Deanship of Graduate Studies

Al-Quds University

Cost Benefit Analysis of Clinical Pharmacist Interventions in MICU: Prospective Interventional Study

Asil K.M. Houso

M.Sc. Thesis

Jerusalem – Palestine

2021/١٤٤٣

Cost Benefit Analysis of Clinical Pharmacist Interventions in MICU: Prospective Interventional Study

Prepared by:

Asil K.M. Houso

B.SC: PharmD (Doctor of Pharmacy) from The University of Jordan - Amman

Supervisor: Prof. Dr. Motasem Hamdan

A thesis submitted in partial fulfillment of requirement for the degree of Master of Policies and Health Management/ Faculty of Public Health/ Al-Quds University

2021/١٤٤٣

Al-Quds University

Deanship of Graduate Studies

Master in Health Policy and Management/ Faculty of Public Health

Thesis Approval

Cost Benefit Analysis of Clinical Pharmacist Interventions in MICU: Prospective interventional study

Prepared by: Asil K.M. Houso

Registration No.:21810013

Supervisor: Prof. Dr. Motasem Hamdan

Master thesis submitted and accepted, Date: 16 / 08 /2021

The name and signature of the examining committee members are as follows:

1) Head of Committee: Prof. Dr. Motasem Hamdan Signature:

2) Internal examiner: Dr. rer. med. Ahmad Amro Signature:

3) External examiner: Dr Mohamad Khleif Signature:

Jerusalem – Palestine

2021 - ١٤٤٣

Dedication

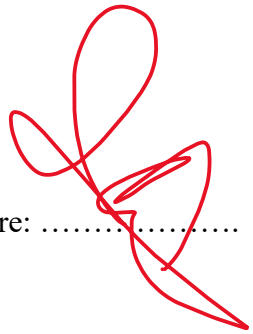
This thesis is dedicated to the memory of my father Dr. Khalid Houso and to my dear mother Sanaa Khraim who have always believed in me and instilled in me the love of learning from an early age and have relentlessly encouraged me to strive for my dreams.

My humble effort I dedicate to my sweet and loving husband Hussam whose affection, love and encouragement make me able to get such success and honor.

Declaration

I certify that this thesis submitted for the degree of Master in Public Health is the result of my own research, except where otherwise acknowledged, and this (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signature: ……



Asil k. M. Houso.

Date: 18/8/2021

Acknowledgment

I would like to take this opportunity to extend my deepest appreciation to all those who have been an integral part of my thesis work for the last year. In particular, I would like to thank my supervisor, Prof. Dr. Motasem Hamdan, for his continuous support, encouragement and guidance throughout the preparation and writing of this thesis.

In addition, special thanks to the Palestinian ministry of Health. And the faculty of public health; Al-Quds University with its entire staff especially Dr. Asma Imam, and. Dr. Nuha El Sharif.

My special thanks to the clinical pharmacist participated in our study Hiba Falaneh.

I wish to express my gratitude to ***Dr. Ahmad Bitawi***; *Head of the PMC for facilitating this study and use of their database* and his colleagues in Ramallah Hospital`s ICU for their help; support and hospitality during data collection phase especially the following physicians;

1. Dr. Mwafaq Naseef,
2. Dr. Hussam Abu Tareef,
3. Dr. Mohammed Jaradat,
4. Dr. Adnan Wahdan.

Lastly, I would like to thank my family and friends for their support throughout the preparation and writing of this thesis.

Abstract

Background: Clinical pharmacy services in the critical care settings have expanded dramatically, they transitioned from dispensing to proactive interventions that yield positive clinical, humanistic and economic impact on patient care and health care institutions.

Study problem and justification: Clinical pharmacy services have limited implementation in Palestine. Many intensive care units (ICUs) patients do not get the intended beneficial effects of their treatment due to administration of unnecessary medication and the consequent huge cost burden. These can be reduced by CP interventions within the national context, which needs to be evaluated.

Aim: To evaluate the impact of the clinical pharmacist interventions on costs of care and safety of patient by assessing treatment related problems among medical intensive care units` patients in Palestine.

Methodology: A prospective interventional study at medical ICU of the major public hospital in Ramallah district was conducted over a 4-month period (between September and December 2020). Patients were randomly assigned to either an intervention (with clinical pharmacist involvement) or a control group (without cp involvement). Treatment related problems were identified in both study groups by the clinical pharmacist, but interventions were only provided to the intervention group. The total economic benefit included both cost savings from intervention and cost avoidance from preventable adverse drug events (ADEs) resulted from CP interventions. The primary outcomes with the clinical pharmacist interventions were net benefit and benefit to cost ratio , which were calculated using previously published methodologies and adjusted to the Palestinian settings . The analysis of CP interventions acceptance by physicians was performed.

Results: During the 4-month study period, the 117 patients admitted to the ICU were included into the analysis; 66 patients in the intervention group and 51 in the control group. The interventions made by a clinical pharmacist resulted in direct cost saving of NIS16,195.32 and cost avoidance of NIS22,087.5. Translated into a net savings of NIS232 per intervention and NIS580 per patient. Comparison of benefits (NIS38,282.82) and costs (NIS19,877.65) indicate a net economic benefit to the institution of (NIS 18,405.17) and a benefit cost ratio of 1.93.

Conclusion: This prospective interventional study documented the significant role of a clinical pharmacist in a multidisciplinary ICU team. Despite using a conservative approach, integrating a clinical pharmacist in the ICU team was investment that resulted in cost saving and cost avoidance. With further formalizing clinical pharmacy services at hospitals and integrating the clinical pharmacist as a part of the critical care team, an even higher economic benefit is anticipated

Table of contents

Dedication	VI
Declaration	VIVI
Acknowledgment	VI
Abstract	VI
List of abbreviations	VI
Definitions	VIVI
Thesis chapters	VI

Chapter One: Introduction

1.1 Background	1
1.2 Problem statement	2
1.3 Justification	3
1.4 Aim	5
1.4.1 Significance of the study	5
1.5 objectives	5
1.6 Hypothesis	5

Chapter Two: Review of Literature

2.1 Role of clinical pharmacist	7
2.2 Competencies	8
2.3 Clinical pharmacy services nationally and internationally	9
2.4 Impact of clinical pharmacy services	11
2.4.1 Humanistic impact:	11
2.4.2 Clinical impact	11
2.4.3 Economic impact	13
2.5 Cost analysis	15

2.6 Physician acceptance of clinical pharmacist interventions 17

Chapter Three: Conceptual framework

3.1 Theoretical definitions: 19
3.2 Conceptual framework 20

Chapter Four: Methodology

4.1 Methods and design 24
4.1.1 Clinical pharmacy service / clinical pharmacist patient care process 24
4.2 Setting of the study 26
4.3 Study population 26
4.4 Inclusion and exclusion criteria 26
4.5 Sample size 27
4.6 Sampling method 27
4.7 Data collection 27
4.7.1 Study tools 28
4.8 Economic analysis 29
4.9 Statistical analysis 35
4.10 Sensitivity analysis 35
4.10.1 One- and two-way sensitivity analysis 35
4.10.2 Scenario analysis 35
4.11 Ethical consideration/ permissions 36

Chapter Five: Results

5.1 Patient characteristics 37
5.2 Treatment related problems 38
5.3 Types of clinical pharmacist interventions 39
5.4 Physician decision 41
5.5 Cost analysis results 43
5.6 Sensitivity analysis results 50

5.6.1 One-way sensitivity analysis results 50
5.6.2 Two-way sensitivity analysis 52
5.6.3 Scenario analysis results 53

Chapter Six: Discussion

6.1 Discussion 56
6.2 Limitations 61
6.4 Conclusion 62
6.5 Recommendation 62
6.5.1 Recommendation to policy and decision makers 62
6.5.2 Future research recommendations 63

References 64

Annexes 75

Abstract (Arabic) 96

Table of Figures

Fig 5.1: The BCR curve with the cost of prolonged hospital LOS due to ADE 52

Table of Flowcharts

Flowchart 3.1: Conceptual framework 23
Flowchart 5.1: study results 49

Table of Boxes

Box 4.1: An example on Cost savings calculations. 31
Box 4.2: Cost avoidance calculations 33

List of Tables

Table 4.1: Cost savings formula for calculations 30

Table 4.2 Nesbit method for calculating cost avoidance 32

Table 4.3: summary table for formulas used in cost benefit analysis model 34

Table 5.1: characteristics of patients who were admitted to ICU for medical services 38

Table 5.2 frequency and percentage of TRPs in both groups 39

Table 5.3: categories of clinical pharmacist assessments/ interventions by the treating ICU team in the intervention group. 40

Table 5.4: Drugs groups involved of Accepted clinical pharmacist interventions by the ICU team in the intervention group 41

Table 5.5: Physician acceptance rate of clinical pharmacist interventions in the intervention group 42

Table 5.6: accepted clinical pharmacist interventions per patient in the intervention group 42

Table 5.7: cost analysis results 43

Table 5.8: Direct cost savings results in both groups 44

Table 5.9: Cost avoidance analysis results 45

Table 5.10: TRPs categories in the intervention group according to Nesbit score 46

Table 5.11: cost avoidance analysis per TRP category in the Intervention group 47

Table 5.12: Cost benefit outcome analysis 48

Table 5.13: One-way Sensitivity analysis input variables and uncertainty distributions of cp salary 51

Table 5.14: One-Way Sensitivity analysis- input variables and uncertainty distributions of cost of extended length of hospital stay due to ADE 51

Table 5.15: Two-way sensitivity analysis- input variables and uncertainty distributions 53

Table 5.16. Show cost avoidance analysis in the control group 54

Table 5.17: Scenario analysis calculations 55

List of Appendices

Annex 1: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome	75
Annex 2: Basic model of evaluation of clinical pharmacy services	85
Annex 3: Consult Note	86
Annex 4: Ethical Approval to conduct the study	88
Annex 5: MoH approval to lunch the study	89
Annex 6: Consent form	90
Annex 7: Examples on cases with high and medium pADE Nesbit score	91
Annex 8: Case from control group	92
Annex 9: Case from intervention group	94

List of Abbreviation

ADE	Adverse drug event
ADR	Adverse drug reaction
APACHE	Acute Physiology and Chronic Health Evaluation
BCR	Benefit cost ratio
CA	Cost avoidance
CP	Clinical pharmacist
CPS	Clinical pharmacy sercice
CS	Cost saving
ICU	Intensive care unit
MICU	Medical Intensive care unit
NC	Negative cost
PharmD	Doctor of pharmacy
PT	Patient
TRP	Treatment related problem
UAE	United Arab Emirates
UK	United Kingdom

Definitions

Adverse drug event (ADE) is “an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy).” (Morimoto et. al, 2004)

Clinical pharmacy is “a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention” (American Collage of Clinical Pharmacy (ACCP), 2008)

Clinical pharmacists are ”licensed practitioners with advanced education and training who practice in all types of patient care settings with a focus on comprehensive medication management” (Jacobi, 2016)

Comprehensive medication management (CMM) is “the standard of care that ensures each patient’s medications are individually assessed to determine that each medication is appropriate for the patient, effective for the medical condition, safe given the comorbidities and other medications being taken, and able to be taken by the patient as intended. CMM includes an individualized care plan that achieves the intended goals of therapy with appropriate follow-up to determine actual patient outcomes. This all occurs because the patient understands, agrees with, and actively participates in the treatment regimen, thus optimizing each patient’s medication experience and clinical outcomes”.(American College of Clinical Pharmacy, 2012)

Dose adjustment*:* Adjusting doses for patients with renal or hepatic impairment, elderly patients, or those receiving inappropriate doses according to the indication (Fahimi, 2010).

Thesis chapters

This thesis is presented in six chapters as follows:

Chapter One: Contains the background of the study, problem statement, study justification, study aim and objectives.

Chapter Two: Includes related data (literature review) of a conducted international, regional and in country studies and researches

Chapter Three: Includes the study conceptual framework.

Chapter Four: Includes the study area, study methods, population, sampling, and sample size, ethical consideration will also include data collection, processing and analyzing.

Chapter Five: Presents the results.

Chapter Six: Includes discussion and recommendations.

Chapter One: Introduction

1.1 Background

Clinical pharmacy services in critical care settings have improved the last decade (ACCP, 2008). Clinical pharmacist activities transitioned from traditional dispensing of medications to proactive interference that ensures the rational and cost-effective use of medicines; promoting the patient safety and quality of care. This proactive patient-centered model of practice necessitates the presence of a clinical pharmacist as a member of multidisciplinary intensive care unit team (SCCM-ACCP, 2000). In the UK national care standards for ICUs; there must be a critical care pharmacist for every critical care unit (Intensive Care Society, 2013).

Critically ill patients who are often older with multiple co-morbidities are at high risk for the occurrence of adverse drug events (ADEs) due to change in organs functions, alterations in pharmacokinetics and polypharmacy, the complexity of this process involving constantly changing doses which contributes to medication errors and adverse drug events (Fuchs et al., 2012; Kane-Gill et al., 2012).

Clinical Pharmacists are permitted to practice collaboratively and formally with physicians in their practice area (Jacobi, 2016); they have the requisite therapeutic knowledge,

experience and judgment to practice in all types of patient care settings with focus on "comprehensive medication management" for the purpose of ensuring optimal patient outcome (American Collage of Clinical Pharmacy (ACCP), 2008) which has the potential to provide additional economic benefit to healthcare institutions.

Clinical pharmacy services are still primitive in Palestine. Only 7 (9%) doctors of pharmacy (PharmDs) working in public hospitals, while 5 (3.6%) PharmDs work in PHC settings (Ministry of Health, 2019). Their pharmaceutical services are delivered from centralized locations which limits opportunities for direct interaction between healthcare providers (Bell et al., 2009; Khdour et al., 2013). Implementing clinical pharmacy services will necessitate collaboration between the Ministry of Health, Physician Association, General Directorate of Pharmacy the Palestinian Pharmaceutical Association, Pharmacy schools in Palestine and other international bodies.

1.2 Problem statement

Securing the funds for initiating clinical pharmacy services in intensive care units (ICUs) is considered an obstacle in Palestine. The current economic crisis has had a negative impact on the financial performance of the healthcare system. As a result, clinical pharmacy services are confined to a small number of clinical pharmacists employed in hospitals (According to the Ministry of Health's 2020 report, only 7 (9%) PharmDs work in public hospitals with heavy workloads and from centralized locations, which result in limited time for providing clinical pharmacy services and limited opportunities for direct interaction between healthcare providers (Khdour et al., 2013; MoH, 2020). Therefore, many patients especially the highest risk (ICU) patients do not receive the desired beneficial effects of their treatment due to treatment related problems that cause both unnecessary suffering and huge costs to society (AbuRuz et al., 2011; Kane-Gill et al., 2012; Kaushal et al., 2007; Rottenkolber et al., 2012.). Thus, there is an urgent need to justify the clinical pharmacy service in ICUs to bring out evidence that such service produces a real 'return on investment' in our hospitals and consequently on patients care.

1.3 Justification

Intensive care unit settings are considered risky; of which adverse drug events (ADEs) are associated with additional treatment needs, extended hospital stays, morbidity and mortality and dispensing unnecessary medications (Michalets et al., 2015). They are also costly due to the combination of population aging, technological advancements, medication errors and increased spending on medicines yearly (Hughes, 2010).

In 2020, cardiovascular disease and Diabetes Miletus were of the main causes of mortality in Palestine, accounting for 24.7% and 14.6% of all deaths, respectively (MoH, 2020). The prevalence of mistakes in cardiovascular medicines can be linked to the increasing quantity and complexity of choices in this therapeutic class (Siddarama et al., 2018). Collaboration between clinical pharmacists and physicians throughout the ordering process can both reduce adverse outcomes and aid in the detection of errors.

Patients requiring intensive care cost between (17.4–39%) of total hospital costs and (5.2–11.2 %) of total USA healthcare spending (Coopersmith et al., 2012). ICU medication costs accounted for 31% of the total hospital drug costs and 18% of the total costs in 2012 in the United States (Altawalbeh et al., 2018). Palestinian MoH allocates a significant portion of its resources to medicine, medical consumables and laboratory materials accounting for 18.4% (NIS 385,218,085) of the total ministry of health expenditure (Ministry of Health, 2019). Inpatient costs contributed about 75% of all costs of public hospitals and primary healthcare centers in Palestine (Younis et al., 2013).

The health-care system, as it is now organized, cannot bear the burden of these costs permanently. Because of the mismatch between rising demand for medications, particularly among the elderly, as well as the rising cost of medications and diminishing resources to

deliver excellent health care and current financial crisis highlight the significance of clinical pharmacy services that must be involved in all medical teams to offer efficient treatment.

The present economic crisis in Palestine has had a significant influence on the healthcare system's financial performance. In order to lower expenses, a range of staff and supplier cost savings strategies have been undertaken. Clinical pharmacy staff have been a main target for such savings due to their relatively high salaries. As a result, clinical pharmacy services are confined to a small number of clinical pharmacists employed in hospitals with heavy workloads, which result in limited time for providing clinical pharmacy services with reasonable quality (Khdour et al., 2013).

Many studies have evaluated the role of the clinical pharmacists in ICU and their positive clinical and economic impact (Jurado & Steelman, 2013; Kopp et al., 2007; Leache et al., 2019; Lee et al., 2020; Leguelinel-Blache et al., 2018; MacLaren et al., 2008; Michalets et al., 2015). Their interventions within multidisciplinary ICU team have significant reduction in the duration of stay in the ICU and ADEs resulting in an overall cost reductions (Gallagher et al., 2014; Leape et al., 1999; Kearney et al., 2018; Rottenkolber et al., 2012; Yasunaga et al., 2016).

Clinical pharmacists participating in medical rounds at Massachusetts General Hospital, a large tertiary care hospital in Boston reduce preventable ADEs by 66% (Leape et al., 1999). On average, a single adverse event in the medical intensive care unit (MICU) and coronary care unit (CCU) of Brigham and Women's Hospital, a large academic hospital in Boston has been reported to cost nearly $4000 (equates $5,241.50 in 2021) and to be associated with an increased ICU stay length of one day (Kaushal et al., 2007).

Despite widespread support from professional organizations, clinical pharmacy service adoption in ICU has been far less than 100 % since the first report of clinical pharmacist interventions in critical care (Miyagawa CI, 1986).

