionals of suspected ADRs. Future research should address patients' specific concerns about interactions with HCPs about ADRs.

A recent analysis of patient reports in the Netherlands has concluded that methods need to be optimised to maximise the use of patient reported information, including closer working with patient organisations and the development of new systems for analysing the data [33]. Research which focuses on developing appropriate text

mining and natural language processing (NLP) techniques could assist with analysis of free text comments and enhance patient reporting.

Strengths and Limitations

A major strength of the study was the novel use of an underused resource – the free text data from YC reports. This approach resulted in increased insight on patient experience of ADRs - how patients perceive and manage their ADRs**.** The most significant limitation was the problem of self-selecting bias. Reporters to the YCS were motivated to report their ADRs and this high level of engagement may offer a limited/skewed perspective which does not represent the opinions and experiences of the wider general population. However, the reports were UK-wide, diverse in reporter type, gender, age and drug type which may have corrected the self-selection distortions. Researcher bias may also have been an additional limitation, but attempts were made to minimise this – documentation of the analytical processes; collaboration with supervisors.

Conclusions

Free text comments on spontaneous reports of ADRs from patients have value and potential to contribute toward knowledge of patients' experiences. The findings reflect the range and multidimensional impact of ADRs. Future research directions could involve the linking of narrative profiles to specific drug types or reactions; using YC reports to improve communication training for HCPs to facilitate effective communication about potential ADRs and record keeping of suspected ADRs and dissemination of information about the impact of ADRs to patients and HCPs. This could involve the expansion of the text in PILs to include examples of the potential impact of ADRs and the addition of summarised experiences of these impacts - identified from free-text - to patient websites by patient organisations.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation and data analysis were performed by BOD, JK and RR. The first draft of the manuscript was written by BOD and all authors contributed to the final manuscript. All authors read and approved the final manuscript.

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Appendices

Appendix 1

Table 2: Thematic and narrative analysis: sub-themes, themes & illustrative quotes

Sub-themes*	***Thematic themes*****	***Narrative themes*****	***Illustrative quotes******
Timing sequence Differential diagnosis HCP confirmed - GPs/hospital doctors, pharmacists - pharmacist often initial contact Confirmed with PILs Confirmed with family/friends Confirmed on internet	Reconstruction of ADR -describing and evaluating the experience	Identification of ADR	*"Nausea from start of treatment, 2nd day I struggled to drink anything. 3rd day, unable to eat or drink and started having visual hallucinations"* *Patient, female, 20 years, clarithromycin, I-Net.* *"Bleeding, bad migraines, memory loss, insomnia, loss of appetite and premenstrual syndrome (PMS) symptoms. The effects of these tablets were readily increasing every day I took one."* *Patient, female, 46 years, Cerazette, I-Net.* *"Heartburn particularly bad at night. Severe enough to interrupt sleep. Only started after a couple of days of taking the medicine. I don't normally get heartburn."* *Patient, female, 38 years, flucloxacillin, I-Net.* *"..hives / rash on palm of left hand, wrist and between fingers. No exposure to anything new which might cause this."* *Patient, male, 27 years, citalopram, I-Net.* *"Change to sense smell. The smell was so profound I felt sick with it. Eventually it dissipated but later it returned but not so bad. Spoke to GP who advised to not take any more."* *Patient, female, 59 years, doxycycline, I-Net.* *"Increased hair loss, easy bruising and muscle twitches..Mentioned to general practitioner (GP) and to pharmacist. Pharmacist suggested I report side effects here."* *Patient, female, 53 years,Venlafaxine, I-Net.*

			"I suffered severe irrational thoughts as well as anxiety, couldn't eat very much…I went on internet to see side effects and couldn't believe the amount of people who felt exactly how I did." *Patient, female, 53 years, Nasonex, I-Net.* *"Diarrhoea got progressively worse as the weeks went on..I was unsure if it was related to my sensitive stomach..I was advised to stop the cough syrup by a friend who is a physiotherapist who knows my medical history and suspected I was having a reaction."* *Patient, female, 34 years, Robitussin chesty cough, I-Net.* *"Very severe aplastic anaemia. Had eye drops prescribed by general practitioner and used them for 2 days only..The leaflet enclosed in drops stated in rare cases can cause aplastic anaemia. It states on some research on the internet that it should not be used in children under 2 years of age."* *Parent, male 1 year, chloramphenicol, I-Net.*
Detailed descriptions of mild, moderate & severe effects 'Severe' used by reporters 'Mild' symptoms e.g. muscle pain but reported as 'severe' Self-assessment not linked to HCP consultation or outcomes	Multidimensional impact of ADR	Severity & impact of ADR	*"I was having the same reaction as my nutmeg allergy which alerted me - mild anaphylactic reaction (itching, disorientation and red splotches on skin)."* *Patient, female, 35 years, amoxycillin, I-Net.* *"Hands became swollen first and feet shortly after. Swollen hands and feet causing severe pain when walking, and pain when using hands for anything. Doctor prescribed strong pain killers and ibuprofen gel."* *Patient, male, 67 years, Januvia, I-Net.* *"Severe myalgia and exhaustion. Began with severe muscle pain in right calf. Gradually spread, getting worse each day, to most muscles all over body to the point that I could hardly walk and trying to lift a knife and fork to eat was an ordeal. Extreme depression caused either by medication or difficulty with daily life."* *Patient, female, 59 years, Januvia, I-Net*

