UNIVERSITY OF RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCE

SCHOOL OF MEDICINE AND PHARMACY

DEPARTMENT OF PHARMACY

:

Patient's Use Of Mobile Phone For Reporting Adverse Drug Reactions: A Pilot Study In Rwanda

THESIS

Submitted for fulfillment of the requirements for award of

Master's degree in Pharmaceutical sciences

OPTION QUALITY ASSURANCE AND QUALITY CONTROL

by

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Academic year 2018-2019

DECLARATION

This thesis is my original work and has not been previously submitted for the award of a degree in any other University or Institution.

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CERTIFICATION

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DEDICATION

To God almighty

To My husband NIYIBAHO Phocas

To Prof. Ahmed Adebowale Adedeji

To My relatives

NYIRANTEZIRYAYO Ruth

ACKNOWLEDGMENT

I might firstly present all thanks to Almighty God. It is by His grace that this work has been accomplished.

I want to thank all my the lecturers at CMHS Pharmacy Department of the University of Rwanda for the support and efforts spent on my regards all along my academic training.

With all my sincere heartfelt gratitude and appreciation, I express my special thanks to our academic supervisor Prof. Kadima Ntokamunda for his pieces of advice and support, without which this work would not be achieved.

I also thank Prof. Ahmed AdebowaleAdedeji, my family, and friends for their support and encouragement.

Finally, I thank my classmates and every person who contributed in any way to the realization of this work.

NYIRANTEZIRYAYO Ruth

ABSTRACT

Background: Pharmacovigilance consists of activities aimed to monitor and to report adverse drug reactions or side effects experienced by the consumers during the marketing period. Consumers should be educated and informed about how to report ADRs through various communication channels.

Objective: This study was designed to explore the feasibility of patients' self-reporting ADRs using the mobile phone channel.

Place and Duration of Study: The study took place at Gitwe Hospital in Southern province, Ruhango district, Bweramana sector, between May and July of 2019.

Methodology: We approached outpatients taking medications at the Gitwe hospital pharmacy and randomly enrolled 80 patients who voluntarily agreed to participate in the study, provided they were using a mobile phone, and could talk about side effects. The investigator collected the phone number and the prescribed medications of every participant. Participants were required to call the investigator after one week of treatment at home or to receive a call from the investigator and answer some questions. The data collected were analyzed to list all types of ADRs reported and match them with the actual side effects documented on each medication received.

Results: Participants received 30 different medications, among which Antibiotics, Analgesics, and Antihypertensive agents were the most ranked. The investigator called 79(98.75%) participants, and one (1.25%) participant himself called the investigator. Among 80 participants, 38(47.5%) experienced some ADRs, while 31(38.75%) did not; 11(13.75%) did not respond to the call. Respondents described 24 incidences of ADRs, all minor and familiar, but two cases that pushed to return to the hospital. Dry cough, headache, dizziness, and swelling dominated (14-21%).

Conclusion: All respondents carried a functional mobile phone and demonstrated interest in self-reporting ADRs. The use of mobile phones may avail early detection of ADRs. Facilitated toll-free- call service may be an effective means of extending the scope of ADR tracking in addition to the Yellow Card Scheme, and enhance the involvement of pharmacists and consumers in the pharmacovigilance program.

Keywords: Pharmacovigilance, Adverse Drug Reactions, Patient Mobile Phones Reporting, Rwanda

LIST OF ACRONYMS AND ABBREVIATIONS

ADRs	Adverse Drug Reactions
ASHP	American Society of Health-System Pharmacists
CAGR	Compound Annual Growth Rate
CHUK	University Central Hospital of Kigali
HIV	Human Immunodeficiency Virus
ICSR	Individual Case Safety Report
MOH	Ministry of Health
NMRA	National Model Railroad Association
NPMIC	National Pharmacovigilance and Medicine Information Center
PHPs	Hypertext Pre-processor
PIDM	Programme for International Drug Monitoring
PV	Pharmacovigilance
RDF	Rwandan Defense Forces
RMH	Rwanda Military Hospital
ROW	Rest of the World
SOPs	Standard Operating Procedures
SPS	Strengthening Pharmaceutical Systems
USAID	United States Agency for International Development
USFDA	United States Food and Drug Administration
VCT	Voluntary Counseling and Testing
WHO	World Health Organization?

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CHAPTER 1. INTRODUCTION

1.1. Background of the study

According to World Health Organization (WHO), Adverse drug reaction (ADR) is "A drug-related event that is noxious and unintended and occurs at doses used in humans for prophylaxis, diagnosis or therapy of disease or the modification of physiological function." ADRs are significant causes of morbidity and mortality worldwide. Studies estimate that ADRs account for more than 5% of hospital admissions, 28% of emergency department visits, and 5% of deaths during hospitalization. (Bouvy et al., 2015)

Pharmacovigilance consists of activities aimed to monitor and to report ADRs or side effects experienced by drug consumers during the marketing period. Hence, consumers should be educated and informed about how to report ADRs through various communication channels. Spontaneous reporting of ADRs is the backbone of the pharmacovigilance system and has been proven to play a role in identifying signs related to drug safety. Descriptions of the safety profiles of drugs during clinical development are not exhaustive and do not reflect potentially late or rare occurrences of ADRs. (Wilson et al., 2004; Thao Doan et al.,2018)

As of 2015, the United States Food and Drug Administration (FDA) received approximately 253,017 serious adverse events and 44,693 deaths associated with ADRs. (Holiday Inn, Kensington High Street, 2018). In Europe, ADRs cause a considerable amount of morbidity and mortality. Bouvy et al. (2015) estimated that ADRs cause approximately 5% of all hospital admissions, 5% of hospitalized patients will experience an ADR during their hospital stay and that ADRs cause 197,000 deaths annually throughout the European Union.