1.4 Study aim

To evaluate the cost benefit of clinical pharmacist interventions in assessing treatment related problems among medical intensive care unit patients in Ramallah Son Wings Hospital.

1.4.1 Significance of the study:

- Improve quality of patient care provided through optimization of patient medications.
- Decrease burden of suffering and cost on patients and healthcare institutions by resolving TRPs.
- Employment of clinical pharmacists.
- Resources allocations; Utilize costs that generated from clinical pharmacist interventions to be used elsewhere in the health system.

1.5 Objectives:

1. To determine the quantity and type of clinical pharmacist interventions in medical intensive care unit patients.
2. To measure the physician acceptance rate of clinical pharmacist interventions.
3. To investigate clinical pharmacist generated - cost savings.
4. To quantify cost avoidance of the accepted clinical pharmacist interventions.

1.6 Hypothesis

The study key hypothesis is that integrating a clinical pharmacist to be part of a multidisciplinary medical intensive care unit team reduces the overall ICU patients` treatment costs.

Chapter Two: Literature review

In this chapter, literature related to the economic impact of clinical pharmacist interventions in ICU will be presented. Annex 1 summarizes all relevant literatures related to economic impact of clinical pharmacist interventions in medical ICU settings.

2.1 Role of clinical pharmacist

Clinical pharmacy practice has steadily expanded. During the 1980s, pharmacy services were expanded to various ICU settings (both adult and pediatric), the operating room, and the emergency department. Clinical Pharmacists developed clinical practice such as therapeutic medication monitoring, dietary counseling, and patient care rounds participation (SCCM-ACCP, 2000). In 1999, the clinical staff pharmacists (CSPs) practice model was implemented in hematology–oncology, medical–surgical intensive care, and general medicine (Nesbit et al., 2001a).

Clinical pharmacists are regarded as the primary source of scientifically valid information and advice on medication safety, appropriateness and cost-effectiveness. As well as a

foundational understanding of the disease states, pharmaceutical, socio-behavioral, and clinical sciences (American Collage of Clinical Pharmacy, 2008) through the application of evidence-based therapeutic guidelines, evolving sciences, emerging technologies, and relevant legal, ethical, social, cultural, economic, and professional principles to achieve desired therapeutic goals through a formal process, or informally as a member of a rounding, multidisciplinary health care (Preslaski et al., 2013; Royal Pharmaceutical Society, 2013).

The clinical pharmacist's role and responsibilities include therapeutic drug monitoring (TDM), rational drug use, medication outcomes, comparative effectiveness, pharmacoepidemiology, medication therapy management, hematology, oncology, pharmacogenomics, Pharmacoeconomics, pharmacokinetics, pharmacodynamics, and transitions-of-care services. Clinical pharmacy services are not confined to a single medical discipline, but rather apply to all medical sectors, including cardiology, infectious disease, ambulatory care, oncology, nephrology, internal medicine, surgery, and intensive care units (ICUs). It also includes both in-patient and out-patient care.(Saseen et al., 2017).

2.2 Competencies

A clinical pharmacist is eligible for licensure in the United States (US) after completing 6 years of education and earning a Doctor of Pharmacy degree (PharmD) (Jacobi, 2016), as well as in the Arab world and Palestine.

Since 2006, An-Najah and Birzait Universities grant the PharmD degree after completing 198 credit hours, which includes 48 weeks of clinical training in various medical specialties such as pediatrics, internal medicine, and surgery. (Faculty of Medicine and Health Science, 2006; Faculty of Nursing Pharmacy and Health Professions, n.d.; Hamouda et al., 2015). An-Najah University also provides a postgraduate master of science (MSc) degree in clinical pharmacy since 2003 (Sweileh et al., 2009).

Clinical pharmacy generalists are practitioners with one year of postgraduate training (PGY1) or equivalent experience. Clinical pharmacy specialists often have postgraduate year one (PGY1) and two (PGY2) residency training and provide direct patient care to specialized/complex patient populations (American Society of Health-System Pharmacist, 2012). These residency programs, however, are not yet offered in the Middle East nor in Palestine.

The six essential elements required for clinical pharmacists to offer CMM in patient-centered, team-based settings are direct patient care, pharmacological expertise, systems-based care, population health, communication, professionalism, and ongoing professional development. It is critical to have the credentials and skills needed to provide clinical pharmacy services in the ICU, which can be gained through graduate degrees, residencies, fellowships, or other specialized practice experiences (Saseen et al., 2017).

2.3 Clinical pharmacy services nationally and internationally

Clinical pharmacists may practice under the terms of a formal collaborative practice agreement with physicians in their practice area or as authorized by the hospital (American Society of Health-System Pharmacist, 2012). Most work as part of a multidisciplinary team for acute care or ambulatory care populations, while others have their own practice (Horn & Jacobi, 2006).

Clinical pharmacy services were not provided by the majority of hospital pharmacies in Europe for many years. The level of CP service provided varied between hospitals and the evolution of CP throughout Europe has been more varied, despite its expansion. For example, in January 2016, the UK issued its most recent policy report on hospital CP (Europian Association of Hospital Pharmacy, 2010; Lord Carter of Coles, 2016; Onatade et al., 2018).

The practice of clinical pharmacy in Egypt, Kuwait, and Qatar is concentrated on distributing and selling pharmaceuticals, clinical pharmacy services are very limited (Kheir et al., 2013).

In Jordan, The University of Jordan (JU) and Jordan University of Science and Technology (JUST) offer a Doctor of Pharmacy (PharmD) degree and a Master of Science (M.Sc) degree in clinical pharmacy program. JU PharmD program was granted by the Certification Council for Pharmacy Education (ACPE) accreditation in 2016 which indicates that the PharmD program offered by the School are designed and implemented in accordance with international standards (the University of Jordan, 2016). However, its implementation is limited to some governmental and private hospitals, and fewer community pharmacy outlets (Kheir et al., 2013). Similarly, in Lebanon, the Lebanese American University (LAU)`s PharmD degree program received (ACPE) accreditation in 2002 (School of Pharmacy, 2002). Gulf Medical University was the UAE's first internationally approved entry-level PharmD program, by ACPE Certification in 2019 (Collage of Pharmacy, 2019). Despite this, the implementation of PharmD program is still limited in those countries. In comparison, all pharmacy programs in Palestine have only local certification (Sweileh et al., 2016). Palestinian universities particularly, An-Najah University and Birzait University, must actively pursue accreditation of their PharmD programs by (ACPE).

In Palestine, A job description for PharmD was prepared in February 2016, and only three PharmDs were employed in 3 hospitals in West Bank. The early stages of involving clinical pharmacists faced some opposition from other healthcare providers, but the medical team soon started to favor the pharmacists' involvement in patient care services. However, clinical pharmacy services are still primitive, with only 7 PharmDs are working in public hospitals providing pharmaceutical services from centralized location (MoH, 2020). One of them is working clinically in direct contact with patient within multidisciplinary team (H.Falaneh, personal communication, Mars 2020). For this reason, clinical pharmacists are facing serious employment problems, many of clinical pharmacists graduates are either leaving the nation to work in other countries (particularly in the more affluent Gulf countries or in America) or working as medical representatives for pharmaceutical corporations and high percentage of them remain unemployed (Hamouda et al., 2015).

2.4 Impact of clinical pharmacy services

Several clinical pharmacy-based services have not only resulted in improved clinical outcomes (improved prescribing quality, reduced medication numbers, drug-related problem resolution, therapeutic goal attainment in specific conditions), but also humanistic (patient knowledge of their medicines, adherence) and economic outcomes (cost savings and cost avoidance). the following are examples on these impacts with focus on economic one:

2.4.1 Humanistic impact:

Patient satisfaction and health-related quality of life are the two most important humanistic outcomes studied. Limited or mixed evidence of the impact of clinical pharmacist interventions on quality of life in older persons has been found by researchers (Spinewine et al., 2012).

2.4.2 Clinical impact:

Many studies assessing the impact of clinical pharmacy services in the hospital settings suggested that CP interventions have a positive effect on patient-relevant outcomes such as shortened length of hospital stay, reduced number of adverse drug events and drug-related readmissions (Graabæk & Kjeldsen, 2013; Klopotowska et al., 2010; MacLaren et al., 2008; Ravn-Nielsen et al., 2018; Skjøt-Arkil et al., 2018).

The clinical pharmacist's specialized knowledge and skills complement the experience of physicians and other team members (Hamblin et al., 2012). Interaction with the team during rounds, interviewing patients, adjusting medication, patient education, and follow-up all

resulted in better outcomes. The presence of cp has been found to help the most vulnerable patients, such as the elderly (Gallagher, McCarthy, et al., 2014). Kaboli and colleagues found that clinical pharmacists practicing in the inpatient setting improved the quality, safety and efficiency of care with no evidence of harm (Kaboli et al., 2006).

Drug-related problems are defined as" events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes". Underlying causes can be related to the selection of a drug, drug form or dose, treatment duration, the logistics of the prescribing and dispensing process, drug administration, patient behavior or outcome monitoring (PCNE, 2019). These errors can be reduced through identifying DRPs and assess them by the CP involvement. A 6-month prospective study was conducted in two internal medicine wards by two clinical pharmacists on two internal medicine wards at the University Hospital in Geneva. The author found an average of 2.7 DRPs per patient (Guignard et al., 2015). Similar results were found in a retrospective analysis of DRPs and subsequent pharmacist interventions that were identified and implemented during interdisciplinary ward rounds in internal medicine at the University Hospital Basel, Switzerland between 2015 and 2017 (Reinau et al., 2019). In 2017, a 4-month prospective observational and interventional study was conducted to assess the prevalence of DRP among patients hospitalized at the surgical ward in Jimma University Medical Center in Ethiopia, identified an average of 1.97 DRPs per patient which was independently predicted by the presence of polypharmacy and > 20 days of hospital stay (Tefera et al., 2020).

Nonadherence to medication especially in chronic diseases leads to worse therapeutic outcomes, higher hospitalization rates, and increased health care costs these can be minimized through clinical pharmacist patient education and counseling (Morgan, 2011). A cross sectional study was conducted between June 2013 and January 2014 among Palestinian geriatrics over the age of 60 discovered that Palestinian geriatrics with chronic disease are more likely to adhere to their prescriptions. According to the study, a better awareness of socio-demographic variables has a demonstrable effect on the degree of knowledge and adherence to drugs (Najjar et al., 2015).

The disease-state specific medication therapy management programs have shown a reduction in frequency of some medication-related problems, A randomized controlled clinical trial research done at Jordan University Hospital's Family Medicine Clinic discovered that a collaborative physician-pharmacist approach to uncontrolled hypertension increased the rate of BP control in hypertensive patients (Albsoul-Younes et al., 2011). According to an Austrian research, clinical pharmacy services in a nephrology ward have also been found to be useful in the treatment of patients with acute or chronic kidney failure, patients receiving various renal replacement therapy, and patients following kidney transplantation (Stemer & Lemmens-Gruber, 2011). A 18-month prospective, cross-sectional study was conducted in October 2011 at 23-bed nephrology ward of an academic referral hospital in Tehran; found that clinical pharmacist interventions assisted in the detection of drug-related issues and the avoidance of prescription mistakes in patients with end-stage renal illness (Gharekhani et al., 2014).

2.4.3 Economic impact:

Clinical pharmacist services are essential in ICUs as described in guidelines and position statements (Intensive Care Society, 2013; SCCM-ACCP, 2000). One of the measurable outcomes of these services is the expected reduction in overall health care costs.

Cost savings interventions frequently involve discontinuing unnecessary medical therapy, substituting more cost-effective drugs, or changing the route of administration (Hamblin et al., 2012). Previous research, however, has shown that cost saving measures, such as avoiding ADEs have the best cost-benefit ratio (Anderson & Schumock, 2009).

ADEs can lead to extending hospital stays, as well as serious harm or death (Forster et al., 2008; Roque et al., 2016). A retrospective study in the ICU of University Medical Center (UMC)in Tucson, Arizona, found that CP who rounded with a critical care team more effectively identified and prevented more adverse drug events than pharmacists involved in order entry and verification, and avoided the potential expenditure of over $210,000 in 4.5

months (equates $281,875.74 in 2021) (Kopp et al., 2007). On-ward participation of clinical pharmacist in a Dutch ICU was associated with significant reductions in preventable ADEs and increase in savings of €26 (equates $34.71 in 2021) to €40 (equates $53.4 in 2021) per intervention (Klopotowska et al., 2010).

Clinical pharmacy services have been demonstrated also in a systemic review of economic studies to be advantageous in a variety of patient care settings. (Gallagher, McCarthy, et al., 2014). Another systematic review was conducted to feature economic evaluations of clinical pharmacy services found that CP services were generally considered cost-effective or provided a good benefit-cost ratio. Benefit-cost ratios from three studies ranged from 1.05:1 to 25.95:1 (Touchette et al., 2014).

In the literatures, the economic impact is stated in terms of cost savings and cost avoidance. Various cost analysis models were employed in economic assessment studies; some utilized CEA, CBA, and others evaluated medication usage and expenditures before and after cp involvement.

Examples on economic evaluation of CP interventions using CBA model; a one-year retrospective study at Cork University Hospital (CUH) and Cork University Maternity Hospital in the Republic of Ireland's southern area in 2012, found that a group of CPs saved a total of $708,221 in costs as compared to the input costs of $81,942. As a result, the net cost benefit was $626,279, with an 8.64:1 cost benefit ratio (Gallagher, Byrne, et al., 2014). Also, in 2012, a retrospective study in Taiwan compared the number of CP interventions 1 year before and after a clinical pharmacist involvement in a nephrology ward. The benefit/cost ratio increased from 4.29 to 9.36, after the on-ward deployment of a CP (Chen et al., 2017). A quality improvement study was performed in the adult ICUs of the Haga Teaching Hospital (GTH) from July to December 2008 and the ICU of the Erasmus University Medical Centre (UH) from July to September 2011 in the Netherlands, found a net cost benefit of €119 ($139.49) (GTH) and €136 ($159.42) (UH) per accepted intervention (Bosma et al., 2018).

To emphasize the association between clinical pharmacist intervention and cost savings; another two studies were conducted in medical ICUs using the same validated framework for cost of ADE by Hammond and colleagues. The first one; A prospective observational study at an urban, tertiary care, academic medical center in US with one clinical pharmacist over 12 months, the clinical pharmacist-generated cost avoidance of $3,270,178 and the benefit-cost ratio of 24.5:1 (Hammond, Flowers, et al., 2019). The second one; an observational prospective multicenter study with 302 ICU pharmacists at 91 centers over 4-week estimated total cost avoidance $24,352,176, average cost avoidance was $406 per intervention, and $80,636 per pharmacist (Hammond, Adams, et al., 2019). Possible reasons for a considerably larger cost avoidance in those 2 studies compared with Bosma and colleagues research (Bosma et al., 2018) are the inclusiveness of types of interventions in addition to the higher cost price used for adverse drug event (ADE). However, these above-mentioned studies lack comparator control group.

Antibiotic consumption and hospital stay costs were analyzed in a prospective control trial that was conducted between July 2009 and April 2010 in two independent respiratory wards in China.; the authors found that cp interaction directly with the physicians at ward level led to the reduction in patients' length of hospital stay and health care cost (Shen et al., 2011). A quasi-experimental study implemented antibiotic stewardship program set in a Brazilian cardiology hospital, reported a significant reduction of 69% in hospital antibiotics costs. when a pharmacist was included as part of a multidisciplinary team (Magedanz et al., 2012). A retrospective observational study in Spain estimated a potential saving of €10,905 ($12,968.248) as a result of pharmacist interventions regarding antimicrobials in ICU over 5-month period (Leache et al., 2019).

2.5 Cost analysis

Cost analysis methods varied between literatures. Direct cost savings are calculated pretty consistently in literatures, however indirect costs (cost avoidance) are appraised variably depending on methodology.

To calculate the cost avoidance, many authors employed the Nesbit probability method in cost analysis especially in countries where cost of ADE is unknown (Al-Qudah et al., 2019; Bosma et al., 2018; Chen et al., 2017; Gallagher, Byrne, et al., 2014; Nesbit et al., 2001a). Other researchers in Japan estimated saving of interventions based on data from previous studies reporting cost of ADE (Yasunaga et al., 2016). In US some researchers used a previously published systematic framework for cost avoidance resulted from systemic review of literature conducted in emergency and ICU department in US (D. A. Hammond et al., 2019). The framework classified the clinical activities that may be performed by pharmacists in the ICU and ED into specific categories 6 pre-established categories and 38 category subgroups. Each provided cost avoidance amount represents the cost avoidance generated from a single intervention in the specific cost avoidance category. Many authors adopted this method (D. Hammond, Adams, et al., 2019; D. Hammond, Flowers, et al., 2019; D. Hammond et al., 2016; Rech et al., 2019). However, it may be not appropriate to our settings because medication costs and service costs differ greatly between US and Palestine.

Accurate ADE costs are rarely known, and previous research determined these costs using a broad range of methodological techniques. Authors who were unable to find the cost of an ADE in their healthcare system, assumed cost of ADE differently based on literatures very close to their settings. For example, Chen and colleagues assumed for each preventable ADE, it would result in a longer hospital stay by 2 days. The cost of a preventable ADE here was estimated to be $5000 for 1 day's admission (Chen et al., 2017). Other researchers (Bosma et al., 2018; Gallagher, Byrne, et al., 2014) used previously published ADE estimates taken from Rottenkolber and colleagues study which utilized a micro-costing approach based on data from German hospitals; cost of an ADE used in their base case scenario was €1057 ($1239) (Rottenkolber et al., 2012). In Jordan, Al-Qudah and colleagues calculated the cost of an ADE based on the assumption that an ADE in an outpatient will lead to a single admission to an internal medicine ward via an emergency department visit; An average internal medicine admission cost of JD522.5 (US $736.7) and a cost of JD 14.1

(US $19.9) per emergency visit (a total of JD536.6 [US $756.6] per case of admission via emergency) (Al-Qudah et al., 2019).