Explicit physical, psychological & social effects - anxiety, depression, irrational thoughts - significant impact on QoL - negative effects on work & family life			*"Been taking citalopram for 7 years. Had similar reaction about a year ago..with this batch experienced increased anxiety and poor sleep."* *Patient, male, 46 years, citalopram, I-Net.* *"Insomnia, anxiety, feeling 'fuzzy headed'. Paranoia about harming my family whilst suffering from insomnia. My head was racing, similar to if I'd drunk a lot of caffeine or was suffering from stress. I couldn't stop being scared that I might turn psychotic and kill my family. It scared the hell out of me!"* *Patient, female, 37 years, Selincro, I-Net.* *"It started when I was in a meeting at work - I started to get tunnel vision and eventually lost consciousness for a split second then I found it very difficult to concentrate and I felt panicky. This has got worse and worse despite my discontinuation of the drug. I constantly have blurred vision, I feel panicky and agitated in social situations (I have never suffered with panic or anxiety before), I get dizzy, I find it incredibly hard to focus and think analytically, as a result I'm developing stress and worry as it is affecting my work. I feel constantly spaced out and slightly removed from myself."* *Patient, male, 26 years, omeprazole, I-Net* *"Severe muscular weakness and pain in both arms. Feels like burning and muscular spasms..Affecting my everyday life - hard to housework, pick things up. Lack of sleep due to pain in arms. Pain is still there whilst resting."* *Patient, female, 60 years, amitriptyline, diclofenac sodium, Lyrica, I-Net.* *"Ruptured post tibial tendon. Joint and tendon, muscle pain. Anxiety. Fatigue. Pins and needles… From a fit and active person to disabled in three days. I rode horses and was able to do all the associated work. I am only just able to walk without crutches for short distances and still need them for rough ground. My husband had to take over the running of the house, the horses and dogs and caring for elderly relatives. This had had a catastrophic effect on our lives as a family."* *Patient, female, 62 years, ciprofloxacin, I-Net*

HCP consultation - some multiple interactions - prescribed medicine to counteract effects - negative interactions Self-directed behaviours - stopping meds/remove device - reducing dose - OTC remedies to counteract symptoms Self-directed non medicine management - CAMs to treat SE Coping strategies - accepted effects - recorded suspect ADR	Coping with ADRs	Management of ADR	*"Issued by the diabetic doctor at the hospital. Went to chemist for guidance and cream. Was advised by pharmacist to stop taking Invokana and report to my doctor. I was away from home at the time but went to the doctor this morning."* *Patient, male, 71 years, Invokana, I-Net.* *"Severe full body skin rash. Began with hives that merged. Arms, hands, legs and feet swollen. Large blisters on tops of feet. Skin turned purple and black..Spoke to radiology department to identify what I was given and to inform them of my condition. Spoke to general practitioner (GP) to have Omnipaque added to my list of allergies and to seek advice about blisters"* *Patient, male, 49 years, omnipaque, I-Net* *"Flickering at the side of my eye briefly. Then 2 weeks later rippling vision over half of my field of vision lasting about 15 minutes. I stopped taking the amlodipine in case they were causing the problem."* *Patient, female, 67 years, amlodipine, paper.* *"Abdominal bloating, pelvic pain. Pelvis felt like it was on fire, it felt like I had a terrible infection, paracetamol did not work, had to stay in bed all day. This was very upsetting, so I also felt emotionally low..Lots of little blister like spots. Then several painful large ones appeared..I should also have mentioned that I found the side effects so unbearable that I took the Mirena out myself."* *Patient, female, 43 years, Mirena, I-Net.* *"Since stopping the medication I'm always constipated, had recurring vaginal yeast infections, need to buy and take high doses of probiotics always now."* *Patient, female, 22 years, doxycycline, I-Net.* *"Dry mouth, especially during exercise. Indigestion - taking omeprazole to counter. Two instances of cystitis requiring antibiotics. The difference the medication has made to my quality of life is such that I am prepared to put up with the side effects.* *Patient, female, 57 years, Betmiga, I-Net.*