As at the end of September 2015, 35 of 54 African countries were Full Member countries of the Program for International Drug Monitoring (PIDM). Although the number of Individual Case Safety Report (ICSR) from Africa has increased substantially, ICSRs from Africa still make up <1 % of the global total in VigiBase®. (Ampadu et al., 2015) The features of ICSRs from Africa differ from those from the rest of the world concerning the classes of products as well as the age group of patients affected. The gender of patients represented in these ICSRs is identical. ADRs

contribute to 2.5–18% of deaths of hospitalized patients. (Jacoline C, 2015) Fatal ADRs are frequently preventable. There is a lack of evidence regarding the burden of ADR-related deaths in low- and middle-income countries, and in settings of high human immunodeficiency virus (HIV) and tuberculosis prevalence. (Johannes P. et al., 2014)

The Rwanda Ministry of Health (MoH) is committed to improving medicine safety monitoring and protecting public health. Guidelines and regulations have been put in place to ensure the safety and effectiveness of medicines available in Rwanda. It is the vision of the MoH that all such related activities should be standardized and coordinated. These Guidelines regarding Pharmacovigilance and Medicine Information System in Rwanda provide standard operating procedures (SOPs) and directions for addressing all issues related to medicines and patient safety in a comprehensive manner. Users are encouraged to regularly refer to these guidelines for a consistent understanding of medicine safety surveillance activities in Rwanda. The USAID and WHO funded Strengthening Pharmaceutical Systems (SPS) program to develop a national framework and guidelines to establish the pharmacovigilance system in Rwanda. (Rwanda Ministry of Health, 2016)

In May 2009, MoH conducted a national baseline assessment and disseminated findings. A National Pharmacovigilance and Medicine Information Centre (NPMIC) was therefore established within the MoH to coordinate pharmacovigilance activities and the ADR reporting system. To date, across the country, more than 2500 health professionals working in hospital settings have been trained. Also, MoH provided health workers with Medicine Quality Problems Notification Forms (MQPNF), patient alert cards, and public job aids. Special emphasize on medicine safety in HIV treatment and malaria, and plans for the development of active surveillance activities within the public health programs have progressed. (http://www.moh.gov.rw, May 2009)

For active Pharmacovigilance and medicine information activities in Rwanda, the NMRA shall identify some performance measures for monitoring Pharmacovigilance activities of both NPMIC and the PHPs. These performance measures include indicators, reports, and performance targets to routinely report to the NMRA. (http://www.moh.gov.rw, May 2009).

Despite this provision, limited information is available on the practice of pharmacovigilance in the hospitals and health centers, frequency of reporting, level of involvement of hospital workers, and participation of those who experience any adverse event outside the hospital setting and would not report to the hospitals in Rwanda.

1.2. Problem statement

A study conducted at CHUK in October 2014 regarding the Establishing of a Pharmacovigilance and Medicine Safety System in Rwanda to improve patients on ART quality of care revealed that ADR reporting identified significant contributions of ADRs to severe morbidity, and identified preventable patterns of ADRs. (Rutaganda et al., 2014). However, this study does not provide enough tools of a reporting system that can solve the current problem to provide a sustainable solution because it is hospital-based, and people can have ADRs and remain at home due to the distance from home to the health facility and social-economic factors.

To my knowledge, to date, there have been no data of research conducted on the instantaneous reporting system of ADRs using mobile phone in our country. I was interested in this research project to bring about the additional facility to the reporting system, which is quicker and spontaneous than the one used today which can lead to the compromise of the results due to non-reported events since this system may not be available to everyone hence prevention of participation of many. This study aimed to explore the effectiveness and gaps of the reporting system in place and then to provide an efficient, easy, and quick mode of reporting ADRs through mobile phone channels.

1.3. Significance of the study

The participation of the people, health care workers, and the use of mobile technology may improve the reporting system of adverse drug reactions (ADRs) and can increase the number of reports of new drug safety information. (Zurovac et al.,2012) The use of mobile phone technology is reachable by many people in Rwanda and is simple, friendly. If someone loses the way or gets stuck in bad weather or any other circumstance, a mobile phone could save help. In pharmacovigilance, it will help patients everywhere they will be when they face adverse drug reactions. The drawback of not reporting may result in the harmful effects of a medicinal product not being noticeable for a long time, for example, phocomelia with thalidomide. For the same cause, it can take too long before finding that long-lasting abuse of a medicinal product can produce debilitating health effects. Therefore, proper implementation of ADRs reporting and

additional use of mobile phone technology will help to reduce the harmful effects resulting from use of medicinal products when reported and contribute to the early detection of drug safety problems in patients, assessing the risk-benefit in an individual and the population, improving the selection, rational use of drugs through provision of timely warning to healthcare professionals.

1.4. Hypothesis

ADR reporting may be promoted by stimulating early reporting using more friendly tools in addition to yellow forms and enhancing participation of the people and health care providers.

1.5. General objective

The main objective of the study was to investigate the effectiveness of mobile phone use in reporting adverse drug reactions and the detection of drug interactions in Rwanda.

1.6. Specific objectives:

To assess the feasibility of a mobile reporting system among outpatients treated at Gitwe Hospital
To evaluate the effectiveness of the mobile phone users to report adverse drug reaction
To describe the type of ADRs self-reported by mobile phone

CHAPTER 2. LITERATURE REVIEW

2.1. Definition of Adverse Drug Reactions (ADR)

According to World Health Organization (WHO), ADR is "A drug-related event that is noxious and unintended and occurs at doses used in humans for prophylaxis, diagnosis or therapy of disease or the modification of physiological function." An ADR can be of mild, moderate, or severe reactions. According to Food and Drug Administration (FDA), a severe adverse drug event (or relating to the devices) is a reaction in which "the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage." American Society of Health-System Pharmacists (ASHP) also consider a significant ADR as any unexpected, undesired, or excessive response to a drug that requires discontinuation of the drug , changing drug therapy, modifying the dose (except for minor dosage adjustments); necessitates hospital admission, prolong stay in a health-care facility, supportive treatment, significantly complicates diagnosis; negatively affects prognosis, or results in temporary or permanent harm, disability, or death.

ASHP defines a side effect as an "expected, well-known reaction resulting in little or no change in patient management; effect with predictable frequency," and an effect with which intensity and occurrence are related to the dose. Drug withdrawal, drug-abuse syndromes, accidental poisonings, and drug-overdose complications are not classified as ADRs. Most ADR definitions also exclude therapeutic failure. (Kimberly S et al., 2009)

2.2. Classification of ADRs

ADRs are classified according to the mechanism, severity, and probability.

2.2.1. Types and Mechanisms of ADRs

Based on the time of appearance, ADRs are acute, chronic, or chronic-delayed reactions. They occur during a single dose or a single cycle of therapy (*acute ADR*), or can be dose- and time-related. A drug-induced adverse reaction that occurs after 10-12 months of treatment is *chronic ADR,* whereas *chronic-delayed* effect occurs years after drug use.