Clinical pharmacy is very slowly progressing in the developing countries. We found little studies from Arab countries reporting the economic impact of clinical pharmacist interventions in ICU patients. One before–after study implemented in Jordan, estimated the total clinical pharmacist-generated cost savings of JD149,946.80 ($211,574.9) which represents an average saving of 36% regarding antimicrobials and cardiovascular medication consumption over 10 month period (Aljbouri et al., 2013). A RCT in the general outpatients of the major hospital in Jordan; estimated the monthly cost of cp intervention of $1078, and the total monthly benefit $6444, leading to a benefit-to-cost ratio of 5.98.(Al-Qudah et al., 2019).

The impact of TRP have been investigated previously in inpatients (Fahimi, 2010; Spinewine et al., 2007), outpatients (Al-Qudah et al., 2019) and other clinical settings (Chen et al., 2017; Shen et al., 2011). However, many of these studies had methodological problems. We were not able to find any adequate study that reveled, in depth, economic impact associated with each specific type of TRPs in The Middle East.

2.6 Physician acceptance of clinical pharmacist interventions

Physicians acceptance of clinical pharmacist interventions is very important to implement these interventions and it can be predicted by variables of clinical pharmacists` education, experience, specialty, medication class and type of recommendations (Saadah et al., 2014).

Physicians` acceptance of the pharmacist interventions was 67.3% in the General Teaching Hospital and 61.8% in the University Hospital in Netherland (Bosma et al., 2018). In Jordan, AbuRuz and colleagues (AbuRuz et al., 2011) found that 91% of the cp recommendations were accepted by physicians.

Khdour and colleagues conducted a cross-sectional survey about physicians' attitudes, expectations, and interactions with pharmacists in West Bank; the author found approximately one-third of participated physicians did not expect pharmacists to be available for consultation during rounds and only 11.5% physicians agreed that pharmacists are willing to solve any drug-related problems (Khdour et al., 2013). A cross-sectional research was done in 2019 in Palestine to assess healthcare providers' (HCPs') acceptability level of clinical pharmacy program. The author found a 70% acceptance rate among HCPs (Naseef et al., 2020).

Chapter Three: Conceptual Framework

In this chapter the study major definitions, concepts, factors, and the study theoretical definitions and conceptual framework were presented.

3.1 Theoretical definitions:

A) clinical pharmacy practice model:

Clinical pharmacists practice includes gathering relevant health information about patients, assessing this information; at this stage, the cp will identify TRPs and ensure that each medication is individually assessed in terms of appropriateness, effectiveness, safety, and patient preference. This involves creating a personalized treatment plan to achieve the desired results followed by monitoring and evaluation (American College of Clinical Pharmacy, 2012).

B) Treatment-related problems (TRPs):

TRPs were defined as “any treatment related issue that may actually or potentially interferes with the optimum outcome for the patients” and were divided into drug related problems, patient related problems and miscellaneous problems (AbuRuz et al., 2006).

C) Economic evaluation using CBA model:

Economic outcomes are the core parameter in most evaluations that take the provider perspective. Most studies consider the impact of the service on health-resource use as the major economic outcome, and a reduction in the size of this impact provides justification for the service. While there are a variety of types of economic evaluations (e.g., cost–effectiveness analysis, cost–utility analysis and cost-minimization analysis), cost–benefit analysis (or net benefit) is the most useful related to study aim because it measures for inputs and outputs in terms of monetary values. This measurement allows for multiple different types of services to be comparatively evaluated (Schumock G et al., 2003).

3.2 Conceptual framework

In this study, the author adopted the basic model for an economic evaluation from hospital perspective driven from Schumock et al., (2003) work (Annex 2) to justify cp interventions in resolving treatment related problems collaboratively with the multidisciplinary medical intensive care unit team. The model identified the inputs (e.g., the costs of providing the service) and outputs (e.g., the clinical, humanistic or economic benefit rendered from the service). The comparator in the evaluation was the absence of clinical pharmacy services.

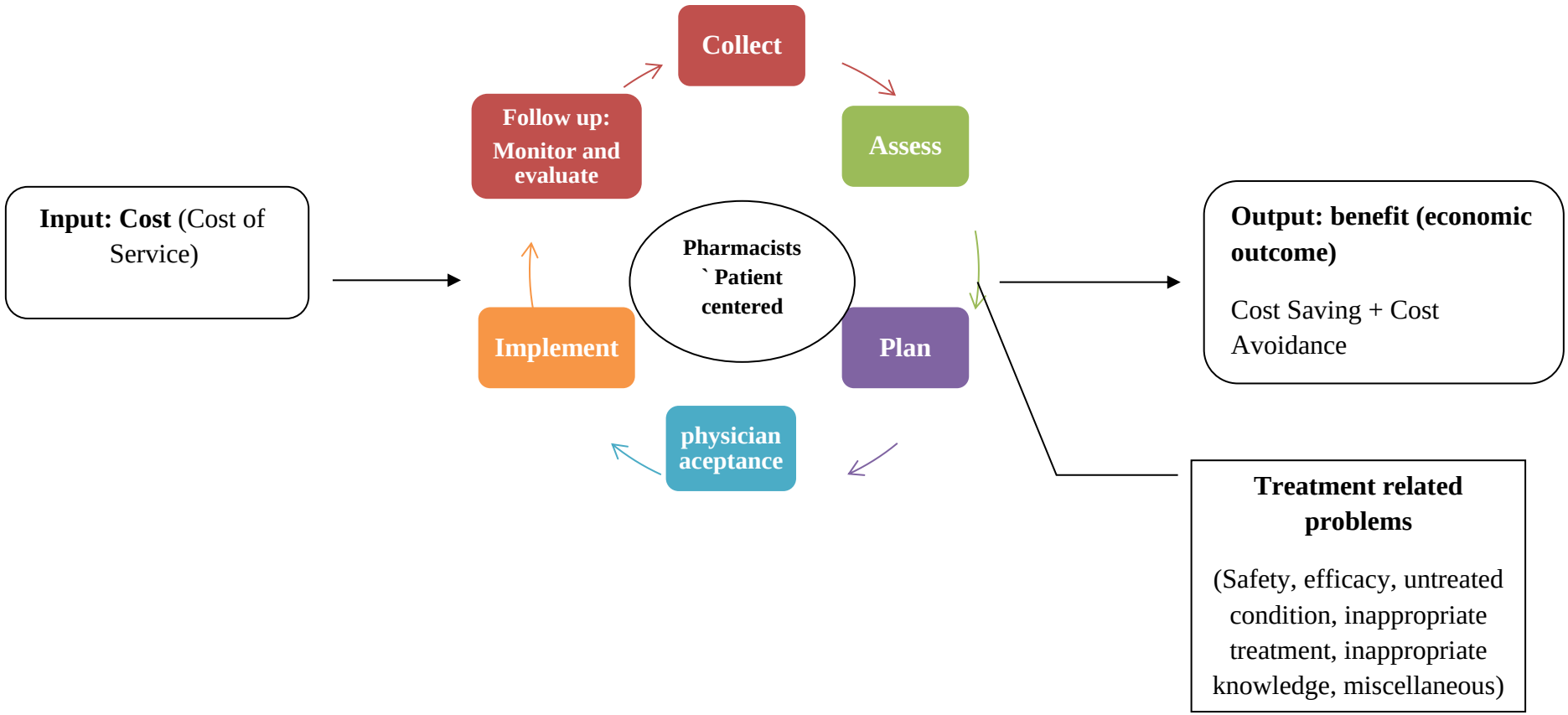
A common method of presenting these data was used; the benefit-to-cost ratio, describing the monetary return (benefit) for each dollar invested (cost) in the clinical pharmacy services. The ratio was, in turn, compared with the ratio calculated in similar literatures, thus providing the evidence for a justified decision. The operational definitions of our variables are as follow:

- **Input (Costs):** Salary of clinical pharmacist plus any increased cost of therapy in the intervention group; negative cost savings (Independent variable).
- **Program**: Clinical pharmacy service using comprehensive medication management approach in assessing and resolving TRPs. TRPs (independent variables) and their assessments categories are derived from AbuRuz and colleagues (AbuRuz et al., 2006, 2007) as following;

1. **Unnecessary drug therapy**: The patient is being given medication for no legitimate medical reason.
2. **Safety interventions**: A present drug is unsafe for the patient's condition, the patient is at high risk of experiencing ADR, allergic reaction, issues with the dosing regimen or interactions.
3. **Efficacy interventions**: A more effective medication is recommended, the patient requires combination therapy or a dose increase, dosage schedule or interactions issues.
4. **Untreated condition interventions** require pharmacological or non-pharmacological therapy.
5. **Inappropriate adherence interventions**: The patient does not follow the advice of health care specialists on his drugs, lifestyle, or non-pharmacological therapy.
6. **Inappropriate knowledge interventions:** The patient is not instructed or does not understand critical issues concerning his drugs, conditions, lifestyle, or/and non-pharmacological therapeutic recommendations.
7. **Miscellaneous interventions:** More regular monitoring is needed, extra diagnostic tests, consultation, the medications chosen are not cost efficient, patient was discharged too early or administration errors.
8. **Treatment related problem on discharge medications**: related to all problems mentioned above on discharge medications.

- **Output (Economic outcome/ Benefits):** including those resulting from clinical pharmacist interventions to resolve TRPs, cost saving **(dependent variable)** and cost avoidance from preventable adverse drug events **(dependent variable).**
- **Physician acceptance** of clinical pharmacist interventions which constituted an objective outcome **(moderator variable);** only accepted interventions were analyzed.
- **Comparator:** Absence of clinical pharmacy service (the control group).

Flowchart 3.1: Conceptual framework



Chapter Four: Methodology

This chapter covers study methodology, sampling, study tools, field work, data collection, data analysis, statistical analysis, economic analysis and sensitivity analysis. In addition, assumptions and ethical considerations for the study are presented.

4.1 Methods and design

A prospective interventional study was conducted for economic evaluation of clinical pharmacist's interventions in detecting and managing of treatment related problems (TRPs) as part of multidisciplinary medical intensive care unit team using cost benefit analysis model adopted from pharmacoeconomic guidelines (Kumar, 2018; G. Liu et al., 2011) and pharmacoeconomic analysis of clinical staff pharmacist practice model (Nesbit et al., 2001b).

After excluding ICU patients admitted for surgical services, patients in ICU who were admitted for medical services were randomly allocated into 4 months (between September-December 2020) either a routine care service (control group) or an interventional clinical pharmacy service (intervention group). Control group to account for natural fluctuation in

the absence of clinical pharmacist intervention (baseline against which the clinical pharmacist intervention is assessed).

Ramallah Hospital's ICU does not yet offer CP services. In order to perform the study, the author acquired a clinical pharmacist with a PharmD degree and three years of clinical experience in ICU settings by supervising PharmD students at Birzait University.

3.1.1 **Clinical pharmacy service / clinical pharmacist patient care process**:

Clinical pharmacist was available at ICU ward for five days a week from 8.00 a.m. to 3.00 p.m. of the day and maintained contact with the ICU team as needed. A day of clinical pharmacist in ICU started by collection the necessary subjective and objective information about the patient prior morning round in order to understand the relevant medical/medication history and clinical status of the patient then the CP assessed the information collected and analyzed the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize TRPs and achieve optimal care using evidence based medicine. For example, the appropriateness of the dosage regimen was determined by using Lexi-Drug comp's Information handbook. During morning rounds, the clinical pharmacist collaborated with the ICU team to develop an individual patient-centered care plan to discuss treatment and recommend improvements in patient treatment-related problems. Both newly admitted patients and patients who had already been admitted to the ICU for medical services were randomly allocated into groups and discussed. The cp's suggestions for altering the course of treatment were discussed. Only interventions approved by the ICU team were carried out. The cp evaluated and tracked the efficacy of the treatment plan, and made changes in collaboration with other health care practitioners (American College of Clinical Pharmacy, 2012).

ICU team maintained the blinding of patients with regard to whether changes were based on recommendations by the CP. All interventions were documented using consult note form (Annex 3).

The clinical pharmacist also collected data from patients in the control group, assessed and analyzed the clinical consequences of the patient's therapy in the context of the patient's overall health objectives, and designed a personalized patient-centered care plan; however, this care plan was not discussed with the ICU team nor implemented in the control group.

4.2 Setting of the study

The study was conducted in Ramallah`s Son Wing`s ICU (Ramallah hospital`s ICU) at the Palestine Medical Complex (PMC), which has 279 beds and 86.4% bed occupancy rate (MoH, 2020).

The PMC serves as a referral hospital in the West Bank of Palestine. The Ramallah`s Son Wing`s ICU department has 10 adult ICU beds for both medical (7 beds) and surgical (3 beds) cases. The average length of patient`s stay in MoH hospitals is 2.8 days (Ministry of Health, 2019). Average length of patient stay at Ramallah hospital ICU is 3-4 days according to Ramallah Hospital`s ICU specialist (M.Naseef, personal communication, Mars 3, 2020).

4.3 Study population

- All patients age over 18 and admitted to Ramallah`s son wing`s ICU during 4-month study period.
- The severity of disease was classified according to Acute and Physiology Chronic Health Evaluation (APACHE) score (Knaus et al., 1985).

4.4 Inclusion and exclusion criteria

- All patients admitted to Ramallah hospital (Son Wing`s ICU) during the 4-month period (between September-December 2020) for medical services were included in the study. The patients enrolled were clinical cases (from emergency or the wards departments).

- Patients who were admitted for surgical services were excluded from the study because, during the pandemic covid 19, only chosen high-priority operations were performed, preventing sample selection bias.

4.5 Sample size

We used empirical approach in determining sample size. The sample size calculation was based on the relative improvement of the TRP with the clinical pharmacy comprehensive medication management approach. Based on previously published work (Al-Qudah et al., 2019) that adopted (Molino et al., 2014) sampling methodology, a study population of 131 patients was identified as necessary to detect a significant change in TRP of 1-point difference, with a confidence level of 95%, and power of 80%, and with a standard deviation of 2.92.

4.6 Sampling method

Recruited patients were randomly assigned to study groups via randomization generator program. The randomization scheme was generated by using the Web site Randomization.com ⟨http://www.randomization.com⟩ (Dallal, 2007).

4.7 Data collection

The clinical pharmacist gathered all the required subjective and objective information about the patient in order to comprehend the patient's relevant medical/medication history and clinical condition. This information was collected from multiple sources; patient electronic medical files, clinical pharmacist bedside evaluation, and participation in physician round medication prescription and monitoring.

4.7.1 Study tool:

The clinical pharmacist recorded the health data for each patient on a consult note form derived from a specially designed and validated Pharmaceutical Care Manual used by clinical pharmacists at the University of Jordan with modifications (Annex 3) (AbuRuz et al., 2007).

The consult note form is divided into four sections, the first for patient information and the rest for clinical pharmacist analysis, assessment, and follow up. In the first section, the clinical pharmacist documented all relevant health information that were collected for each patient. The information includes the following; current medication list, past medication history, medical history, health and wellness information, biometric test results, and physical assessment findings.

In the second part, the clinical pharmacist (CP) documented the types of TRPs (unnecessary drug therapy, untreated condition, safety, efficacy, inappropriate knowledge, inappropriate adherence, miscellaneous and TRP on discharge) for each patient then assigned the assessment to each category according to a validated classification system for treatment related problems derived from AbuRuz et al., (2006) work in collaboration with the ICU team to create personalized patient-centered care plan. In this part the cp addressed TRPs, optimized medication therapy, set goals of therapy for achieving clinical outcomes.

The third part includes follow-up, monitoring and evaluating the effectiveness of the care plan according to medication appropriateness, effectiveness, safety and patient adherence through available health data, biometric test results, patient feedback, clinical endpoints that contribute to the patient's overall health and outcomes of care including progress toward or the achievement of goals of therapy.

The last part included the references that were used by the cp to do the assessments and physician acceptance of clinical pharmacist interventions.

In the control group, the cp documented the collected data in the first section of the consult note form, from the routine care service provided by the ICU team without cp involvement. Then the cp evaluated the collected data, identified TRPs, and assessed them solely without collaboration with the ICU team in the control group and documented them in the second part related to cp assessments.

4.8 Economic analysis

Economic analysis (CBA of cp interventions in ICU) was performed to estimate the value of the CP services to the institution. Each CP intervention was assessed for drug related cost savings and cost avoidance related to averted ADEs due to CP intervention. Benefits in terms of cost savings and cost avoidance were compared with the cost of the CP intervention to determine the net economic impact on the institution.

The cost savings generated by CP interventions were compared to cost savings resulted in the control group due to physician interventions.

Cost avoidance were not calculated in the control group as it was the cost avoided by eliminating the occurrence of ADEs as a consequence of the pharmacist interventions.

A. Direct Cost savings analysis:

Direct cost savings were related to interventions that resulted in either a lower or higher direct drug cost.

Cost savings formula for both groups are presented in table 4.1. And an example on cost savings is illustrated in box 1.

Table 4.1: Cost savings formula for calculations

Variable	**Formula**
Cost savings in intervention group	(Cost of drug therapy assumed to extend to the end of therapy with the new agent before intervention) minus (cost of drug therapy after intervention plus cost of drug that was used before intervention).
Cost savings in control group	The cost of drug therapy at baseline in the control group minus the cost of patient therapy at follow-up.
Negative cost savings in the intervention group	Any increased cost of patient`s therapy as a result of clinical pharmacist intervention
The cost of any drug therapy = The cost of drug therapy per unit * frequency per day * duration of therapy.	
Cost savings will be calculated as the reduced cost of therapy in the intervention group minus the reduced cost of therapy in the control group.	

Because the information " medications generic prices at MoH" is not given for tendering reasons, medication costs were computed using selling prices at the Ministry of Health rather than generic pricing. (General Directorate of Pharmacy, 2020).

Box 4.1: An example on Cost savings calculations.

Case from intervention group
A patient was receiving Fortum "ceftazidime" (1 g every 8 hrs.) to treat Pseudomonas aeruginosa. Three days later, patient's renal function was worsening; calculated creatinine clearance was 17 ml/min. The pharmacist then gave team an intervention. After intervention, the order was changed, based on renal guideline, to ceftazidime (1 g every 24 hrs.). The duration of therapy was 7 days. The cost of each 1 g-vial of ceftazidime is 35 NIS
Cost saving = (35 NIS/ 1 g-vial x 3 times/day x 7 days) – [(35 NIS /1 g-vial x 1 time/day x 4 days) + (35 NIS/ 1 g-vial x 3 times/day x 3 days)] = NIS280.
It means 280 NIS decreased or saved.