*Sub-themes = elements of text which are generated during coding and contribute to an overall pattern/theme; ‘**Thematic themes = central patterns that emerge in thematic analysis to form a thematic framework; ***Narrative themes = key aspects of narrative cases that emerge during analysis; **** Quotes selected to highlight themes/patterns in data

Appendix 2

Causative drug as reported in YC reports	rINN
Propranolol	Propranolol
Sertraline	Sertraline
Picato	Picato
Naproxen	Naproxen
Zamadol SR	Zamadol SR
Xeristar	Duloxetine
Ramipril	Ramipril
Seroxat	Paroxetine
Risperdal Consta	Risperdal
Champix	Varenicline
Esmya	Ulipristal
Fluoxetine	Fluoxetine
Atorvastatin	Atorvastatin
Stelara	Ustekinumab
Omeprazole	Omeprazole
Nefopam hydrochloride	Nefopam
Clarithromycin	Clarithromycin
Cerazette	Cerazette
Citalopram	Citalopram
Flucloxacillin	Flucloxacillin
Doxycycline	Doxycycline
Venlafaxine	Venlafaxine
Nasonex	Nasonex
Robitussin chesty cough	Robitussin chesty cough
Chloramphenicol	Chloramphenicol
Amoxycillin	Amoxycillin
Januvia	Sitagliptin
Citalopram	Citalopram
Selincro	Nalmefene
Amitriptyline	Amitriptyline
Lyrica	Pregabalin
Diclofenac sodium	Diclofenac sodium
Ciprofloxacin	Ciprofloxacin
Amlodipine	Amlodipine
Mirena	Mirena IUD
Doxycycline	Doxycycline
Betmiga	Mirabegron

Appendix 3

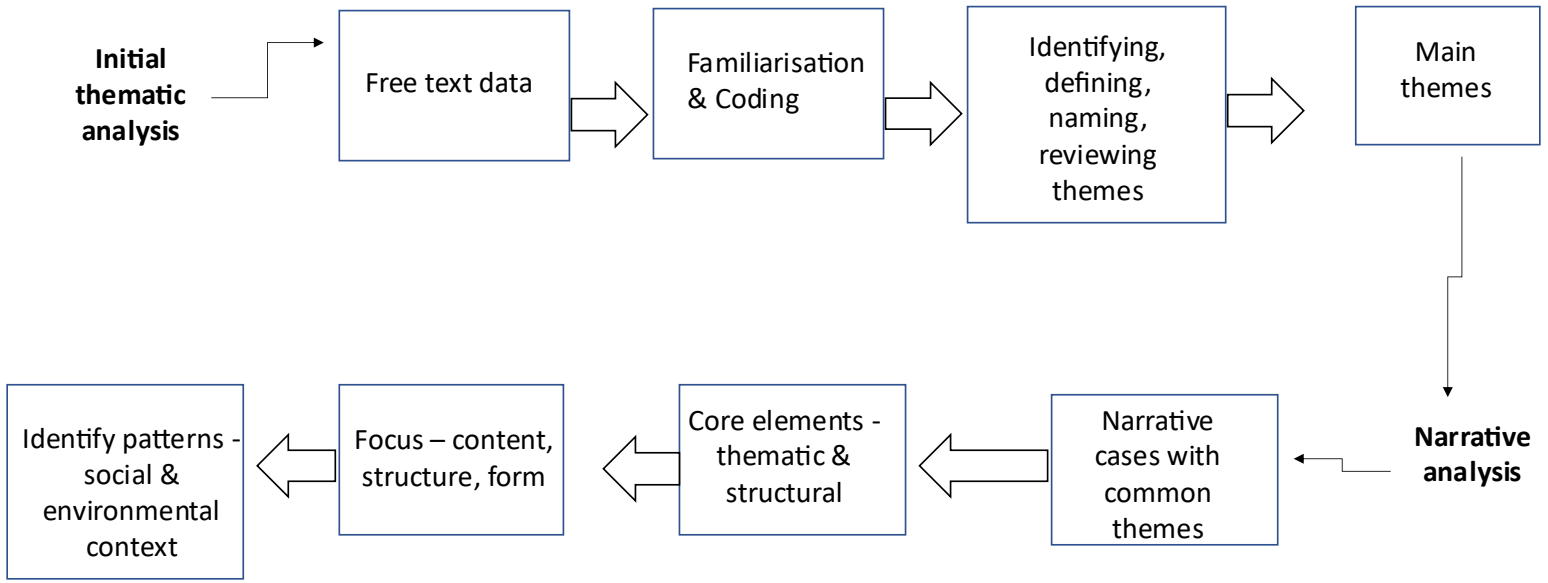

Figure 1: Coding processes – thematic & narrative analysis