Regarding the mechanism of occurrence, in 1977, it was observed that ADRs could be *pharmacologically-induced (type A)* or the result of *idiosyncratic lesions (type B)*. The most common ADRs (80%) are type A that are dose-dependent and can be reversible after drug cessation. About 75-80% of type-A reactions are predictable. Type-B adverse reactions are immune-mediated, cannot be predicted, are dose-independent, and occur only in susceptible individuals. (Gurzu et al.,2017)

2.2.2. Severity of ADRs

The patient-related factors of severity of non-immune ADRs are the following: female gender, older age, associated severe comorbidities (renal failure, hepatic disorders, systemic lupus erythematosus), polypragmasia associated viral infections (e.g., human immunodeficiency virus [HIV], herpes virus, cytomegalovirus), alcohol consumption, etc. Females, asthmatic patients, users of beta-blockers, and patients with HIV and other autoimmune disorders, such as systemic lupus erythematosus, have a higher risk of developing hypersensitivity-related ADRs (Fig.1).

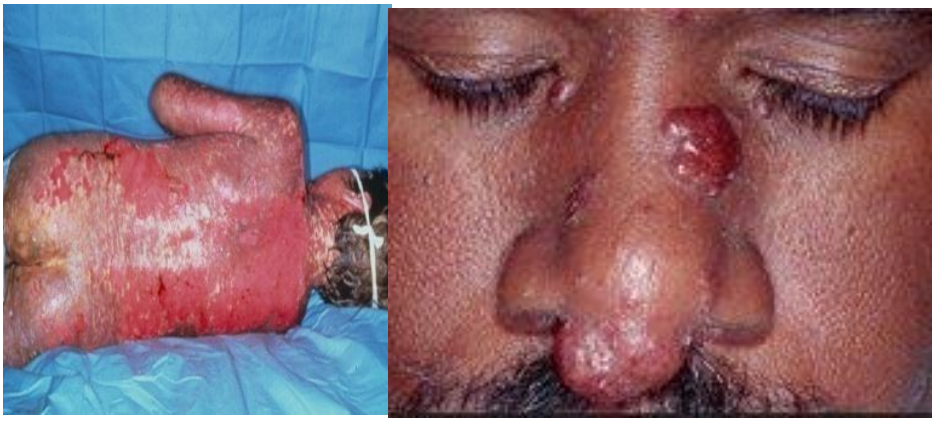

Figure 1. Rash (Lars Grimm, MD, MHS; March 2015)

The Drug-Related Factors of Severity refer to the chemical properties and molecular weight of the drug. For example, heterologous (sera non-human proteins) are highly immunogenic, but other medications may also have immunogenic properties by coupling with proteins to form haptens (antigen-antibody immunogenic complexes). The risk of developing hypersensitivity-related ADRs also depends on the route of drug administration. The most common allergic phenomena occur after intramuscular or intravenous drug administration. (Gurzu, S., and Jung, I., 2017)

2.3. Adverse events and their management

Some adverse events are reviewed below according to their frequency. Frequencies presented here are approximate; they are established according to the experience of the author and one of his publications, to an article by McGraw MJ et al. (2010), and the figures released by the Internet site. Adverse events are highly variable in their severity, sometimes easy to handle, sometimes extremely uncomfortable, possibly leading to treatment cessation. All events tend to spontaneously resolve over time, most often within a reasonable delay, but some may be very enduring events.

2.3.1. Fatigue and Sleepiness (More than 70% of Patients)

These are the most common symptoms, often challenging to differentiate from one another. They are highly variable in severity, intense in some patients, very light in others. They may be accompanied by feelings of weakness and lack of energy. Fatigue may be permanent or occur over a limited period during the day, often within the hour following the intake of baclofen tablets. Fatigue is generally accompanied by more or less intense feelings of sleepiness. Extreme sleepiness may result in really falling asleep for a short time (a few seconds), enough to be potentially dangerous (for instance, when driving a car or using hazardous tools). Fatigue may also be accompanied by dizziness or impairment in balance, even potentially dangerous because of the risk of falls and fracture. Fatigue and sleepiness are less intense when people are active, during working hours, but resume when coming back home. Many falls rapidly asleep on their sofa just after dinner. There are no treatments for fatigue and sleepiness. Some patients are improved by stimulants such as vitamins or coffee, but most are not. Another way to handle fatigue and sleepiness is to target baclofen treatment on episodes of cravings better, as mentioned above: for patients who drink only in the evening, it is recommended to take baclofen in the late afternoon, within the hour that precedes the occurrence of craving, and not the rest of the day. (McGraw MJ et al.,2010)

2.3.2. Insomnia (30-40% of Patients)

Baclofen-treated patients are commonly sleepy during day and insomniac at night. Typically, they fall rapidly asleep after dinner, sleep for two or three hours, wake up, and then cannot go back to

sleep. Or they go back to sleep once or twice during the night but globally do not sleep more than four or five hours. Many are sleepy during the day, but, surprisingly, many others say they do not feel sleepy during the day despite sleeping four or five hours per night when they slept seven or eight before starting the treatment, as if baclofen had changed their sleep needs. Baclofen-induced insomnia alleviated by hypnotics, but only moderately. Insomnia is also often associated with other disorders, such as nightmares, worsening of sleep apnea, sweating, and, rarely, restless legs. Nightmares are frequent during baclofen treatment. They are very vivid nightmares, often extremely impressive, patients having the impression that they live the awful scenarios of the nightmares, and they may cause serious psychological distress. These nightmares generally disappear completely with a low dose of prazosin (prazosin is an antihypertensive drug used for the treatment of nightmares in post-traumatic stress disorder). Obstructive sleep apnea is a worrying condition, generally associated with sleepiness, fatigue, impaired cognitive function, and, often, metabolic disorders. Individuals with sleep apnea are at increased risk for cardiovascular events. Studies have shown that baclofen may cause or worsen sleep apnea. Patients with sleep apnea should, therefore, be treated with continuous positive airway pressure before baclofen initiation. Conversely, it should be mentioned that sleep disorders are common in AUD patients and that it is not exceptional to see patients' sleep much improved by baclofen. (Author Unknown., 2017)

Patients must be involved in their treatment; they have to continue learning how to manage and change doses according to the occurrence of side effects, the time of the day they usually drink alcohol, and the impact of the treatment on their daily activities. When a difficult-to-tolerate adverse event occurs, dose increases should slow for a while, or the dosage should be reduced from one or two tablets; a few days later, when the adverse effect has disappeared or is bearable, the dose can be increased again, this more slowly (for example, using half-tablets, or taking one more tablet every five days or every week instead of one more every three days). The principle is to progressively overcome the barrier of adverse effects and increase the dose until the patient becomes utterly indifferent to alcohol. Patients should be informed that concomitant alcohol use hinders the positive effects of baclofen. Qualified prescribers know that alcohol potentiates the adverse effects of baclofen and that the effective dose of baclofen is substantially higher in those who continue to drink as usual during the treatment, compared to those who make efforts to stop drinking or lower their alcohol consumption. The decrease or stoppage of craving occurs in almost

all patients who can increase the dosage to one that is effective for them. However, this does not mean that all patients stop drinking. The anti-craving effect of baclofen may not be strong enough for some patients (a minority), many patients are not motivated to stop drinking, or some may be too firmly attached to their drinking habits.