B. Cost avoidance analysis (for intervention group only):

This cost is related to the cp interventions with potential to avoid adverse drug events (ADEs). Each intervention was evaluated to estimate the probability of an ADE in the absence of the cp intervention using Nesbit methodology (Nesbit et al., 2001a).

The Nesbit methodology was used to determine the likelihood that a patient would be harmed if a cp did not intervene. A 7-member panel of cp specialists (3 cp specialized in main area,

6 of them had residency certification, and 6 of them had board certification) used a consensus approach to determine the chance that a patient would be harmed if no action was taken by the cp. The probability of an ADE in the absence of the intervention is set at 0, 0.01, 0.1, 0.4, or 0.6. These categories correspond to the likelihood of an ADE being zero, very low, low, medium, or high as clarified in table 4.2.

Table 4.2: Nesbit method for calculating cost avoidance (Nesbit et al., 2001a).

Probability score	**Probability of ADE occurring**	**Explanation of the probability**	**Example**
0.6	**high**	Harm is expected life threatening, prevented a potentially fatal or severe reaction	• 10x normal dose • narrow therapeutic range • life-threatening reaction/anaphylaxis
0.4	**medium**	Harm is expected, clinically relevant, prevented a potentially serious reaction	• Allergy to drug ordered • allergy information • adjustment of renal failure
0.1	**low**	Some harm is expected, but poorly clinically relevant; i.e., prevented a potentially significant reaction	• 2-4x normal dose • dose inadequate to produce therapeutic effect • incorrect schedule/route with potential for therapeutic failure/toxicity • duplicate therapy with potential for additive toxicity
0.01	**very low**	Problem orders, clarifications, missing information etc.	
0	**zero**	Information only	

Since cost of ADE in ICU settings was not previously evaluated or calculated in Palestine, Nesbit probability score is the most appropriate method in estimating the cost avoidance of probably occurring ADE in the absence of clinical pharmacist interventions (cost avoidance). Cost avoidance calculations formula are presented in Box 2.

Box 4.2: Cost avoidance calculations formula

Cost avoidance formula = The probability of an ADE in the absence of the cp intervention * cost of an ADE in ICU. = (0 or 0.01 or 0.1 or 0.4 or 0.6) * NIS750
The cost of an ADE was calculated on the assumption that the cost of ADE in ICU settings would be extend length of ICU stay by 1 day which equates NIS750
The overall cost avoidance was the sum of avoided cost with all interventions.

B.1) Assumptions for cost of ADE in ICU settings

There were no studies in Arab world nor in developing countries to estimate the economic burden of adverse drug event (ADE) in ICU patients. The author assumed that for each ADE in ICU settings, it would result in longer hospital stay by one day (cost of one day ICU stay is NIS750), considering the high occupancy rate of the PMC and average length of ICU stay of 3-4 days according to Ramallah Hospital`s ICU specialist (M.Naseef, personal communication, Mars 3, 2020).

This assumption is based on conclusions of literatures; that adverse drug events in ICU settings increase length of ICU stay between 0.77 days found in Kaushal et al., (2007) work

and an average of 31 days found in Forster et al., (2008) work. Chen and colleagues assumed for each preventable ADE; it would result in a longer hospital stay by 2 days. The cost of a preventable ADE here was estimated to be $5000 for 1 day's admission. In Jordan, Al-Qudah and colleagues calculated the cost of an ADE based on the assumption that an ADE in an outpatient will lead to a single admission to an internal medicine ward via an emergency department visit (Al-Qudah et al., 2019).

C. The cost of service:

The cost of providing cp service, is comprised of the salary of newly employed clinical pharmacist plus any increased cost of therapy in the intervention group (negative cost savings). Table 4.3. Summary table for the formulas used in cost benefit analysis model

Table 4.3: summary table for formulas used in cost benefit analysis model

	Variable (dependent)	**Formula for calculations**
A	Cost saving	(Cost of previous therapy) minus (cost of the new therapy recommended by pharmacist).
B	Cost avoidance	(The probability of an adverse drug event (Annex 2) in the absence of the intervention) multiple by * (ADE cost).
C	Cost of service	(Clinical pharmacist salary) plus (any increased cost of treatment due to intervention; negative cost saving).
D	Benefits	The sum of cost savings and cost avoidance (**A+B).**
D	Net benefit of the intervention	The sum of cost savings and cost avoidance minus cost of the service **(D– C).**
E	Benefit to cost ratio	The sum of cost savings and cost avoidance divided by cost of the intervention **(D/ C).**

4.9 Statistical analysis

IBM SPSS (v.20) was used to tabulate and analyze the collected data. Categorical data was expressed as proportions (%) and the continuous data as mean ± SD. Chi squared tests (for sex and patient status at discharge), APACHE score (for severity of cases) and independent sample t tests (was used to assess the differences between the two groups at baseline).

4.10 Sensitivity analysis

4.10.1 One- and two-way sensitivity analysis:

For the cost-benefit analysis, one- and two-way deterministic sensitivity analysis were undertaken in the base case of the cost analysis in order to assess the impact that changes in a certain input (clinical pharmacist salary, cost of ADE) will have on the output results of an economic evaluation (Benefit to cost ratio).

To vary the clinical pharmacist salary cost; we used the salary of newly employed clinical pharmacist at MOH institutions (base case), we used the highest point on a basic clinical pharmacist salary scale; clinical pharmacist salary with advancements, and we used the lowest point on a basic clinical pharmacist scale.

For estimated ADE costs, we used previously published lengths of hospital stay due to ADE in critical care settings that ranged from 0.77 day (Kaushal et al., 2007) to 31 days (Forster et al., 2008). We varied ADE cost based on the literature's variance of the length of ICU stay due to ADE.

4.10.2 Scenario analysis:

The sensitivity analysis compared the study's findings to an alternative scenario in which the Nesbit method was used to estimate cost avoidance due to routine practice in the control group. The resulting cost avoidance was then used as the baseline against which the cost avoidance of the intervention group was calculated.

4.11 Ethical considerations

Before beginning the study, we obtained approval from the research committee of Al Quds University's School of Public Health (Annex 4). We also received MOH approval to conduct the study at PMC-Son Ramallah's Wing Hospital (Annex 5). Furthermore, before signing a consent form, all participants were informed about the study's purpose (Annex 6).

While there are some ethical problems (safety and efficacy) about the use of placebo controls in clinical trials (in our case placebo control is control group with no cp involvement), the necessity of utilizing placebos in most such investigations has been shown beyond doubt. The investigator must treat both the intervention and control groups in the same way to determine if the improvement in the treated group is attributable to the CP service or the act of being treated. with the exception of the presence of CPS. Blinding is an effective and necessary approach of preventing treatment-related bias (Clark & Leaverton, 1994).

Chapter Five: The Results

During the 4-month study period 117 patients were admitted to ICU for medical services and 24 patients were admitted for surgical services. The 24 patients admitted for surgical services were excluded from the study, whereas the 117 patients admitted for medical services were randomly allocated into study groups (66 patients in the intervention group and 51 in the control group), all were included into the analysis.

5.1 Patient characteristics

There is no significant difference with respect to age, sex, and APACHE 2 score, length of stay, patient status at discharge between groups (p value > 0.05). Moreover, there is no significant difference between intervention and control groups with respect to number of TRP identified by the clinical pharmacist. Table 5.1 shows patient characteristics in both groups. There were also non-life-threatening TRPs identified in control group.

Table 5.1: characteristics of patients who were admitted to ICU for medical services.

Characteristic	Intervention group (n=66)	Control group (n=51)	P value
Age, mean (SD) year	58.30 (18.913)	64.78 (16.952)	0.057**
Gender (%) Male	59.1	54.9	0.79*
Female	40.9	45.1	
APACHE-2 score Mean, (SD)	12.14 (7.321)	13.37 (7.4)	0.369**
Length of stay Mean, (SD)	5.55 (3.347)	5.55 (3.306)	0.955**
Pt status at discharge (%)			0.262*
Alive	65.2	76.5	
Dead	34.8	23.5	
TRP [MK1][H2]**detected cp # (mean), {SD}**	165 (2.48) {1.947}	131 (2.56) {1.9}	0.816**

*Chi square test. ** Two sample t-test[MK3][H4][H5].

5.2 Treatment related problem (TRP)

The clinical pharmacist identified 296 TRPs in both groups, 172 TRPs in the intervention group of which 7 cp interventions were rejected by the physician and the remaining and 165 cp interventions were accepted by physician and implemented in the intervention group by the ICU team on 66 patients in 8 categories; unnecessary drug therapy 58 (34%), safety 36 (21%), untreated condition 28 (16%), efficacy 28 (16%), inappropriate knowledge 1 (1%), miscellaneous 10 (6%), TRP on discharge from ICU to ward 4 (2%) Clinical pharmacist didn`t find any TRP in seven patients in the intervention group as represented in table 5.2.

Table 5.2 frequency and percentage of TRPs in both groups

TRP categories	Intervention group		Control group	
	No	%	No	%
Unnecessary drug therapy	58	34.0	17	30.0
Safety	36	21.0	4	7.0
Untreated condition	28	16.0	0	0.0
Efficacy	28	16.0	2	4.0
Miscellaneous	10	6.0	1	2.0
No TRP found	7	4.0	32	57.0
TRP on discharge	4	2.0	0	0.0
Inappropriate knowledge	1	1.0	0	0.0
Total	172	100.0	56	100.0

Many of the TRPs were detected by the clinical pharmacist during participation in round with medical ICU team and many of them were prevented before they reached the patients in the intervention group. Unnecessary drug therapy related problems were the most common TRP category identified by the cp in the intervention group followed by safety and untreated condition related problems.

ICU physician detected 56 TRPs in the control group and resolved 24 TRPs in the control group. Unnecessary drug therapy were the most common TRPs category.

5.3 Types of clinical pharmacist interventions /assessments

Table 5.3 shows the accepted clinical pharmacist assessment categories. Stepping down current therapy was the most frequent type of intervention occurring (22%). Untreated

conditions that require adding pharmacological therapy (17%) and safety issues that require dosage adjustment (17%) were scored most.

Table 5.3: categories of clinical pharmacist assessments/ interventions by the treating ICU team in the intervention group.

Type of assessment/cp intervention	**No**	**%**
Treatment should be stepped down	37	22
Untreated conditions that require pharmacological therapy	30	17
Safety dosage regimen issues	29	17
The patient requires additional/ combination therapy or stepping up	16	9
Discontinue / drug used without indication	12	7
Efficacy dosage regimen issues	7	4
No interventions (not detected or physician disagreed)	7	4
rejected	7	4
The patient is at high risk for developing ADR and needs monitoring or prophylaxis	6	3
Duplication needs to discontinue one medication	4	2
More effective drug is available/ recommended	3	2
Unnecessary drug therapy on discharge	3	2
The chosen medication(s) is not (are not) cost effective	2	1
Other dosage regimen issues; e.g. (a) Dosage too low or (b)Dosage too (c) The route or dosage form is not appropriate, considering efficacy, safety and/or guidelines recommendations (d) Timing	2	1
patient adherence /information only	2	1
A safer drug is recommended	1	1
The patient is not instructed or does not understand non-pharmacological therapy or self-care advice	1	1
A need for consultation	1	1
A need for additional or more frequent monitoring	1	1
Patient was discharged too early (i.e., before achieving recommended target)	1	1
Total	**172**	**100**

The clinical pharmacist most frequently advised to intervene on antibiotics group of medication (22%). The second type of medication that necessitated the intervention of the clinical pharmacist was gastrointestinal medications specifically proton pump inhibitors (PPI) and ranitidine (16%). For untreated hyper/hypoglycemia, the clinical pharmacist frequently recommended adding/adjusting the dose of antidiabetic insulin (NPH) (15%). Furthermore, the anticoagulants class of medications frequently required dose adjustments by clinical pharmacists (13%) as presented in table 5.4.

Table 5.4: Drugs groups involved of Accepted clinical pharmacist interventions by the ICU team in the intervention group

Drug involved	**no**	**%**
Antibiotic (e.g., vancomycin, ceftriaxone, piperacillin-tazobactam, teicoplanin)	36	22
Gastro intestinal (PPI, Ranitidine)	26	16
Antidiabetic NPH insulin	25	15
Others; e.g., … SPS kayexalate for hyperkalemia.	25	15
Anticoagulants (enoxaparin)	21	13
Blood pressure and cardiac	16	10
Intervention not involved drugs (e.g., a need for consultation, lab monitoring, adding dextrose water for hypoglycemia ….)	9	5
Central nervous system	6	4
Sedatives and pain	1	1
Total	**165**	**100**

5.4 Physician decision

It has been observed that 158 (92%) of clinical pharmacist interventions accepted by physicians and implemented in the intervention group. Seven (4%) CP interventions were rejected (under the category of unnecessary drug therapy and miscellaneous), while the rest were accepted with proposed modified plan as presented in table 5.5.

Table 5.5: Physician acceptance rate of clinical pharmacist interventions in the intervention group

Physician agreement	**No. of interventions**	**%**
Totally Agree with CP intervention	158	92
Agree with modification	7	4
Disagree with CP plan	7	4
Total	**172**	**100**

In the intervention group, 59 (89%) patients in the intervention group had at least one TRPs and 46 (69%) patients had at least two TRPs, one patient (2%) had 12 TRPs, while 7 patients (11%) had no TRPs as presented in table 5.6

Table 5.6: accepted clinical pharmacist interventions per patient in the intervention group

Patients in the intervention group with	**No of patients**	**%**
0 accepted intervention *	7	11
1 accepted intervention	13	20
2 accepted interventions	23	35
3 accepted interventions	8	12
4 accepted interventions	5	8
5 accepted interventions	9	14
12 accepted interventions	1	2
Total	**66**	**100**

* No TRP found

5.5 Cost analysis results

Over a 4-month period, 172 TRPs were identified by the clinical pharmacist and 165 TRPs were resolved and implemented in the intervention group resulted in direct cost saving of NIS16,195.32, cost avoidance of NIS22,087.5, and added cost on therapy (negative cost savings) of NIS3,877.65.

In contrast, 56 TRPs were identified and 24 TRPs were resolved by the physician in the control group resulted in direct cost saving of NIS2,441.12. as presented in table 5.7.

A case from control group (annex 8) and case from intervention group (annex 9) are provided to illustrate analysis.

Table 5.7: cost analysis results

	Intervention group	**Control group**
Total No. of interventions	172	56
Implemented interventions	165	24
Cost savings (NIS)	**16,195.32**	**2,441.12**
Cost Avoidance (NIS)	22,087.50	-
Added cost (NIS)	-3,877.65	-

A) Cost saving:

The majority of TRPs associated with the most cost savings and cost avoidance generated by the clinical pharmacist in the intervention group were under the categories of

"unnecessary drug therapy" (34%) and "safety," (21%) resulting in direct cost savings of (NIS8,677.94) and (NIS7,149.55) respectively.

Interventions, on the other hand, associated with most increased cost of therapy in the intervention group were for TRPs in the categories of "efficacy" (NIS 2,352.3) and "untreated condition" (NIS1,490.5) as illustrated in table5.8.

There were 24 TRPs in the control group resolved by physicians and associated with a total reduced cost of **NIS2,441.12** under the category of "unnecessary drug therapy" (30%) which resulted in direct cost savings of (NIS2,195.5). The remaining resolutions were categorized under "miscellaneous" 2% and "safety" 7% with cost savings of (NIS185.67), (NIS58.95) respectively. Cost analysis results in the both groups are summarized in Table 5.8

Table 5.8: Direct cost savings results in both groups

Groups	**Intervention group**				**Control group ****		
TRP categories	**No. of interventions by CP**	**%**	**Cost savings (NIS)**	**Added cost (Negative cost) NIS**	**No. of interventions by physicians**	**%**	**Cost saving (NIS)**
Unnecessary drug therapy	58	34	8,677.94	-19.52	17	30	2,195.50
Safety	36	21	7,149.55	-15.33	4	7	58.95
Untreated condition	28	16	0	-1,490.50	0	0	0
Efficacy	28	16	3.78	-2,352.30	2	4	1
Miscellaneous	10	6	42.09	0	1	2	185.67
No TRP found	7	4	0	0	32	57	0
TRP on discharge	4	2	321.96	0	0	0	0
Inappropriate knowledge	1	1	0	0	0	0	0
Total	**172**	**100**	**16,195.32**	**-3,877.65**	**56**	**100**	**2,441.12**

**Only the +ve cost saving included in analysis

B) Cost avoidance (For intervention group only):

Based on a reported one day stay in Son Wing`s ICU cost of NIS750 (M.Nassef, personal communication, Mars 3, 2020), the overall cost avoidance generated by the clinical pharmacist in the intervention group during the 4-month period using Nesbit methodology was **NIS22,087.5**.

The number of interventions that potentially avoided ADEs were as the following: For a probability of an ADE of 0, 18 interventions (10.5% of all interventions); for a probability of 0.01, 5 (2.9%); for a probability of 0.1, 108 (62.2%); for a probability of 0.4, 30 (18%); and for a probability of 0.6, 11 (6.4%) as shown in table 5.9.

Table 5.9: Cost avoidance analysis results

	pADE (Nesbit score)	**risk**	**No of interventions**	**%**	**Cost avoidance (nis) = pADE *no interventions *750 NIS**
Intervention (by CP)	Zero	zero	18	10.5	0
	0.01	very low	5	2.9	37.5
	0.1	low	107	62.2	8100
	0.4	medium	31	18	9000
	0.6	high	11	6.4	4950
Total			**172**	**100**	**22087.5**

Most of CP interventions within low and very low probability of preventable ADE fall under the category of “unnecessary drug therapy” TRP and most of CP interventions within medium and high probability of preventable ADE fall under the category of “safety” TRPs AS presented in table 5.10.

Table 5.10: TRPs categories in the intervention group according to Nesbit score

Risk	TRP category	No. of CP interventions	%
zero	No TRP found	7	39
	Unnecessary drug therapy	5	28
	Miscellaneous	3	17
	Efficacy	1	6
	Safety	1	6
	Inappropriate knowledge	1	6
	Total	18	100
low	unnecessary drug therapy	47	44
	untreated condition	24	22
	efficacy	22	21
	safety	7	7
	miscellaneous	4	4
	TRP on discharge medications	3	3
	Total	107	100
very low	unnecessary drug therapy	3	60
	miscellaneous	1	20
	TRP on discharge medications	1	20
	Total	5	100
medium	safety	23	74
	unnecessary drug therapy	3	10
	efficacy	3	10
	untreated condition	2	6
	Total	31	100
high	safety	5	45
	untreated condition	2	18
	efficacy	2	18
	miscellaneous	2	18
	Total	11	100

Cost avoidance was highest for “safety” TRPs estimated NIS9,675 followed by “unnecessary drug therapy” TRPs estimated NIS4,447.5. Cost avoidance results are illustrated in table 5.11

Table 5.11: Cost avoidance analysis per TRP category in the Intervention group

TRP categories	No. of interventions by CP	%	Cost Avoidance (NIS)
Safety	36	21	9,675
Unnecessary drug therapy	58	34	4,447.50
Untreated condition	28	16	3,300
Efficacy	28	16	3,225
Miscellaneous	10	6	1,207.50
TRP on discharge	4	2	232.5
No TRP found	7	4	0
Inappropriate knowledge	1	1	0
Total	**172**	**100**	**22,087.50**

C) Cost of clinical pharmacist services:

In the West Bank, the average monthly salary of a clinical pharmacist (Pharm D) working in public hospital is NIS4,000 according (D.saleh, personal communications, June 1, 2021) Taking into consideration this and the negative cost saving (**NIS3,877.65**) in the intervention group, the total cost of the clinical pharmacy service totaled NIS19,877.65 during the 4-month period.

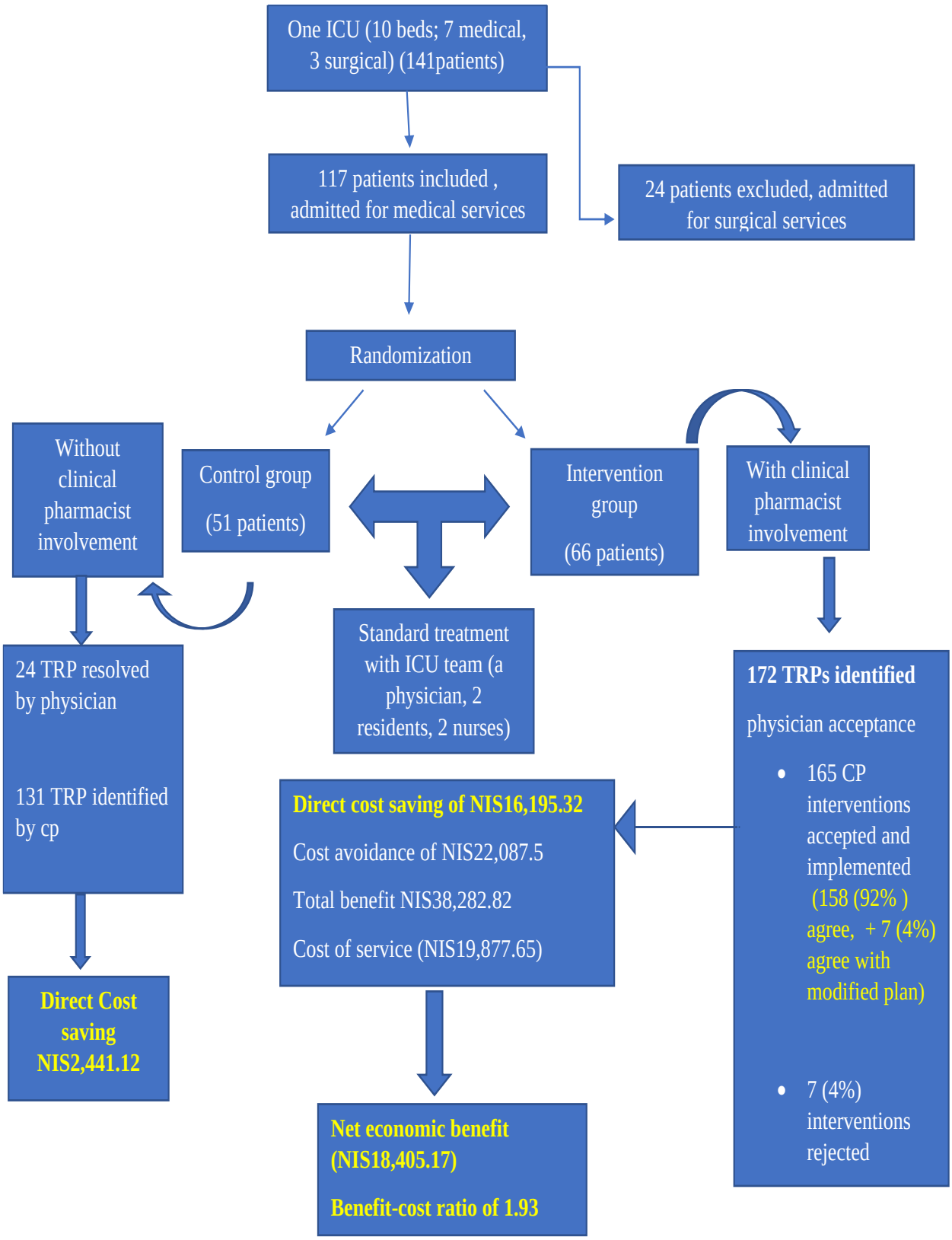
D) Cost benefit analysis

The interventions made by clinical pharmacist resulted in direct cost saving of NIS16,195.32 and cost avoidance of NIS22,087.5 totaled NIS38,282.82 during the study period. Translated into total cost savings of NIS232 per CP intervention. Comparison of benefits (NIS38,282.82) and costs (NIS19,877.65) indicates a net economic benefit to the institution of (NIS18,405.17) and a benefit-cost ratio of 1.93 as reported in table 5.12 and illustrated in Flowchart 5.1: study results**.**

Table 5.12: Cost benefit outcome analysis

	Variable	**Formula for calculations**	**Results**
A	Cost saving (NIS)	Cost of drug therapy assumed to extend to the end of therapy with the new agent before intervention) minus (cost of drug therapy after intervention plus cost of drug that was used before intervention).	16,195.32
B	Cost avoidance (NIS)	(The probability of an adverse drug event in the absence of the intervention) multiple by * (ADE cost).	22,087.5
C	Cost of service (NIS)	(Clinical pharmacist salary) plus (any increased cost of treatment due to intervention; negative cost saving).	3877.65+ 16000 = 19,877.65
D	Benefits (NIS)	A+B	38,282.82
E	**Net benefit (NIS)**	**D– C**	**18,405.17**
F	**Benefit to cost ratio (BCR)**	**D / C**	**1.93**
G	Retrurn on investment (ROI)	E / C *100%	92.59%
H	Benefit / intervention	D/165	232.02
I	Benefit/patient	D/66	580.04

Flowchart 5.1: Study Results



5.6 Sensitivity analysis

Sensitivity analyses were performed to determine how cost estimates might vary if our base case assumptions were changed. One- and two-way analysis were conducted to determine the break-even point at which the BCR is 1:1. When key parameters were varied within reasonable ranges, the results were robust, and the overall assumptions did not change significantly

5.6.1 One-way sensitivity analysis:

The cost-benefit ratio remained positive in all measured scenarios in the one-way sensitivity analysis. Table 5.13 displays the distributions of input uncertainties and their sensitivity analyses (cp salary).

The economic model was insensitive to uncertainty in the clinical pharmacist salary. Varying the salary within the established limits (NIS2492 - NIS5500) did not push the benefit-cost ratio below 1:1.

The largest variance was found in cost assigned to an ADE cost. However, varying the cost estimates within the established limits (extended length of stay due to ADE between 1 and 30 days) had no effect on the benefit-cost ratio falling below 1:1. As presented in table 5.14. The benefit-cost ratio became 1:1 if the cost of an ADE was reduced to NIS 125 (LOS 4 hrs.). The BCR curve with the cost of admission is shown in Figure 5.2.

Table 5.13: One-way Sensitivity analysis (input variable: cp salary)

Input variable	**Uncertainty distribution**	**(BCR)**
CP salary	**NIS2492** average **basic** salary of clinical pharmacist with no advancements.	**2.764**
	NIS4000 average salary of newly employed clinical pharmacist with regular advancements.	**1.925**
	NIS5500 average salary of clinical pharmacist with promotions and advancements.	**1.479**

Table 5.14: One-Way Sensitivity analysis (input variable: cost of extended length of hospital stays due to ADE)

Input variable	**Extended LOS due to ADE**	**Cost of ADE** (LOS* 750 NIS)	**BCR**
	0 hr.	0	0.81
	4 hrs.	**125**	**0.999**
	5 hrs.	156.25	1.046
	6 hrs.	187.5	1.092
	7 hrs.	218.75	1.138
	8 hrs.	250	1.185
	9 hrs.	281.25	1.231
	10 hrs.	312.5	1.277
	11 hrs.	343.75	1.324
	12 hrs.	375	1.370
	1 days	**750**	**1.925**
	2 days	1500	3.037
	3 days	2250	4.148
	4 days	3000	5.259
	5 days	3750	6.370
	10 days	7500	11.926
	15 days	11250	17.48
	20 days	15000	23.038
	30 days	22500	34.149

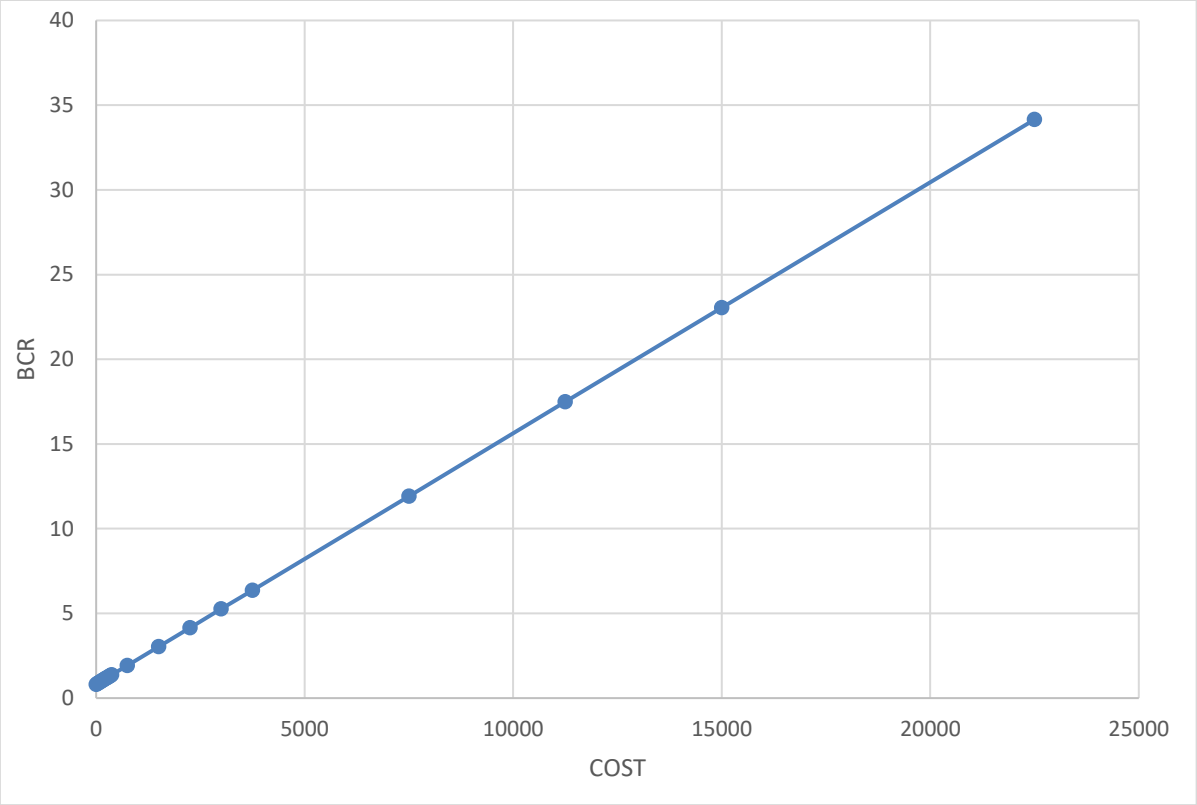


Fig. 5.1: The BCR curve with the cost of prolonged hospital LOS due to ADE

5.6.2 Two-way sensitivity analysis:

Varying the salaries and cost estimates simultaneously within the established limits did not push the benefit-cost ratio below 1:1. The benefit-cost ratio became 1:1 if the cost of an ADE was reduced to NIS125 (LOS 4 hrs.) at salary estimate of NIS4000 or if both salary estimates were set to NIS5500 and cost of ADE estimate reduced to NIS312.5 simultaneously. Analysis is reported in table 5.15.

Table 5.15: Two-way sensitivity analysis- input variables and uncertainty distributions

Extended LOS due to ADE	**Cost of ADE NIS**	**Clinical Pharmacist salary**			
		2492	**4000**	**5500**	**BCR**
0 hr	0	1.1697	0.81475	0.62584	
1 hr.	31.25	1.23617	0.86105	0.66141	
2 hrs.	62.5	1.30264	0.90735	0.69697	
3 hrs.	93.75	1.36911	0.95365	0.73253	
4 hrs.	**125**	1.43558	**0.99995**	0.7681	
5 hrs.	156.25	1.50205	1.04624	0.80366	
6 hrs.	187.5	1.56852	1.09254	0.83923	
7 hrs.	218.75	1.63499	1.13884	0.87479	
8 hrs.	250	1.70146	1.18514	0.91035	
9 hrs.	281.25	1.76793	1.23144	0.94592	
10 hrs.	**312.5**	1.8344	1.27774	**0.98148**	
11hrs.	343.75	1.90087	1.32404	1.01705	
12 hrs.	375	1.96734	1.37034	1.05261	
1 day	**750**	**2.76497**	**1.92592**	**1.47938**	
2 days	1500	4.36024	3.0371	2.33291	
3 days	2250	5.9555	4.14827	3.18645	
4 days	3000	7.55077	5.25944	4.03999	
5 days	3750	9.14604	6.37061	4.89352	
10 days	7500	17.1224	11.9265	9.1612	
15 days	11250	25.0987	17.4823	13.4289	
20 days	15000	33.075	23.0382	17.6966	
30 days	22500	49.0277	34.1499	26.2319	

5.6.3 Scenario analysis:

Based on the scenario analysis that accounted for resolving TRPs under the usual course of care in the control group, the consequential total reduced cost of preventable ADEs in the control group was NIS3,941.12 during 4-month period.

The adjusted final cost avoidance of the study intervention was, therefore, **NIS20,588** (i.e., NIS22,087.5 minus NIS1,500), translating into a net benefit of **NIS16,905** and a benefit-to-cost ratio of **1.85** during the 4-month period as presented in Table 5.16

Table 5.16. Show cost avoidance analysis in the control group

risk	**P ADE score**	**TRP category**	**no of physician interventions**	**%**
zero	zero	Unnecessary drug therapy	2	5.6
		Efficacy	1	2.8
		Miscellaneous	1	2.8
		No TRP found	32	88.9
low	0.1	Unnecessary drug therapy	15	75
		Efficacy	1	5
		Safety	4	20
Total			**56**	**100**

Table 5.17: Scenario analysis calculations

Variable	control group	Intervention group
cost saving	$2,441.12	16 195.32
cost avoidance (CA)	$1,500	22 087.5
sum of savings	$3,941.12	38 282.82
CP Salary (over 4 months)	-	16 000
negative costs	-	3 877.65
scenario analysis: adjusted cost avoidance for intervention group = CA intervention group - CA control group	-	$20,588
net benefit = adjusted CA + cost saving study group – (salary +added costs)	-	$16,905
cost benefit ratio	-	1.85

Chapter Six: Discussion

The author can conclude that the clinical pharmacist interventions have positive economic impact on patient care in ICU settings by reducing costs of care. This chapter will discuss the study's major findings and compare them to the existing literature.

6.1 Discussion

To our knowledge, this is the first prospective interventional study in a Palestinian hospital that economically assesses clinical pharmacist interventions to resolve TRPs in ICU patients within multidisciplinary team. A few studies have been done in the Middle East to examine the economic impact of disease-specific clinical pharmacy services in ICU settings (Aljbouri et al., 2013).

To persuade policy and decision makers that a clinical pharmacist will generate a positive "return on investment" in ICU settings, clinical pharmacists must demonstrate the economic

value of their interventions to institutions by avoiding costs rather than generating revenues. In this study, the aim was to assess the cost benefit of the clinical pharmacist interventions for resolving treatment related problems as part of a multidisciplinary medical intensive care unit (MICU) team.

A wide variety of TRPs were enrolled in this study, with the clinical pharmacist identifying 172 TRPs in the intervention group. The fact that 46 patients (69%) in the intervention group had at least two TRPs, highlights the magnitude of the problem. The most common TRPs associated with the most cost saving due to clinical pharmacist interventions were unnecessary drug therapy totaling NIS13,125.44 that required stepping down (22.5%) and safety related problems totaling NIS16,824.55 that required dosage adjustment (17%). Despite the fact that adding a drug therapy (17%) for untreated conditions resulted in an additional cost on therapy estimated to be NIS1490.5, the benefit of avoiding probable occurring ADE was estimated to be NIS3300, which outweighed those negative costs.

These results are consistent with those of other researchers; Allameh and colleagues reported that improper medication use (36.2%) was the most common clinical pharmacists interventions in Masih Daneshvari hospital in Iran (Allameh et al., 2012). Another study by Fahimi, (2010) discovered that dose adjustment (13.57%) and therapeutic reduction/addition (12.88%) were the most common clinical interventions in the same hospital. Similar to a retrospective study that was conducted in internal medicine at the University Hospital Basel, Switzerland (Reinau et al., 2019) found the most frequent types of pharmacist interventions were dose adjustment (24.0%), followed by drug discontinuation (23.5%) respectively. Gallagher and colleagues (Gallagher, Byrne, et al., 2014) found that the most common types of CP interventions were medication omissions (65.93%), followed by dosage adjustments (21.61%). This information might be highly valuable in identifying at-risk patients and avoiding future TRPs and the expenditures associated with them.