2.4. ADR reporting systems

The reporting system is fundamental in the management of adverse drug reactions; however, countries are looking at how they can improve their ADR reporting systems due to the failure of the current system in use and burdens of adverse drug reaction upon the population. As mentioned by Ethan B.,2010, some studies have well documented the limitations of current safety-reporting systems. In the United Kingdom, the use of the Yellow Card Scheme for adverse drug reaction has proven to remain low. "The United Kingdom's Yellow Card Scheme for reporting of ADRs has been operating for 50 years, but reporting rates by community pharmacists remain low". (Hughes ML and Weiss M, 2018) This was due to the lack of knowledge of the reporting schemes and processes, lack of awareness of the system, lack of access to reporting forms, lack of certainty regarding causality, reactions seen too mild to report, reactions that are well known, workload and time pressures.

In terms of technology, a smartphone ADR reporting application was launched by the MHRA31 in 2015, but this idea was not particularly popular with the study respondents as a facilitator. Instead, they preferred a system, which would enable the pre-population of yellow card report forms from dispensary software, the use of such systems linkage between GP software and ADR reporting software resulted in significant increases of GP reports submitted in England. (Hughes ML and Weiss M, 2018)

In Rwanda, ADRs reporting is processed by written using adverse event notification forms, which is in the French version (fiche de notification des evénéments indésirables)[1]. This reporting system is the official tool, and it is supposed to be used by all health systems working in Rwanda, whether traditional healers who use herbal medicines and other health care systems because it shall apply for different health settings. "Reporting adverse events related to herbal medicines shall be the

[1] See (annex A–French; annex B–English) Guidelines for Pharmacovigilance and Medicine Information in Rwanda 2016

same as for the other health products mentioned in this guideline and shall involve cooperatives made up of traditional healers that are officially approved by the appropriate authorities."

The patient is required to carry his or her card (as it has translated in Kinyarwanda) all the time and show it to the health care providers or physicians during the time of consultation or health care visit. Therefore, the use of a mobile phone as a familial tool for most of our population in reporting adverse drug reactions can help to reduce the harmful effects resulting from the use of medicinal products by early help in early and more comfortable reporting of drug safety problems.

CHAPTER 3. METHODOLOGY

3.1. Study area

We selected the locality of the GITWE area by convenience since it is a small center located in Karambo village, Murama cell, Bweramana sector, Ruhango district, in Nyanza District in the Southern Province. In this area, we have the District Hospital called Gitwe District Hospital Gitwe Hospital created by Adventist parents of the surrounding sectors of this small square. This hospital is supervising thirteen health centers in Ruhango District: Gitwe; Nyarurama; Ruhango; Muyunzwe; Kizibere; Byimana; Mbuye; Kigoma; Gishweru; Mukoma; Kinazi; Muremure and Karambi, even if it is still receiving patients from Kinazi Health center, Mbuye, Kizibere, Kigoma, Mukoma, Ruhango, and Nyarurama health centers attached to Kinazi hospital inaugurated recently. The Hospital has acquired its legal status following the ministerial order No131/05 of 09/04/1984.

The organizational structure of Gitwe hospital is composed of three primary services, such as clinical services, paraclinical services, and administration services. The clinical services are consisting of gynecology-obstetrics, internal medicine, stomatology, and pediatric and Surgery departments. The paraclinical services are composed of radiology, laboratory, and pharmacy services. The administration services comprise of central administration, accounting, technical service statistical service, social service, and general services. The hospital has a total capacity of 400 beds.

3.2. Study design

The study was a cross-sectional survey conducted in 2019 among outpatients taking medications at the Gitwe hospital pharmacy.

3.3. Participants

Patients who come to take drugs prescribed by doctors at the hospital pharmacy and having a mobile phone and consenting to participate. As a prospective exploratory study, we fixed a convenient size of 60-100 participants. The respondents were the targeted patients coming into the pharmacy, and we randomly enrolled 80 patients who voluntarily agreed to participate in the study, provided they were using a mobile phone and could talk about side effects.

Initial contact with the hospital staff and the pharmacist, in particular, were made to make known objectives and activity procedures.

3.4. Data collection

To get the needed information, I decided to proceed with the use of a questionnaire, observations for primary data, and the documentary technique has been used to collect the secondary data.

On different days, I went to the hospital pharmacy to contact the patients. I randomly asked some of them if they were willing to respond to my call asking if they faced adverse drug events or if they will call me and report themselves any ADR experienced. The talk was in the local language (Kinyarwanda). The investigator collected the phone number and the prescribed medications of every participant. Participants were required to call the investigator after one week of treatment at home or to receive a call from the investigator and answer some questions. The parents were responsible for answering in place of younger than 18 years.

3.5. Ethics

Institutional review board of the University of Rwanda approved the study. The clinical director of Gitwe hospital permitted to interview patients. We obtained verbal or written informed consent from each participant before data collection. We notified the participants of their right to withdraw from the interview at any time and assured them for the confidentiality of their information, and the privacy of the respondents was maintained.

3.6. Data analysis

The data collected were analyzed to list all types of ADRs reported and match them with the actual side effects documented on each medication received. We accordingly used Microsoft Excel and SPSS software tools to analyze the information regarding the findings. Statistical significance was considered at $p < 0.05$.

CHAPTER 4. RESULTS AND DISCUSSION

4.1. Results

4.1.1. Interview with the management of the hospital pharmacy

Meeting with the management of the hospital pharmacy showed that there were rarely any complaints received before the study period. The patients went out without returning to report any side effects or adverse reactions to the drugs.

4.1.2. Demographic data

Table 1 shows the distribution of respondents according to their age and sex. The majority (86.25%) were aged people over 40 years and younger (13.75%). There were more females (65%) who received drugs from the hospital pharmacy than males (35%).

Table 1. Distribution of respondents by Age and Gender

Age					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	12-40	11	13.75	13.75	13.75
	41-68	69	86.25	86.25	100.0
	Total	80	100.0	100.0	
Sex					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	28	35.0	35.0	35.0
	Female	52	65.0	65.0	100.0
	Total	80	100.0	100.0	

4.1.3. Assessment of potential for uptake of the use of mobile phone for ADR tracking

All patients enrolled (100%) carried at least one mobile phone. Most participants were reachable through calls to their mobile phones 70(87.5%). In a few cases, the unavailability of network service was one of the factors for no contact at the time of call 10(12.5%) (Table 2).

Table 2. Rate of participants' reachability

Accessible	Frequency	Percent	Valid Percent	Cumulative Percent
No	10	12.5	12.5	12.5
Yes	70	87.5	87.5	100.0
Total	80	100.0	100.0	

4.1.4. Medicines prescribed to patients

From the prescription forms of patients, we calculated the frequencies of all drugs prescribed, as shown in Table 3. Overall, the prescriptions consisted of 35 drugs used in monotherapy or combination. The most frequent drugs were Captopril (42.86%), Amoxicillin(40%), Paracetamol (34.29%), Diclofenac (28.57%), Tramadol (22.86%), Hydrochlorothiazide (22.86%), Nifedipine (14.29%), Ibuprofen (14.29%), Metronidazole (14.29%), and Valproate sodium (11.43%).

Table 3. List and Frequency of 35 medicines prescribed to patients

CLASS AND MEDICINES							
ANTIHYPERTENSION	CODE	N	%	PAINKILLERS	CODE	N	%
Amlodipine	D1	1	2.86	Buscopan	D17	1	2.86
Atenolol	D2	1	2.86	Dexamethasone	D18	4	11.43
Captopril	D3	15	42.86	Diclofenac	D19	10	28.57
Furosemide	D4	1	2.86	Hydrocortisone	D20	1	2.86
Hydrochlorothiazide	D5	8	22.86	Ibuprofen	D21	5	14.29
Methyldopa	D6	3	8.57	Paracetamol	D22	12	34.29
Nifedipine	D7	5	14.29	Prednisolone	D23	1	2.86
Spironolactone	D8	1	2.86	Tramadol	D24	8	22.86
ANTIBIOTICS	CODE	N	%	MISCELLANEOUS	CODE	N	%
Amoxicillin	D9	14	40.00	Salbutamol	D25	1	2.86
Coartem	D10	1	2.86	Bisacodyl	D26	2	5.71
Ciprofloxacin	D11	3	8.57	Amitriptyline	D27	1	2.86
Cloxacillin	D12	1	2.86	Metformin	D28	3	8.57
Erythromycin	D13	3	8.57	Cinnarizine	D29	1	2.86
Metronidazole	D14	1	14.29	Carbamazepine	D30	1	2.86

Nitrofurantoin	D15	1	2.86	Valproate sodium	D31	4	11.43
Penicillin V	D16	3	8.57	Biperiden	D32	1	2.86
				Haloperidol	D33	1	2.86
				Omeprazole	D34	3	8.57
				Thiamine	D35	3	8.57