Stepping down unnecessary drug therapy can save both direct and indirect costs by avoiding preventable ADRs and their associated cost. In this study, clinical pharmacist interventions to resolve 58 unnecessary drug therapy related problems resulted in an estimated cost

avoidance of probable occurring ADE NIS4,447.5. Approximately 37 stepped down drugs intervened by clinical pharmacist were clinically unwarranted (e.g., conversion route of administration from IV to PO), 12 discontinued drugs were used without indication and four cases of discontinued drugs were duplicates of a drug with a similar effect. In this study antibiotics (e.g., vancomycin), PPI (pantoprazole and esomeprazole) and anticoagulant (enoxaparin) represented the majority of drugs requiring dose adjustment by the clinical pharmacists based on individual renal function. These types of TRPs reflect a problem in ICU patients medication prescribing and monitoring, emphasizing the importance of clinical pharmacists in optimizing prescriptions that will contribute to the avoidance of preventable ADRs and associated costs in ICU patients.

The proportion of accepted interventions in this study is 91.9% which is comparable with a study conducted in a Jordanian general hospital's internal medicine department (91%) (AbuRuz et al., 2011). Similar to a study by Mahmoodpoor et al., (2018), in which intensivists accepted (93.6%) of clinical pharmacist recommendations in the ICU of Shohada hospital in Tabriz. Acceptance rate in this study is apparently higher than the (71%) recorded in Klopotowska's study, which was conducted in the adult medical-surgical ICU of the Academic Medical Centre in Amsterdam (Klopotowska et al., 2010) and for sure higher than the (57.6%) found in Reinau and colleagues study, which was conducted in internal medicine department at the University Hospital Basel, Switzerland (Reinau et al., 2019).

Despite the fact that clinical pharmacy service was not yet a formal service in all these hospitals, the high acceptance rate of this study interventions reflects the high quality of the recommendations made by the clinical pharmacist. This can be attributed to the clinical pharmacist “comprehensive medication management approach” which entails optimizing patient medication by assessing the appropriateness, safety and efficacy of each patient`s medications and actively participating in patient care rounds collaboratively with the ICU team (American College of Clinical Pharmacy, 2012).

The Nesbit method produces the most accurate published estimate of the cost of an ADE (Bates et al., 1997; Chen et al., 2017; Kopp et al., 2006; Nesbit et al., 2001). The probability

categories used in the cost-avoidance calculation in the absence of intervention were conservative, with the maximum probability of an ADE set at 0.6. In this study ,the majority of estimated probability scores were low, which is consistent with most relevant studies using the same method (Al-Qudah et al., 2019; Bosma et al., 2018; Gallagher et al., 2014).

Earlier studies' estimates of the ADE cost price differed. While Rottenkolber and colleagues (Rottenkolber et al., 2012) estimated the mean excess treatment of ADE patients equal €970 ($1,153.4), Nesbit and colleagues estimated ADE cost price as $5006 (Nesbit et al., 2001). A scoping review conducted with 38 cost intervention categories ranging from ($55.45 to $19,897.16) (Hammond, Gurnani, et al., 2019).

There was a clear evidence of the value of CP interventions. Almost 172 interventions were implemented in the intervention group, and most of them had clear potential for cost savings or/and cost avoidance. The savings resulted from managing treatment related problems significantly outweighed the costs of clinical pharmacist involvement described in this study. Total cost savings was estimated to be NIS38,282.82 ($11,639.66), similar favorable results were found with a retrospective study estimated a potential saving of €10,905 ($12,982.62) as a result of pharmacist interventions regarding antimicrobials in ICU over 5-month in Spain (Leache et al., 2019). These findings highlight the critical role of cp in enhancing the quality of treatment offered, as well as lowering TRP patient suffering and associated costs to health institutions and society.

It may be unreasonable to compare the cost benefit of this study to studies conducted in other countries because the medication costs, clinical pharmacist salaries and medical service costs differ greatly. Moreover, many of the variations are possibly due to different methodologies or cost calculations. For example, Al Qudah and colleagues found in their RCT CBA study the BCR of cp interventions in outpatient settings equate 5.98 (Al-Qudah et al., 2019). Similarly a retrospective study, which compared the number of pharmacist interventions 1 year before and after a clinical pharmacist was deployed in a nephrology ward in Taiwan found the benefit/cost ratio increased from 4.29 to 9.36 after the on-ward deployment of a clinical pharmacist(Chen et al., 2017). Also A one-year retrospective research at Cork

University Hospital (CUH) and Cork University Maternity Hospital in the southern area of the Republic of Ireland discovered a total cost avoidance of $830077.51 was produced. The total input costs were assessed to be $96040.94. As a consequence, the net cost benefit was $734036.56, with a cost benefit ratio of 8.64: 1 (Gallagher, Byrne, et al., 2014). A quality improvement research was carried out in the Netherlands at a general teaching hospital (GTH) and a university hospital (UH). The cost benefit for each accepted intervention was $139.48 (GTH) and $159.40 (UH).(Bosma et al., 2018) compared to study results; the cp generated benefits of NIS232 ($71.2) per intervention. This large disparity can be explained by the higher cost price used for an ADE as well as the fact that pharmacist salary expenditures were not included in their study. Regardless of the cost savings recorded in published studies, they all support the clinical pharmacist's importance in ICU.

The ACCP estimated that a benefit of $16.70 was realized for every $1.00 invested in clinical pharmacy programs (SCCM-ACCP, 2000). Compared to our study, the clinical pharmacist generated a benefit of NIS2 for every NIS1.00 invested in clinical pharmacy program in ICU; which is within the range of (1.05:1 to 25.95:1) reported by Touchette et al., (2014) work but lower when compared with the BCR of Nesbit et al., (2001), that ranged from 3.1 to 13.33.

In February 2016, a PharmD job description was created in Palestine. However, clinical pharmacy services are still rudimentary with only 7 PharmDs working in public hospitals delivering pharmaceutical services from centralized locations (MoH, 2020), and many decision makers resist the employment of PharmDs due to current economic crises. This study provides an evidence to decision makers that clinical pharmacy services are a worthwhile investment; by employing a benefit-cost analysis model, which is used to decide whether to implement one specific intervention or program, and can be determined if net benefits are greater than zero and BCR is greater than one (Kumar, 2018). According to the conclusions of the study (Net Benefit: NIS18,405.17, BCR: 1.93), cp service is a good investment that should be introduced in ICU.

The Palestinian Ministry of Health must take a more active role in integrating clinical pharmacists into the health system and promoting their interactions with other specialties, which will alleviate the current serious problem of "clinical pharmacist unemployment" by creating jobs and reducing the number of clinical pharmacists who are either leaving the town to work in other countries (particularly in the Gulf countries or in America) or working as medical representatives for pharmaceutical corporation.

In Palestine, there are no set goals, measurements or policy documents to improve cp services. the Palestinian pharmaceutical syndicate should publish an influential policy statement that will contribute to the development of CP in Palestine.

the current study had several strengths. It is the first study in Palestine measuring the acceptance of clinical pharmacist interventions in ICU settings and its impact on costs of care and safety of patients. In addition, we used prospective interventional design; the control group prevents an overestimation of economic impact. the author used a comprehensive and evidence-based medicine approach recommended by Joint Commission of Pharmacy Practitioners (JointCommission of Pharmacy Practitioners, 2014) rather than retrospective evaluation of patients' medical files, the author have assessed and monitored the patients daily until discharge from ICU for developing new problems. Finally, the cost-benefit analysis was preliminary and based on a model used panel of multidisciplinary experts to estimate probability of avoiding ADEs.

6.2 Limitations

The study has some limitations. To begin with, Medication costs were calculated using selling prices at the Ministry of Health rather than generic pricing because this information is not available for tendering purposes, according to this limitation the study results may be overestimated. Secondly, accurate data on the cost of a preventable ADE are not available in Palestine. As a result, cost avoidance calculations were based on estimated ADE probabilities rather than real economic data. Thirdly, the data collection was dependent on

clinical pharmacist`s documentation and voluntary reports therefore we can’t guarantee that all implemented recommendations were documented.

6.4 Conclusions

The clinical pharmacist played an active role in Ramallah Son wing` ICU. This study documented that integrating a clinical pharmacist in the ICU team was an investment that resulted in cost savings and cost avoidance. These results are be helpful for institutions to consider in their strategic decision to employ clinical pharmacists in ICU setting. With further formalizing clinical pharmacy services at hospital and integrating the clinical pharmacist as part of the critical care team, an even higher economic benefit is anticipated.

6.5 Recommendations

6.5.1 Recommendations for policy and decision makers:

Clinical pharmacists will not be able to produce revenue for a health system without prescriptive authority. Legislative changes may be required to allow for reimbursement of clinical pharmacy services and further expansion of the clinical pharmacist role in ICU.

the author urges policy makers to implement clinical pharmacy service (CPS) in Palestinian healthcare facilities and the following are the recommendations to facilitate the implementation:

1. Create a process for implementing CPS; adopt strategies similar to those used and recommended in a Brazilian study (Ramos et al., 2018). These strategies are summarized as follows; perform collaborative partnerships with local health managers; recruit a team of supporters; provide pharmacotherapy clinical training

and finally accreditation by the MoH to clinical pharmacists who implemented CPS in their workplaces.

2. Start the CPS implementation phase in critical care settings, and then extend the process to other hospital departments.
3. There is a scarcity of clinical pharmacists with specialized residency training. This reflects the scarcity of academic and research resources, as well as the struggle to attract suitable and well-trained faculty members in pharmacy administration. The Ministry of Health need to consider about developing clinical pharmacy residency programs as well as a high-quality Palestinian Pharmacy Board Examination for clinical pharmacists.

6.5.2 Future research recommendations:

- Conduct more long-term studies with larger sample sizes and for longer periods of time.
- Involve more hospitals and clinical pharmacists in the study, allowing them to practice in a variety of patient care settings.
- Use Cost-Consequence Analyses (CCAs) for future research that allows for different types of benefits that cannot be combined to be disaggregated and studied (Hunter & Shearer, 2014). The impact that the CP service has on clinical and humanistic outcomes are also of great significance and should be taken into consideration.

References

1. A. Albsoul-Younes, E.Hammad, Yasein, N., & L.Tahaineh. (2011). Pharmacist-physician collaboration improves blood pressure control. *Saudi Medical Journal*. https://pubmed.ncbi.nlm.nih.gov/21384066/
2. AbuRuz, S. M., Bulatova, N. R., & Yousef, A. M. (2006). Validation of a comprehensive classification tool for treatment-related problems. *Pharmacy World and Science*, *28*(4), 222–232. https://doi.org/10.1007/s11096-006-9048-0
3. AbuRuz, S. M., Bulatova, N. R., & Yousef, A. M. (2007). Pharmaceutical care manual. *National LibraryJordan, Copyright number 2007/ 12/3856.*
4. AbuRuz, S. M., Bulatova, N. R., Yousef, A. M. M., Al-Ghazawi, M. A., Alawwa, I. A., & Al-Saleh, A. (2011). Comprehensive assessment of treatment related problems in hospitalized medicine patients in Jordan. *International Journal of Clinical Pharmacy*, *33*(3), 501–511. https://doi.org/10.1007/s11096-011-9497-y
5. Al-Qudah, R. A., Al-Badriyeh, D., Al-Ali, F. M., Altawalbeh, S. M., & Basheti, I. A. (2019). Cost-benefit analysis of clinical pharmacist intervention in preventing adverse drug events in the general chronic diseases outpatients. *Journal of Evaluation in Clinical Practice*, *26*(1), 115–124. https://doi.org/10.1111/jep.13209
6. Aljbouri, T. M., Alkhawaldeh, M. S., Abu-Rumman, A. eddeen K., Hasan, T. A., Khattar, H. M., & Abu-Oliem, A. S. (2013). Impact of clinical pharmacist on cost of drug therapy in the ICU. *Saudi Pharmaceutical Journal*, *21*(4), 371–374. https://doi.org/10.1016/j.jsps.2012.12.004
7. Allameh, Z., Mehrpooya, M., Baniasadi, S., & Fahimi, F. (2012). *Clinic al pharmacists ' interventions in a teaching hospital : Types , severity , procedures , and accuracy*. *7*(5), 2012.
8. Altawalbeh, S. M., Saul, M. I., Seybert, A. L., Thorpe, J. M., & Kane-Gill, S. L. (2018). Intensive care unit drug costs in the context of total hospital drug expenditures with suggestions for targeted cost containment efforts. *Journal of Critical Care*, *44*, 77–81. https://doi.org/10.1016/j.jcrc.2017.10.029
9. American Collage of Clinical Pharmacy (ACCP). (2008). The definition of clinical pharmacy. *Pharmacotherapy*, *28*(6), 816–817.

https://doi.org/10.1592/phco.28.6.816

10. American College of Clinical Pharmacy. (2012). *Comprehensive Medication Management in Team-Based Care*. 1–8.
11. American Society of Health-System Pharmacist. (2012). *ASHP Accreditation standard for postgraduate year one (PGY1)*. 1–23. http://www.ashp.org/DocLibrary/Accreditation/ASD-PGY1-Standard.aspx
12. Bell, J. S., O'Reilly, C. L., & Chen, T. F. (2009). Use of consumer educators in mental health pharmacy education. *American Journal of Pharmaceutical Education, 73*(2), 2–4.
13. Bosma, B. E., van den Bemt, P. M. L. A., Melief, P. H. G. J., van Bommel, J., Tan, S. S., & Hunfeld, N. G. M. (2018). Pharmacist interventions during patient rounds in two intensive care units: Clinical and financial impact. *Netherlands Journal of Medicine, 76*(3), 115–124.
14. Chen, C. C., Hsiao, F. Y., Shen, L. J., & Wu, C. C. (2017). The cost-saving effect and prevention of medication errors by clinical pharmacist intervention in a nephrology unit. *Medicine (United States), 96*(34), 1–5. https://doi.org/10.1097/MD.0000000000007883
15. Clark, P. I., & Leaverton, P. E. (1994). SCIENTIFIC AND ETHICAL ISSUES IN THE USE OF PLACEBO CONTROLS IN CLINICAL TRIALS. *Annual Reviews Public Health.* https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/1097-0142%2819900915%2966%3A6%3C1091%3A%3AAID-CNCR2820660602%3E3.0.CO%3B2-F
16. Collage of Pharmacy. (2019). *PHARMD PROGRAM IN GMU RECEIVES CERTIFICATION FROM ACCREDITATION COUNCIL FOR PHARMACY EDUCATION (ACPE)*. Gulf Medical University. https://gmu.ac.ae/cop_news/pharmd-program-in-gmu-receives-certification-from-accreditation-council-for-pharmacy-education-acpe/
17. Coopersmith, C. M., Wunsch, H., Fink, M. P., Linde-Zwirble, W. T., Olsen, K. M., Sommers, M. S., Anand, K. J. S., Tchorz, K. M., Angus, D. C., & Deutschman, C. S. (2012). A comparison of critical care research funding and the financial burden of critical illness in the United States. *Critical Care Medicine*, *40*(4), 1072–1079. https://doi.org/10.1097/CCM.0b013e31823c8d03
18. Faculty of Medicine and Health Science. (2006). *Pharm.Dprogram*. An-Najah National University. https://fmhs.najah.edu/en/education-admissions/pharmacy-

programs/pharmacy-doctor/

19. Faculty of Nursing Pharmacy and Health Professions. (n.d.). *Doctor of Pharmacy (BA)*. Birzeit University Palestine. Retrieved August 9, 2021, from https://www.birzeit.edu/en/study/programs/BA-doctor-pharmacy
20. Fahimi, F. (2010). Implementation of a clinical pharmacy education program in a teaching hospital: Resident oriented documentation and intervention. *Iranian Journal of Pharmaceutical Research*, *9*(3), 297–302. https://doi.org/10.22037/ijpr.2010.870
21. Forster, A. J., Kyeremanteng, K., Hooper, J., Shojania, K. G., & Van Walraven, C. (2008). The impact of adverse events in the intensive care unit on hospital mortality and length of stay. *BMC Health Services Research*, *8*, 1–8. https://doi.org/10.1186/1472-6963-8-259
22. Fuchs, L., Chronaki, C. E., Park, S., Novack, V., Baumfeld, Y., Scott, D., McLennan, S., Talmor, D., & Celi, L. (2012). ICU admission characteristics and mortality rates among elderly and very elderly patients. *Intensive Care Medicine*, *38*(10), 1654–1661. https://doi.org/10.1007/s00134-012-2629-6
23. Gallagher, J., Byrne, S., Woods, N., Lynch, D., & McCarthy, S. (2014). Cost-outcome description of clinical pharmacist interventions in a university teaching hospital. *BMC Health Services Research*, *14*(1), 1–8. https://doi.org/10.1186/1472-6963-14-177
24. Gallagher, J., McCarthy, S., & Byrne, S. (2014). Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. *International Journal of Clinical Pharmacy*, *36*(6), 1101–1114. https://doi.org/10.1007/s11096-014-0008-9
25. General Directorate of Pharmacy. (2020). *No Title*. MoH. http://pharmacy.moh.ps/index/PriceList/years/2020/Language/en
26. Gharekhani, A., Kanani, N., Khalili, H., & Dashti-Khavidaki, S. (2014). Frequency, types, and direct related costs of medication errors in an academic nephrology ward in Iran. *Renal Failure*, *36*(8), 1268–1272. https://doi.org/10.3109/0886022X.2014.934650
27. Graabæk, T., & Kjeldsen, L. J. (2013). Medication Reviews by Clinical Pharmacists at Hospitals Lead to Improved Patient Outcomes: A Systematic Review. *Basic and Clinical Pharmacology and Toxicology*, *112*(6), 359–373. https://doi.org/10.1111/bcpt.12062