4.1.5. Reporting Side effects

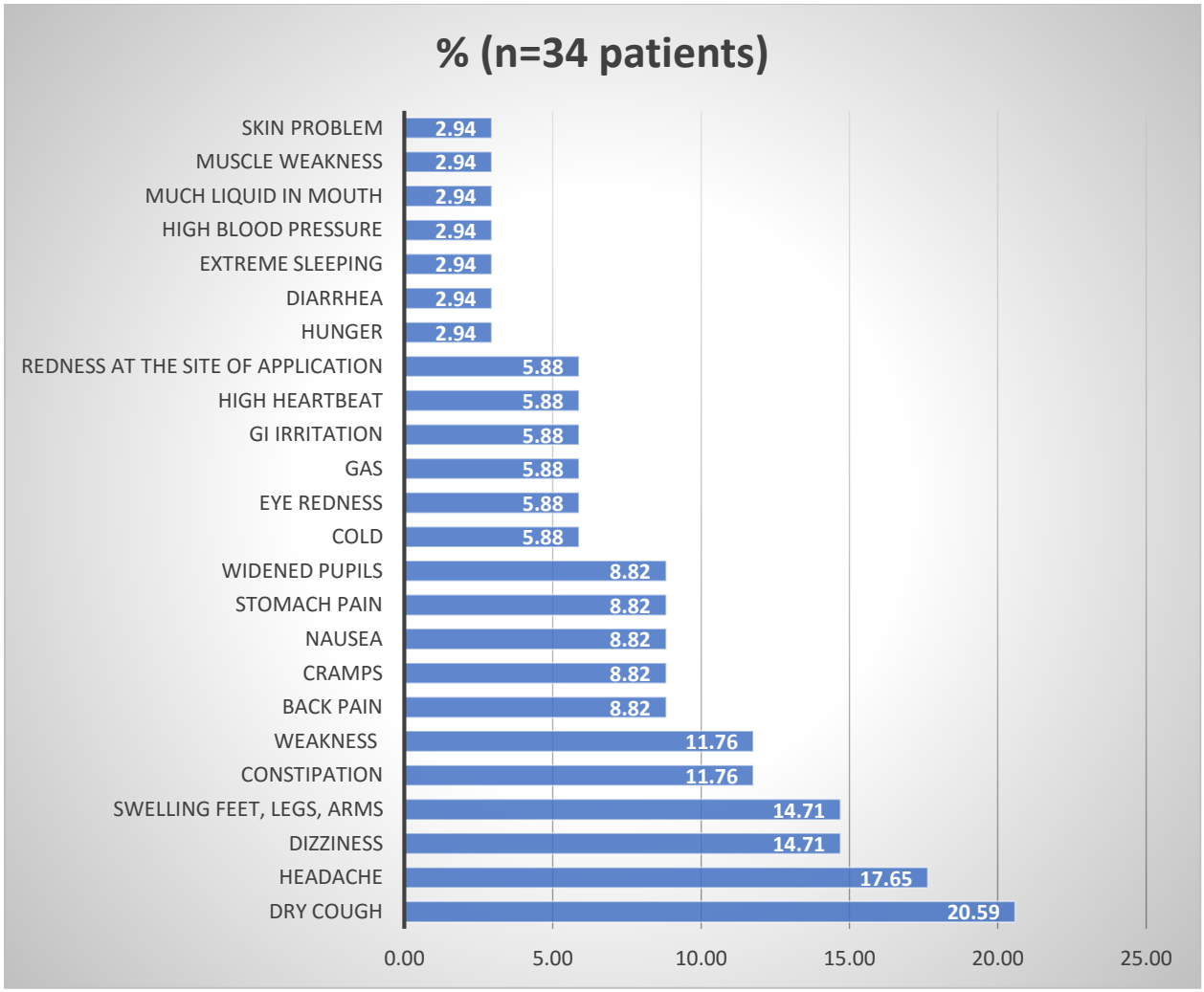

Figure 2. Side effects reported by participants

In total, of 70 participants who picked calls, 36(51.43%) said not having experienced any side effects, and 34(48.57%) participants did.

Figure 1 shows the frequency of all types of ADRs reported by the participants.

Participants who were followed up using mobile phones reported 24 incidences of different reactions to drugs.

The most experienced were dry cough (20.59%), headache (17.65%), dizziness (14.71%), swelling(14.71%), constipation (11.78%) , weakness (11.76%).

The others comprised back pain, cramps, nausea, stomach pain, widened pupils, cold, eye redness, gas, GI irritation, high heartbeat, redness at the site of application, hunger, diarrhea, extreme sleeping, high blood pressure, much liquid in mouth, muscle weakness and skin problem.

Table 4 shows the medications received and related side effects reported.

Table 4. Side effects reported by 34 patients under different medication regimens

Patient	MEDICATION TAKEN	SIDE EFFECT AFTER DRUG USE
1	Captopril and nifedipine	Back pain, swelling feet
2	Omeprazole, captopril, and tramadol	Back pain, gas, high blood pressure
3	Cinnarizine	Back pain, cold, GI irritation, skin problem, dry mouth
4	Diclofenac and tramadol	Being hungry
5	Atenolol and nifedipine	Cold, weakness, dizziness, headache
6	Ciprofloxacin, tramadol,omeprazole	Constipation
7	Tramadol capsules	Constipation, cough
8	Tramadol capsules	Constipation
9	Captopril and Hydrochlorothiazide	Cramps, muscle weakness
10	Captopril and hydrochlorothiazide	Cramps, headache, dry cough
11	Captopril and hydrochlorothiazide	Cramps, weakness
12	Diclofenac	Diarrhea
13	Tramadol capsules	Dizziness and headache
14	Carbamazepine	Dizziness and weakness
15	Captopril-Hydrochlorothiazide	Dry cough
16	Buscopan	Dry mouth
17	Spironolactone	Dry mouth
18	Dexamethasone sodium phosphate	Eye redness
19	Diclofenac and paracetamol	Gas
20	Furosemide and nifedipine	GI irritation, constipation, swelling feet
21	Tramadol Capsules	Headache
22	Captopril and Hydrochlorothiazide	Headache, Dizziness, high beat heart
23	Methyldopa	High heartbeat
24	Erythromycin	Much liquid in mouth
25	Thiamine and ibuprofen	Nausea
26	Penicillin V and metformin	Nausea, stomach pain
27	Dexamethasone	Redness and widened pupils

28	Hydrocortisone cream	Redness at the site of application
29	Collyresolution eye drops	Redness in the eye and widened pupils
30	Valproatesodium gastro-resistant	Stomach pain
31	Omeprazole, amoxicillin, and metronidazole	Swelling arms and legs
32	Captopril and nifedipine	Swelling feet, dry cough, headache, weakness
33	Amlodipine besylate tablets	Swelling legs, extreme sleeping, stomach pain, nausea, dizziness
34	Dexamethasone	Widened pupils

Primary source

By relating the side effects of drugs reported during the study and their known sides effect, no new side effects appeared; all of them were known ones according to Table 5. Except for two cases reported that required returning to the hospital, all reactions were minor common adverse reactions to the drugs used.

Table 5. Drugs taken and their known side effects

DRUGS TAKEN	Expected Known SIDE EFFECTS
Antihypertensive: Captopril, methyldopa, amlodipine, hydrochlorothiazide, furosemide, and atenolol	Cough, dizziness, ankle swelling, headache, weakness, chest, discomfort. (Joshi VD et al., 2010)
Analgesics: Ibuprofen, diclofenac, prednisolone, paracetamol, dexamethasone	Hepatotoxicity, ulceration of GIT, sedation, dizziness, nausea, vomiting, headache, back pain, gas, high blood pressure, pupil constriction, dry mouth, chest pain, constipation
Antipsychotics Amitriptyline, carbamazepine	Weight gain, constipation, sleepiness, uncomfortable restlessness, dry mouth, blurred vision, sexual problem due to hormonal changes.
Antibiotics: Amoxicillin, metronidazole, ciprofloxacin, and erythromycin	Vomiting, swelling of lips, abdominal cramps, rash, vaginal itching or discharge, diarrhea, constipation (Granowitz EV et al., 2008)
Buscopan	Constipation, dry mouth, eye pain, swelling feet, and hands. Retrieved from https: // www.medicinenet.com
Coartem	Loss of appetite, joint pain, fever, weakness, dizziness, headache. Retrieved from https: // www. Rxlist.com
Tramadol capsules	Constipation, cough, diarrhea, headache, dizziness
Nifedipine	GI irritation, constipation, swelling feet, dizziness, weakness
Thiamine	Nausea, throat,rash,itching,headache,constipation,diarrhea,dizzines s.
Metformin	Nausea, stomach pain,weakness,diarrhea,gas,muscle pain.
Hydrocortisone cream	Redness at the site of application, dryness
Collyreeye drops	Redness in the eye and widened pupils
Valproate sodium gastro-resistant	Stomach pain, bleeding, feeling shaky.

Retrieved from https://www.webmd.com>drugs>details

4.1.6. Post-treatment assessment

Two participants returned to the hospital due to the persistent of the reaction that they faced one it was for swelling legs and other it was high beating of the heart after use of the drug.

4.2. Correlation analysis

First, we tried to describe whether the number of co-prescribed drugs correlates with the number of side effects reported by each patient (r^2=0.0118). Of all 80 participants, 47.5% received one drug, 43.8% received two drugs, and 8.8 % received three. As shown in Fig.3, the one patient-33 who reported five ADRs had received only one drug (amlodipine besylate), while patient-6 who received Ciprofloxacin, tramadol, and omeprazole reported only constipation.

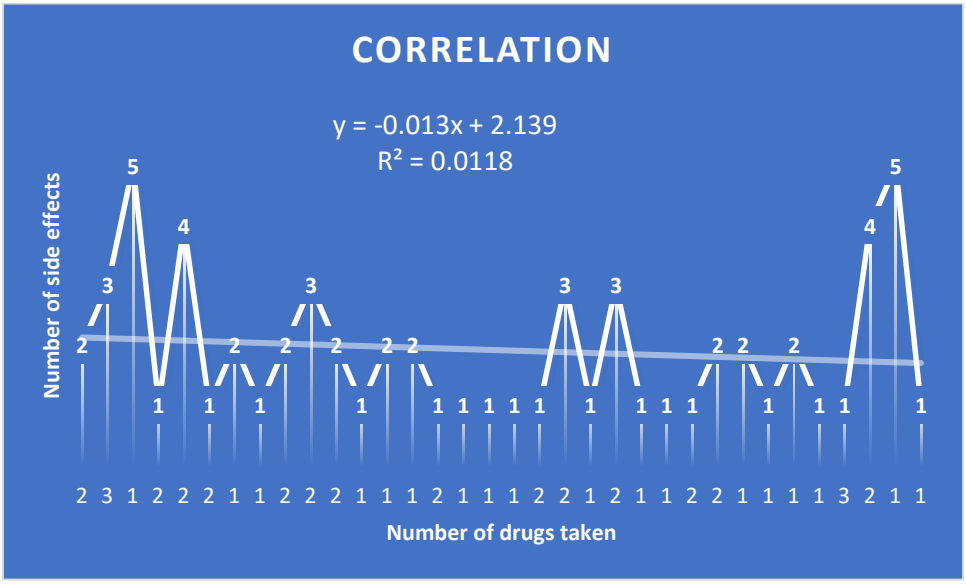

Figure 3 Impact of the number of drugs taken on the number of ADRs reported

Secondarily, we inspected the prevalence of reporting ADR by sex with 95% CI in the survey done at Gitwe district Hospital Pharmacy. Between 23 males who picked the phone call, 15(65.2%) did not report any ADR, while among 47 females who picked the phone call, 21(44,7%) did not report any ADR. For those who experienced any ADR, there were 8(34.8%) males compared to 26(55.3%) females. It is more likely that females would experience more ADR than males.

However, with this small sample, the difference is not statistically significant (P<0.086), as shown in Table 6 below.

Table 6. Influence of sex on ADR reporting rates

ADR * Sex Crosstabulation						
			Sex		Total	Exact Sig. (1-sided)
			Male	Female		
Any ADR reported	No	Count	15	21	36	
		% within Sex	65.2%	44.7%	51.4%	
	Yes	Count	8	26	34	
		% within Sex	34.8%	55.3%	48.6%	
Total		Count	23	47	70	
		% within Sex	100.0 %	100.0%	100.0%	.086

4.3. DISCUSSION

Demographics

The demographic profile of the participants presented a sex-ratio of 65% female over 35% male, all in the age range of 12-68 years old. The high proportion of females justifies the significant vulnerability of women as observed worldwide, and one shall consider this in the modelization of the application.

Feasibility of Mobile phone in ADR reporting

Among 70 participants who picked calls, 36(51.43%) said not having experienced any side effects, and 34(48.57%) participants did. One can expect that half of the patients medicated will report at least one any side effect. Bouvy et al. (2015) estimated that ADRs cause approximately 5% of all hospital admissions, 5% of hospitalized patients will experience an ADR during their hospital stay and that ADRs cause 197,000 deaths annually throughout the European Union. As mentioned by Ampadu et al. (2015), the features of ICSRs from Africa differ from those from the rest of the

world concerning the classes of products as well as the age group of patients affected. The use of a mobile phone would increase ICSRs.

In the present study, the readiness to report and use mobile phone technology for monitoring ADRs in communities exposed to the relative consumption of numerous medications is feasible. Therefore, given the necessary system support, patients or drug users centered reporting approach may enhance Pharmacovigilance on the one hand and complement reporting of ADRs using the existing hospital-based yellow form tracking methods on the other.

Compared to the information provided by the manager of the Hospital Pharmacy, There was no case of ADR reported within the previous months.

The carriage of the mobile phone by all participants studied is indicative of the convenience of communication and importance in day to day activities of the people in the study area. That may not be too surprising as Sub-Saharan Africa has for decades recorded an increase in the use of mobile telephony, despite poor road, water and electricity supply. (Aker JC, Mbiti IM,2010)

The mobile phone has brought new possibilities on the continent, connecting individuals to individuals, information, market, and services.

Previously, in several studies, effective use of mobile phone in health-related services aiming to improve health care service have been reported, for example, use of mobile phone to remind HIV and AIDS patients to take their medicine in Malawi, and to inform violent confrontations in Kenya, Nigeria, and Mozambique. (Granowitz EV, Brown RB,2008). Of recent, the advocacy for the use of mobile phone text messaging has been stepped up for malaria control in Africa. (Zurovac D et al., 2012) Therefore, mobile phone technology may, in Rwanda, provide a medium to support the reporting of effects of drugs administered outside the hospital setting and un-supervised by medical experts, with notable high contact ratio.