28. Guignard, B., Bonnabry, P., Perrier, A., Dayer, P., Desmeules, J., & Samer, C. F. (2015). Drug-related problems identification in general internal medicine: The impact and role of the clinical pharmacist and pharmacologist. *European Journal of Internal Medicine*, *26*(6), 399–406. https://doi.org/10.1016/j.ejim.2015.05.012
29. Hamblin, S., Rumbaugh, K., & Miller, R. (2012). Prevention of adverse drug events and cost savings associated with PharmD interventions in an academic Level i trauma center: An evidence-based approach. *Journal of Trauma and Acute Care Surgery*, *73*(6), 1484–1490. https://doi.org/10.1097/TA.0b013e318267cd80
30. Hammond, D. A., Gurnani, P. K., Flannery, A. H., Smetana, K. S., Westrick, J. C., Lat, I., & Rech, M. A. (2019). Scoping Review of Interventions Associated with Cost Avoidance Able to Be Performed in the Intensive Care Unit and Emergency Department. *Pharmacotherapy*, *39*(3), 215–231. https://doi.org/10.1002/phar.2224
31. Hammond, D., Adams, W., Flannery, A., Smetana, K., Gurnani, P., Patel, M. V. B., Peppard, W., & Rech, M. (2019). Pharmacit Avoidnce or Reductions in Medication Costs in Critically Ill Patients : Pharm-Crit Study. *Critical Care Medicine*, *48*(1).
32. Hammond, D., Flowers, H. J. C., Meena, N., Painter, J. T., & Rech, M. A. (2019). Cost avoidance associated with clinical pharmacist presence in a medical intensive care unit. *Journal of the American College of Clinical Pharmacy*, *2*(6), 610–615. https://doi.org/10.1002/jac5.1111
33. Hammond, D., Flowers, H., & Painter, J. (2016). Cost Avoidance from Pharmacist Interventions Documented in a Medical ICU over a Five- Month Period. *Crit Care Med*, *44*(12).
34. Hamouda, A., Al-Rousan, R. M., & Alkhateeb, F. M. (2015). Pharmacy education in the palestinian territories. *American Journal of Pharmaceutical Education*, *79*(1), 1–2. https://doi.org/10.5688/ajpe79103
35. Horn, E., & Jacobi, J. (2006). The critical care clinical pharmacist: Evolution of an essential team member. *Critical Care Medicine*, *34*(3 SUPPL.). https://doi.org/10.1097/01.CCM.0000199990.68341.33
36. Hughes, D. A. (2010). From NCE to NICE: The role of pharmacoeconomics. *British Journal of Clinical Pharmacology*, *70*(3), 317–319. https://doi.org/10.1111/j.1365-2125.2010.03708.x
37. Hunter, R., & Shearer, J. (2014). Cost-consequences analysis - an underused method of economic evaluation. *National Institute for Health Research*, 4–5. http://www.rds-london.nihr.ac.uk/How-to-design-a-study-find-funding/Health-economics/Cost-

consequences-analysis.aspx

38. Intensive Care Society. (2013). Core Standards for Intensive Care Units. *Core Standards for Intensive Care Units*, *1*, 1–27.
39. Jacobi, J. (2016). Clinical Pharmacists: Practitioners Who Are Essential Members of Your Clinical Care Team. *Revista Médica Clínica Las Condes*, *27*(5), 571–577. https://doi.org/10.1016/j.rmclc.2016.09.002
40. JointCommission of Pharmacy Practitioners. (2014). Pharmacists' patient care process. *Pharmacy Times*. https://doi.org/10.21019/preceptor.1001.13
41. Jurado, L. V., & Steelman, J. D. (2013). The role of the pharmacist in the intensive care unit. *Critical Care Nursing Quarterly*, *36*(4), 407–414. https://doi.org/10.1097/CNQ.0b013e3182a11057
42. Kaboli, P. J., Hoth, A. B., McClimon, B. J., & Schnipper, J. L. (2006). Clinical Pharmacists and Inpatient Medical Care. *Archives of Internal Medicine*, *166*(9), 955–964.
43. Kane-Gill, S. L., Kirisci, L., Verrico, M. M., & Rothschild, J. M. (2012). Analysis of risk factors for adverse drug events in critically ill patients*. *Critical Care Medicine*, *40*(3), 823–828. https://doi.org/10.1097/CCM.0b013e318236f473
44. Kaushal, R., Bates, D. W., Franz, C., Soukup, J. R., & Rothschild, J. M. (2007). Costs of adverse events in intensive care units. *Critical Care Medicine*, *35*(11), 2479–2483. https://doi.org/10.1097/01.CCM.0000284510.04248.66
45. Kearney, A., Walsh, E. K., Kirby, A., Halleran, C., Byrne, D., Haugh, J., & Sahm, L. J. (2018). A budget impact analysis of a clinical medication review of patients in an Irish university teaching hospital. *Global & Regional Health Technology Assessment: Italian; Northern Europe and Spanish*, *2018*, 228424031880772. https://doi.org/10.1177/2284240318807726
46. Khdour, M. R., Alayasa, K. S., Alshahed, Q. N., & Hawwa, A. F. (2013). Physicians' perceptions, attitudes and expectations regarding the role of hospital-based pharmacists in the West Bank, Palestine. *International Journal of Pharmacy Practice*, *21*(3), 178–184. https://doi.org/10.1111/j.2042-7174.2012.00246.x
47. Kheir, N., Al Saad, D., & Al Naimi, S. (2013). Pharmaceutical care in the Arabic-speaking Middle East: literature review and country informant feedback. *Avicenna*, *2013*(1). https://doi.org/10.5339/avi.2013.2
48. Klopotowska, J. E., Kuiper, R., van Kan, H. J., de Pont, A. C., Dijkgraaf, M. G., Lie-A-Huen, L., Vroom, M. B., & Smorenburg, S. M. (2010). On-ward participation of

a hospital pharmacist in a Dutch intensive care unit reduces prescribing errors and related patient harm: An intervention study. *Critical Care*, *14*(5), 1–11. https://doi.org/10.1186/cc9278

49. Kopp, B. J., Erstad, B. L., Allen, M. E., Theodorou, A. A., & Priestley, G. (2006). Medication errors and adverse drug events in an intensive care unit: Direct observation approach for detection. *Critical Care Medicine*, *34*(2), 415–425. https://doi.org/10.1097/01.CCM.0000198106.54306.D7
50. Kopp, B. J., Mrsan, M., Erstad, B. L., & Duby, J. J. (2007). Cost implications of and potential adverse events prevented by interventions of a critical care pharmacist. *American Journal of Health-System Pharmacy*, *64*(23), 2483–2487. https://doi.org/10.2146/ajhp060674
51. Kumar, P. (2018). Pharmacoeconomics: an overview. *Universal Journal of Pharmacy*.
52. Leache, L., Aquerreta, I., Aldaz, A., Monedero, P., Idoate, A., & Ortega, A. (2019). Clinical and economic impact of clinical pharmacist interventions regarding antimicrobials on critically ill patients. *Research in Social and Administrative Pharmacy*, *July*, 1–5. https://doi.org/10.1016/j.sapharm.2019.07.006
53. Leape, L. L., Cullen, D. J., Clapp, M. D., Burdick, E., Demonaco, H. J., Erickson, J. I., & Bates, D. W. (1999). Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *Journal of the American Medical Association*, *282*(3), 267–270. https://doi.org/10.1001/jama.282.3.267
54. Lee, H., Ryu, K., Sohn, Y., Kim, J., Suh, G. Y., & Kim, E. Y. (2020). Impact on Patient Outcomes of Pharmacist Participation in Multidisciplinary Critical Care Teams: A Systematic Review and Meta-Analysis∗. *Critical Care Medicine*, *5*, 1243–1250. https://doi.org/10.1097/CCM.0000000000003830
55. Leguelinel-Blache, G., Nguyen, T. L., Louart, B., Poujol, H., Lavigne, J. P., Roberts, J. A., Muller, L., Kinowski, J. M., Roger, C., & Lefrant, J. Y. (2018). Impact of quality bundle enforcement by a critical care pharmacist on patient outcome and costs. *Critical Care Medicine*, *46*(2), 199–207. https://doi.org/10.1097/CCM.0000000000002827
56. Liu, G., Hu, S., Wu, J., Wu, J., Dong, Z., & Li, H. (2020). *China Guidelines for Pharmacoeconomic Evaluations.* 65–70.
57. Lord Carter of Coles. (2016). *Operational productivity and performance in English NHS acute hospitals : Unwarranted variations*. *February*.

58. MacLaren, R., Bond, C. A., Martin, S. J., & Fike, D. (2008). Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. *Critical Care Medicine*, *36*(12), 3184–3189. https://doi.org/10.1097/CCM.0b013e31818f2269
59. Magedanz, L., Silliprandi, E. M., & Dos Santos, R. P. (2012). Impact of the pharmacist on a multidisciplinary team in an antimicrobial stewardship program: A quasi-experimental study. *International Journal of Clinical Pharmacy*, *34*(2), 290–294. https://doi.org/10.1007/s11096-012-9621-7
60. Mahmoodpoor, A., Kalami, A., Shadvar, K., Entezari-Maleki, T., & Hamishehkar, H. (2018). Evaluation of Clinical Pharmacy Services in the Intensive Care Unit of a Tertiary University Hospital in the Northwest of Iran. *Journal of Research in Pharmacy Practice*, *7*(1), 30–35. https://doi.org/10.4103/jrpp.JRPP_17_82
61. Michalets, E., Creger, J., & Shillinglaw, W. R. (2015). Outcomes of expanded use of clinical pharmacist practitioners in addition to team-based care in a community health system intensive care unit. *American Journal of Health-System Pharmacy*, *72*(1), 47–53. https://doi.org/10.2146/ajhp140105
62. Ministry of Health. (2018). *Health Annual Report*.
63. Ministry of Health, 2019. (2019). *Ministry of Health. (2019). Annual Report for Ministry of Health in Palestine. Retrieved from www.moh.ps*.
64. Miyagawa CI, R. J. (1986). Effect of pharmacist interventions on drug therapy costs in a surgical intensive-care unit. *American Journal of Hospital Pharmacy*, *43*(12), 3008_13.
65. MoH. (2020). *Health Annual Report Palestine 2020*. http://site.moh.ps/index/Books/BookType/2/Language/ar
66. Molino, C. de G. R. C., Carnevale, R. C., Rodrigues, A. T., Visacri, M. B., Moriel, P., & Mazzola, P. G. (2014). Impact of pharmacist interventions on drug-related problems and laboratory markers in outpatients with human immunodeficiency virus infection. *Therapeutics and Clinical Risk Management*, *10*(1), 631–639. https://doi.org/10.2147/TCRM.S61821
67. Morgan, S. (2011). The pharmacist's role in medication adherence. *U.S. Pharmacist*, *36*(June).
68. Morimoto T, Gandhi K , Sege A , T C Hsieh, B. D. (2006). Adverse drug events and medication errors. *BMJ Quality and Safety*, *13*(13), 306-315.[last accessed 2020 Feb 17]. https://qualitysafety.bmj.com/content/qhc/13/4/306.full.pdf

69. Najjar, A., Amro, Y., Kitaneh, I., Abu-Sharar, S., Sawalha, M., Jamous, A., Qiq, M., Makharzeh, E., Laban, B. S., Amro, W., & Amro, A. A. (2015). Knowledge and adherence to medications among Palestinian geriatrics living with chronic diseases in the West Bank and East Jerusalem. *PLoS ONE*, *10*(6). https://doi.org/10.1371/journal.pone.0129240
70. Naseef, H., Amria, A., Asrawi, A., Al-Shami, N. M., & Dreidi, M. (2020). The acceptance and awareness of healthcare providers towards doctor of pharmacy (Phram D) in the Palestinian health care system. *Saudi Pharmaceutical Journal*, *28*(9), 1068–1074. https://doi.org/10.1016/j.jsps.2020.07.007
71. Nesbit, T. W., Shermock, K. M., Bobek, M. B., Capozzi, D. L., Flores, P. A., Leonard, M. C., Long, J. K., Militello, M. A., White, D. A., Barone, L. D., Goldman, M. P., & Kvancz, D. A. (2001a). Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. *American Journal of Health-System Pharmacy*, *58*(9), 784–790. https://doi.org/10.1093/ajhp/58.9.784
72. Nesbit, T. W., Shermock, K. M., Bobek, M. B., Capozzi, D. L., Flores, P. A., Leonard, M. C., Long, J. K., Militello, M. A., White, D. A., Barone, L. D., Goldman, M. P., & Kvancz, D. A. (2001b). Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. *American Journal of Health-System Pharmacy*, *58*(9), 784–790. https://doi.org/10.1093/ajhp/58.9.784
73. Onatade, R., Appiah, S., Stephens, M., & Garelick, H. (2018). Evidence for the outcomes and impact of clinical pharmacy: Context of UK hospital pharmacy practice. *European Journal of Hospital Pharmacy* , *25*(e1), E21–E28. https://doi.org/10.1136/ejhpharm-2017-001303
74. PCNE, 2019. (2019). Classification for Drug Related Problems V8.02. Pharmaceutical Care Network Europe Foundation, Zuidlaren. *Pharmaceutical Care Network Europe Association*, *V8.02*, 3. https://www.pcne.org/upload/files/318_PCNE_classification_V8-03.pdf
75. Preslaski, C. R., Lat, I., MacLaren, R., & Poston, J. (2013). Pharmacist contributions as members of the multidisciplinary ICU team. *Chest*, *144*(5), 1687–1695. https://doi.org/10.1378/chest.12-1615
76. Ramos, S. F., Santos Júnior, G. A. Dos, Pereira, A. M., Dosea, A. S., Rocha, K. S. S., Pimentel, D. M. M., & Lyra-Jr, D. P. De. (2018). Facilitators and strategies to implement clinical pharmacy services in a metropolis in Northeast Brazil: A qualitative approach. *BMC Health Services Research*, *18*(1), 1–12.

https://doi.org/10.1186/s12913-018-3403-4

77. Ravn-Nielsen, L. V., Duckert, M. L., Lund, M. L., Henriksen, J. P., Nielsen, M. L., Eriksen, C. S., Buck, T. C., Pottegård, A., Hansen, M. R., & Hallas, J. (2018). Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission a randomized clinical trial. *JAMA Internal Medicine*, *178*(3), 375–382. https://doi.org/10.1001/jamainternmed.2017.8274
78. Rech, M., Alexander Flannery, K. S.-W. A., Tana, P. G., Megan Van Berkel Patel, W. P., & Hammond, D. (2019). Pharmacist Avoidance or Reductions in Medication Costs in Emergently Ill Patients: Pharm-Em Study. *Critical Care Medicine*, *48*(1).
79. Reinau, D., Furrer, C., Stämpfli, D., Bornand, D., & Meier, C. R. (2019). Evaluation of drug-related problems and subsequent clinical pharmacists' interventions at a Swiss university hospital. *Journal of Clinical Pharmacy and Therapeutics*, *44*(6), 924–931. https://doi.org/10.1111/jcpt.13017
80. Roque, K. E., Tonini, T., & Melo, E. C. P. (2016). Adverse events in the intensive care unit: impact on mortality and length of stay in a prospective study. *Cadernos de Saúde Pública*, *32*(10), 1–14. https://doi.org/10.1590/0102-311x00081815
81. Rottenkolber, D., Hasford, J., & Stausberg, J. (2012). Costs of adverse drug events in German hospitals - A microcosting study. *Value in Health*, *15*(6), 868–875. https://doi.org/10.1016/j.jval.2012.05.007
82. Royal Pharmaceutical Society. (2013). Medicines Optimisation : Helping patients to make the most of medicines. *RPS Good Practice Guidance*, *May*.
83. Saadah, L. M., Nazzal, Y. M., Abdelmaksoud, S. I., Nazzal, M. K., Abu, E. L., & Qasemi, A. A. Al. (2014). Predictors of Physicians Acceptance of Clinical Pharmacy Recommendation at a military hospital in the United Arab Emirates. *International Journal of Pharmacy*, *4*(4), 78–85.
84. Saokaew, S., Maphanta, S., & Thangsomboon, P. (2009). Impact of pharmacist's interventions on cost of drug therapy in intensive care unit. *Pharmacy Practice (Granada)*, *7*(2), 81–87. https://doi.org/10.1097/MPH.0b013e3182707aff
85. Saseen, J. J., Ripley, T. L., Bondi, D., Burke, J. M., Cohen, L. J., Mcbane, S., Mcconnell, K. J., Sackey, B., Sanoski, C., Simonyan, A., Taylor, J., & Griend, J. P. Vande. (2017). ACCP Clinical Pharmacist Competencies. *Pharmacotherapy*. https://doi.org/10.1002/phar.1923
86. SCCM-ACCP. (2000). Position paper on critical care pharmacy services. *Pharmacotherapy*, *20*(11), 1400–1406.

https://doi.org/10.1592/phco.20.17.1400.34893

87. School of Pharmacy. (2002). Pharm.D. Program Accreditation. *LAU*. https://pharmacy.lau.edu.lb/about/accreditation.php
88. Schumock G, DW, B. M. G., J, L., & TD, O. (2003). Evaluating and justifying clinical pharmacy services. In: Pharmacoeconomics & Outcomes. In *American College of Clinical Pharmacy* (2nd editio).
89. Shen, J., Sun, Q., Zhou, X., Wei, Y., Qi, Y., Zhu, J., & Yan, T. (2011). Pharmacist interventions on antibiotic use in inpatients with respiratory tract infections in a Chinese hospital. *International Journal of Clinical Pharmacy*, *33*(6), 929–933. https://doi.org/10.1007/s11096-011-9577-z
90. Siddarama, R., Prasad, T. S. D., & Mandha, M. (2018). *Clinical pharmacy services in cardiovascular disease patients*. *July 2015*.
91. Skjøt-Arkil, H., Lundby, C., Kjeldsen, L. J., Skovgårds, D. M., Almarsdóttir, A. B., Kjølhede, T., Duedahl, T. H., Pottegård, A., & Graabæk, T. (2018). Multifaceted Pharmacist-led Interventions in the Hospital Setting: A Systematic Review. *Basic and Clinical Pharmacology and Toxicology*, *123*(4), 363–379. https://doi.org/10.1111/bcpt.13030
92. Spinewine, A., Fialová, D., & Byrne, S. (2012). The role of the pharmacist in optimizing pharmacotherapy in older people. *Drugs and Aging*, *29*(6), 495–510. https://doi.org/10.2165/11631720-000000000-00000
93. Stemer, G., & Lemmens-Gruber, R. (2011). The clinical pharmacist's contributions within the multidisciplinary patient care team of an intern nephrology ward. *International Journal of Clinical Pharmacy*, *33*(5), 759–762. https://doi.org/10.1007/s11096-011-9548-4
94. Sweileh, W. M., Al-Jabi, S. W., Sawalha, A. F., & Zyoud, S. H. (2009). Pharmacy education and practice in west bank, palestine. *American Journal of Pharmaceutical Education*, *73*(2). https://doi.org/10.5688/aj730238
95. Sweileh, W. M., Zyoud, S. H., & Al-Haddad, M. S. (2016). Pharmacy Practice in Palestine. In *Pharmacy Practice in Developing Countries: Achievements and Challenges* (Vol. 253, Issue Area C). Elsevier Inc. https://doi.org/10.1016/B978-0-12-801714-2.00013-7
96. Tefera, G. M., Zeleke, A. Z., Jima, Y. M., & Kebede, T. M. (2020). Drug therapy problems and the role of clinical pharmacist in surgery ward: Prospective observational and interventional study. *Drug, Healthcare and Patient Safety*, *12*, 71–