Common medication regimens

This study also allowed figuring out the most frequent medications prescribed in the study area. Overall, the prescriptions consisted of 35 drugs used individually or in combination. The most frequent drugs were Captopril (42.86%), Amoxicillin(40%), Paracetamol (34.29%), Diclofenac (28.57%), Tramadol (22.86%), Hydrochlorothiazide (22.86%), Nifedipine (14.29%), Ibuprofen (14.29%), Metronidazole (14.29%), and Valproate sodium (11.43%), Omeprazole (8.6%) and

Metformin (8.6%), Coartem(2.89%). These drugs reflect a dominance of hypertension, infections, epilepsy, intestinal parasites, stomach ulcer, rheumatoid pain, and malaria as prevalent diseases.
According to MoH statistics 2016, the top ten causes of morbidity in health centers, 2016 (all age groups) were Malaria 23.9%, ARI 23.4%, Intestinal parasites 5.2%, Eye disease 4.6%, Skin infections 3.2%, Gastro-intestinal disease 3.0%, Tooth and gum disease 2.9%, Urinary tract infections 2.0%, Pneumopathies 1.8% , Gynecological problems 1.3%, Other diseases 28.7%.
The top ten causes of death in health centers and district/provincial and referral hospitals, 2016 (all age groups) were Neonatal illness 28.9%, ARI 20.0%, Cardio-vascular disease 7.1%, Malaria 5.6%, Congenital anomalies 4.6%, Pneumopathies 4.3%, Physical trauma and fractures 3.8%, Gynecological problems 3.7%, Asthma 2.8%, HIV_AIDS opportunistic infections 2.8%, Other diseases 16.4%.

Hazard risk of side effects

An understanding of the relationship between the type of drug prescription and the prevalence and severity of side effects is crucial in making appropriate treatment decisions. (Ulrich V et al., 2018) Twenty-four incidences of different reactions to drugs were reported by participants who were followed up in the study area. The most experienced were dry cough (20.59%), headache (17.65%), dizziness (14.71%), swelling(14.71%), constipation (11.78%) , weakness (11.76%) alongside back pain, cramps, nausea, stomach pain, widened pupils, cold, eye redness, gas, GI irritation, high heartbeat, redness at the site of application, hunger, diarrhea, extreme sleeping, high blood pressure, much liquid in mouth, muscle weakness and skin problem.
The concordance between side effects well described in therapeutic literature (Hughes M, 2019; Noble M et al.,2018; Antoun et al.,2019), and those reported by the participants indicated the accuracy of the information collected. By relating the side effects of drugs reported during the study and their known sides effect, no new side effects appeared. All reactions were minor common adverse reactions to the medications used, except for two cases that required returning to the hospital. There is no relationship between the number of drugs by prescription and the number of potential side effects. Very few clinical signs are truly pathognomonic for a specific drug.

Gender similarity

No difference exists between females and males about the types of ADRs reported. However, it is more likely that females would experience more ADRs than males. Between 23 males who picked the phone call, 15(65.2%) did not report any ADR, while among 47 females who picked the phone call, 21(44,7%) did not report any ADR. For those who experienced any ADR, there were 8(34.8%) males compared to 26(55.3%) females. It is more likely that females would experience more ADR than males. After all, with this small sample, the difference is not statistically significant ($P<0.086$), as shown in Table 6.

CONCLUSION AND RECOMMENDATIONS

Conclusion

The use of mobile phones can help early detection of ADR and reporting system. Facilitated toll-free- call service may be an effective means of extending the scope of ADR tracking in addition to the Yellow Card Scheme, and augment the involvement of pharmacists and consumers in the safe use of drugs. Pharmacovigilance can be more friendly and facilitated, especially in the case of a report from consumers of medicines. Being most currently diffused Information Communication Technology, mobile phones usage make convenience to obtaining information from participants who receive and or use the drugs on the events following the use of the drugs, including adverse reaction, and may potentiate detection of such in hard to reach areas. The achievement of ADR monitoring using mobile phones may benefit from the Cooperate Social Responsibilities (CSR) of available network providers to support health systems.

Referring to the research hypothesis that previously proposed and correlating them with the results from the study we may conclude that our formulated research hypothesis stating that ADR reporting may be promoted by stimulating early reporting using more friendly tools in addition to yellow forms and enhancing participation of the people and health care providers was therefore strongly confirmed. The mobile phone ADR self-reporting system is significant compared yellow card ADR reporting system.

Recommendations

To achieve our goals, as the country is advancing rapidly in the technology system, and from the results of this study, we recommend:

To the government of Rwanda to set up a center in charge of the management of adverse drug reaction where the phone calls will be received 24 hours a day.

To the Ministry of Health to elaborate policy that regulates the use of the mobile phone as a new reporting system in adverse drug reactions and facilitate Pharmacists at the hospital level to access the information so that the help may assist patients as early as possible.

To agencies such as MTN, TIGO, to avail toll-free- call service to facilitate every patient experiencing adverse drug reactions to report on time to avoid reasons that can hinder the reporting system.

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ANNEXES

Annex 1: RESEARCH PARTICIPANT INFORMED CONSENT FORM

Research topic: USE OF MOBILE PHONES FOR ASSURING REPORTING OF ADVERSE DRUG EVENTS IN RWANDA

Researcher: Ruth Nyiranteziryayo

Address: Student at the University of Rwanda, College of Medicine and Health Sciences
School of Medicine and Pharmacy, Rwanda country

As a student who is about to finish my postgraduate studies at the University of Rwanda, College of Medicine and Health Sciences, I am conducting a study survey on "USE OF MOBILE PHONES FOR ASSURING REPORTING OF ADVERSE DRUG EVENTS IN RWANDA."

The main objective of this study is to investigate reports of Adverse Drug Reaction (ADR) following the use of drugs from hospitals and the effect of mobile phones for reporting drug reactions and detection of drug interactions.

The information in this document is meant to help you decide whether or not to take part in this study once you agree to participate, please feel free to ask if you have any questions or concern at any time during the conduct of the research

The study concerns asking questions on mobile phone regarding the drug taken from the hospital pharmacy after its use. I expect that your participation in the study presents no risk to you and there will be no direct benefit to you and any form of compensation, monetary or otherwise for participating in the study. There will be no cost to the participant, but the time as a result of taking part in this survey.

The information you give during the conduct of this research will be kept confidential.

Having understood all the information about this study, I, therefore, agree to my participation in this study by appending my signature.

Research Participant

Number: **Signature:**

Date: Tel number

ANNEX 2: PATIENT'S USE OF MOBILE PHONE FORM FOR REPORTING ADVERSE DRUG REACTIONS: A PILOT STUDY IN RWANDA

Participant Name:

Tel:

Name of data collector:

Table 7. Participant information and medical history.

Gender: Male or Female	Age (Years):
District:	Hospital name:
Sector:	Cell:
Are you responding to the phone at any time? Y or N	
If no, When can you be found to respond to the call?	Answer:
Kind of drugs given	Answer:

Note:

Y= Yes

N= No

2. ASSESSMENT INFORMATION FROM THE CALL DURING OR AFTER USE OF DRUG:

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