83. https://doi.org/10.2147/DHPS.S251200

97. The University of Jordan. (2016). *School of Pharmacy Granted ACPE International Certification*. UJ Newsletter. http://www.ju.edu.jo/Lists/NewsLetter/Disp_f.aspx?ID=1148&Issue=July 2016&order=

98. Touchette, D. R., Doloresco, F., Suda, K. J., Perez, A., Turner, S., Jalundhwala, Y., Tangonan, M. C., & Hoffman, J. M. (2014). Economic evaluations of clinical pharmacy services: 2006-2010. *Pharmacotherapy*, *34*(8), 771–793. https://doi.org/10.1002/phar.1414

99. V Anderson, S., & Schumock, G. T. (2009). Evaluation and justification of clinical pharmacy services. *Expert Review of Pharmacoeconomics and Outcomes Research*, *9*(6), 539–545. https://doi.org/10.1586/erp.09.57

100. Yasunaga, D., Tasaka, Y., Murakami, S., Tanaka, A., Tanaka, M., & Araki, H. (2016). Economic contributions of pharmaceutical interventions by pharmacists: A retrospective report in Japan. *Journal of Pharmaceutical Policy and Practice*, *10*(1), 1–7. https://doi.org/10.1186/s40545-016-0073-7

101. Younis, M. Z., Jaber, S., Mawson, A. R., & Hartmann, M. (2013). Estimating the unit costs of public hospitals and primary healthcare centers. *International Journal of Health Planning and Management*, *28*(4), 320–332. https://doi.org/10.1002/hpm.2147

Annex 1-A: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
France (Leguelinel-Blache et al., 2018)	Before and after study	To describe the effect of pharmacist-led interventions on drug therapy and clinical strategies on ICU patient outcome and hospital costs	One Medical ICU and one surgical (16 and 10 beds). From January 1, 2013, to June 30, 2015	1,519 during the observation period and 1,268 during intervention periods,	1,164 patients	A critical care pharmacist provided recommendations to clinicians regarding sedative drugs and doses, choice of mechanical ventilation mode and related settings, antimicrobial de-escalation, and central venous and urinary catheters removal.	The overall cost savings were 10,840 Euros (10,727–10,952 Euros) per month, mostly due to reduced consumption of sedatives and antimicrobials. In addition, hospital costs per stay (2,560) Euros [3,728–1,392 Euros]; $p < 0.001$).	Critical care pharmacist-led interventions were associated with decreases in ICU and hospital length of stays and ICU drug costs

Annex 1-B: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
North Carolina (Michalets et al., 2015)	A retrospective pre–post comparison	Report clinical and cost benefits achieved through expanded use of state licensed clinical pharmacist practitioners (cpps) with prescribing authority on a critical care team	Community health system's neurotrauma ICU (2009–11).	2,198 patients	13,386 Interventions	During year 1 of the study only one pharmacist, year 2 include three pharmacists Total medication errors, error origin, and the number of category D or higher-severity errors were compared between the study periods.	Associated cost savings estimated $2,118,426. 182% increase in encounters for therapeutic optimization (p = 0.01), with an associated 29% increase in cost savings and an improved return on investment.	With expanded CPP involvement on the NTICU team, there was a substantial increase in therapeutic optimization interventions and a clinically reduction in preventable ADEs, as well as an estimated 30% increase in associated cost savings

Annex 1-C: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
Spain (Leache et al., 2019)	A retrospective observational study	To evaluate the clinical and economic impact of clinical pharmacist interventions on antimicrobials in an ICU. To identify drug related problems and medication errors detected by the pharmacist	University hospital ICU over 5-month period.	114 patients	212 drug related problems Physicians accepted 97.6% of the interventions	Data related to patients, DRPs, medication errors and CP interventions were extracted from the hospital information system. A second pharmacist validated the registered information contrasting it with the patient chart. In case of discrepancy, a physician was consulted	A potential saving of 10,905 € was estimated as a result of pharmacist interventions and 4.8 € were avoided per euro invested in a clinical pharmacist.	A clinical pharmacist performing interventions on antimicrobials in the ICU has a positive impact on patient care and decreases costs

Annex 1-D: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
Chicago (D. Hammond, Flowers, et al., 2019)	Observational study	To determine the clinical pharmacist-generated cost avoidance and benefit-cost ratio in a medical intensive care unit (MICU).	MICU over 12-month period	222 patients	8866 clinical pharmacist-interventions Averaging 38.9 interventions per day	any exchange of information and/or recommendation provided by the clinical pharmacist regarding a specific patient's medication or nutrition regimen	Cost avoidance was $3 270 178 and the benefit-cost ratio was 24.5:1.	Employing a clinical pharmacist to be part of the multidisciplinary MICU team can reduce health care expenditures through cost avoidance.
Chicago (Hammond et al., 2016)	A single-center, retrospective, cohort study.	To determine the clinical pharmacist-generated cost avoidance in a medical ICU	MICU During a five-month period	NA	4,280 clinical pharmacist-interventions were implemented, averaging 44.6 /day	All accepted recommendations from a clinical pharmacist who rounds in the medical ICU	A total cost avoidance of $2,526,974, averaging $26,323 per day and $6,581 per hour, respectively.	Employing a clinical pharmacist reduces healthcare costs through cost avoidance.

Annex 1-E: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
Chicago (D. Hammond, Adams, et al., 2019)	Observational study	To comprehensively classify and quantify CA interventions from pharmacists in the ICU	91 centers 302 ICU pharmacists During a 4-week period between August 2018 and January 2019.	27,681 patients	60,013 interventions	Interventions were grouped into 6 pre-established categories with 38 different subcategories from a validated systematic framework for CA interventions. CA values from each intervention were determined using the same framework	CU pharmacist-generated CA totaled $24,352,176 Average CA was $406 per intervention, $880 per patient, and $80,636 per pharmacist in the 4-week period	ICU clinical pharmacists perform interventions that significantly reduce healthcare expenditures

Annex 1-F: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
German (Klopotowska et al., 2010)	A prospective study compared a baseline period with an intervention period. During	To investigate whether participation of a hospital pharmacist can also be an effective approach in reducing prescribing errors and related patient harm (preventable ADEs) in this specific setting	ICU over 8.5-month period	1,173	(659 recommendations	An ICU hospital pharmacist reviewed medication orders; noted issues related to prescribing, formulated recommendations and discussed those during patient review meetings with the attending ICU physicians.	Per monitored patient-day, the intervention itself cost €3, but might have saved €26 to €40 by preventing ADEs	On-ward participation of a hospital pharmacist in a Dutch ICU was associated with significant reductions in prescribing errors and related patient harm (preventable ADEs) at acceptable costs per monitored patient-day

Annex 1-G: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
German (Bosma et al., 2018)	interventional, prospective quality improvement study 2008-2011	This study looks into the clinical and financial impact of interventions made by pharmacists during patient rounds	ICU in general teaching hospital (GTH) and a university hospital (UH)	In the GTH 160 patients were included and in the UH 174.	A total of 332 and 280 interventions were analyzed	Review of medication orders and participation in patient rounds by an ICU-trained pharmacist.	. Acceptance of the interventions was 67.3% in the GTH and 61.8% in the UH. The cost benefit was €119 (GTH) and €136 (UH) per accepted intervention.	the model appeared to be cost-effective in both ICU settings
Thailand (Saokaew et al., 2009)	A Prospective, standard care-controlled study design	to determine pharmacist's interventions led to change in cost saving and cost avoidance in intensive care unit	2 (ICU). One study group and other control group Over 5 weeks period	65 patients	127 interventions in ICU-1 team. 98% of the interventions were accepted	Participated in morning rounds. CP was full responsibility for providing drug information, pharmacotherapeutic.	The overall Drug cost saving 1,971.43 USD The overall adverse drug event cost 294.62 USD The net cost saved and avoided was 2,266.05 USD.	Although the statistical was not significant, having a pharmacist participated in ICU patient care team tend to reduced overall drug cost

Annex 1-H: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
Tucson, Arizona (Kopp et al., 2007)	Retrospective.	To study the cost implications of and potential adverse events prevented by the interventions of a critical care pharmacist	Surgical (ICU) over form 4.5 months. The period from mid-October 2003 through February 2004	100	129 interventions	The decentralized pharmacists were required to document their activities in an existing database to help justify the clinical positions.	The potential cost avoidance of the documented interventions was $205,919–$280,421.	Among the interventions performed and documented by a clinical pharmacist in an ICU, patient care rounds and chart-review activities were associated with the greatest number of interventions and the greatest potential cost avoidance

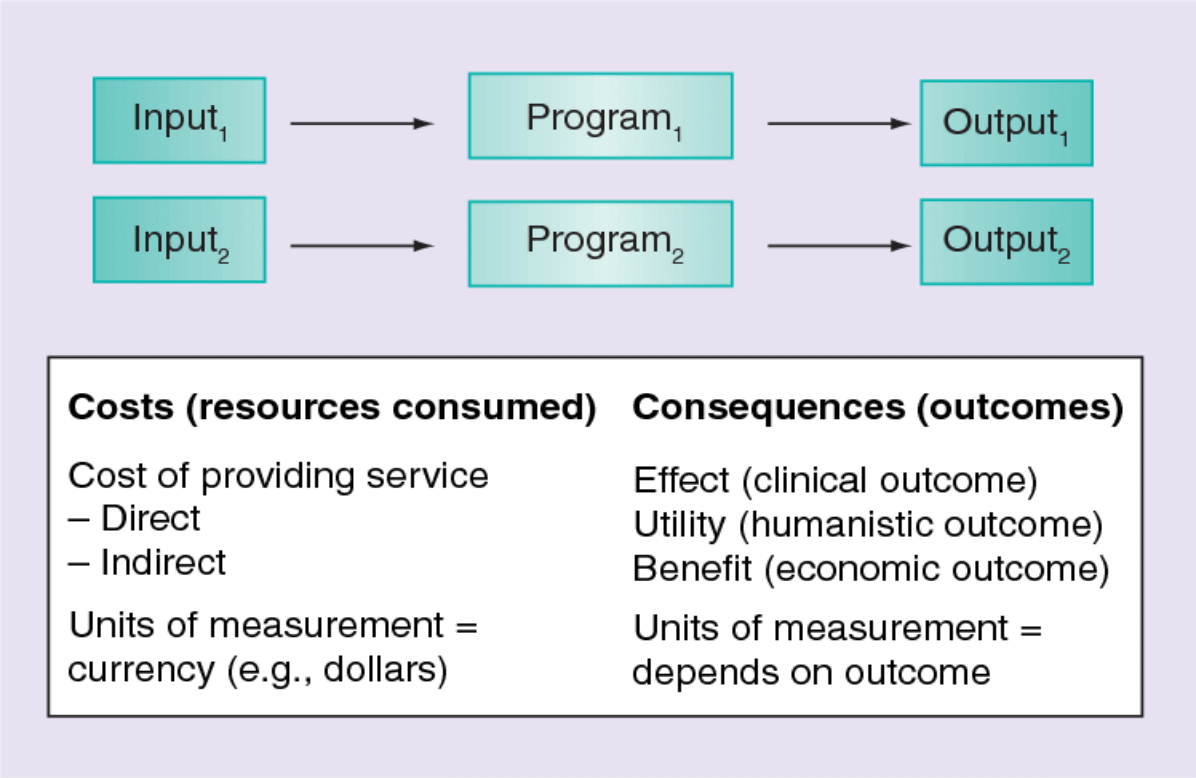
Annex 1-I: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	Economic outcome	Conclusion
US (MacLaren et al., 2008)	comparative study based on national survey of previous study	To determine whether the absence or presence of clinical pharmacists in ICU results in differences in mortality rates, length of ICU stay, and ICU charges for Medicare patients with nosocomial-acquired infections, community acquired infections, and sepsis	ICUs of 265 to 276 hospitals	8,927–54,042 patients.	ICUs that did not have clinical pharmacists had greater total Medicare billings of 12% ($p < 0.001$, $132,978,807 extra billing charges), 11.9% ($p < 0.001$, $32,240,378 extra billing charges), and 12.9% ($p < 0.001$, $224,694,784 extra billing charges) for nosocomial-acquired infections, community-acquired infections, and sepsis, respectively.	The involvement of clinical pharmacists in the care of critically ill Medicare patients with infections is associated with improved clinical and economic outcomes. Hospitals should consider employing clinical ICU pharmacists.

Annex 1-J: Summary of literature review regarding the association between clinical pharmacist interventions and economic outcome

Location/author	Study design	Objectives	Settings	Sample size	#CP interventions	Interventions	Economic outcome	Conclusion
Amman, Jordan (Aljbouri et al., 2013)	Comparative study between 2 periods	To determine whether the presence of Clinical Pharmacist affects the cost of drug therapy for patients admitted to the Intensive Care Unit (ICU) at Al-Hussein hospital at Royal Medical Services	ICU At Al-Hussein hospital at Royal Medical Services (RMS).	This study compares the consumed quantities of drugs over two periods of time. Each period was ten months long. In the second period there was a Clinical Pharmacist		The decrease in consumption rate of drugs is considered an indicator of the success of Clinical Pharmacist in the ICU, as any decrease in consumption rate reflects the correct application of Clinical Pharmacy practices. The cost of this decrease in consumption rate represents the total reduction of drug therapy cost	The total reduction of drug therapy cost after applying Clinical Pharmacy practices in the ICU over a period of ten months was 149946.80 JD (211574.90 USD), which represents an average saving of 35.8% when compared to the first period in this study	The results of this study showed a significant reduction in the consumed quantities of drugs and therefore a reduction in cost of drug therapy. Such findings highlight the importance of the presence of Clinical Pharmacist in all Jordanian hospital's wards and units

Annex 2 : Basic model of evaluation of clinical pharmacy services (Schumock et al., 2003)



Annex 3: Consult Note form

Patient information	
Name (abbreviated)	Admission Date
MD (consultant)	Discharge Date
Date of Birth (dd/mm/yy) Age	APACHE 2 score
Gender	group: control / interventional
Weight (kg)	IBW BMI

Case Summary (chief compliant and what happened to the patient during hospitalization)	
Past Medical History/ Surgery	

Medications				
Indication	**Drug Name, Generic and brand/Strength/Frequency/ Route**	**Start-Stop Dates**		**Time**

Cp Consult note

date Disease

Assessment: (Treatment Related Problems)	**Plan**

Desired Outcomes and Goals	**Recommendation**

Monitoring:

Efficacy target	Toxicity sign	Counseling

Follow up note:

Reference:

Physician Decision Agree with Plan Recommended Proposed Modified Plan Disagree

Annex 4: Ethical Approval to conduct the study

Al-Quds University
Jerusalem
Deanship of Scientific Research

بسم الله الرحمن الرحيم

جامعة القدس
القدس
عمادة البحث العلمي

Research Ethics Committee
Committee's Decision Letter

Date: 17 June 2020
Ref No: 142/REC/2020

Dears Prof. Motasem Hamdan, Mrs. Asil Houso

Thank you for submitting your application for research ethics approval. After reviewing your application entitled **"Cost benefit analysis of clinical pharmacist interventions in medical intensive care unit ",** the Research Ethics Committee confirms that your application is in accordance with the research ethics guidelines at Al-Quds University.

We would appreciate receiving a copy of your final research report/ publication. Thank you again and wish you a productive research that serves the best interests of your subjects.

PS: This letter will be valid for two years.

Nuha El Sharif, PhD
Research Ethics Committee Chair

Cc. Prof. Imad Abu Kishek - President
Cc. Members of the committee
Cc. file

Abu-Dies, Jerusalem P.O.Box 20002
Tel-Fax: #970-02-2791293
research@admin.alquds.edu
أبوديس، القدس ص.ب. 20002
تلفاكس: #970-02-2791293

Annex 5: MoH approval to lunch the study

State of Palestine
Ministry of Health - Nablus
General Directorate of Education in Health

Zoom in (Ctrl+Plus)

وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Ref.: .....
Date:.....

الرقم: ٢٠٢٠/١٣٧/١٦٤
التاريخ: ١٥/٧/٢٠٢٠

الأخ مدير مجمع فلسطين الطبي المحترم ،،،

تحية واحترام،،

الموضـــوع: تسهيل مهمة بحث

لاحقاً لموافقة معالي وزيرة الصحة، يرجى تسهيل مهمة الطالبة: أسيل حوسو، برنامج ماجستير السياسات والادارة الصحية- كلية الصحة العامة - جامعة القدس، لاجراء بحث بعنوان:

Cost benefit analysis of clinical pharmacist interventions in resolving treatment related problem in medical intensive care unit

حيث تهدف الدراسة الى تقييم الفوائد الاقتصادية للتدخل الصيدلاني كجزء من فريق وحدة العناية المكثفة الطبية لحل المشاكل المتعلقة بالعلاج. وذلك في:

- مجمع فلسطين الطبي/ رام الله.

علما أن الطالبة ستلتزم باخلاقيات البحث العلمي وستكون المعلومات لأغراض البحث فقط.

وتقبلوا فائق الاحترام،،

د. أمل أبو عوض
مدير عام التعليم الصحي

نسخة: عميد كلية الصحة العامة/ جامعة القدس

P.O .Box: 14
Tel.:09-2333901

ص.ب. 14
تلفون: 09-2333901

Annex 6: Consent Form

جامعة القدس
Al-Quds University

موافقة على المشاركة في بحث علمي

تحية طيبة وبعد،

نطلب منك أن تأخذ\اي وقتك لقراءة النموذج وأن تطرح\اي أي أسئلة قد تكون لديك قبل الموافقة على المشاركة في الدراسة .

أنت\اي مدعو\اة للمشاركة ببحث علمي سريري سيجرى في مستشفى رام الله بعنوان " تحليل الجدوى الاقتصادية للتدخلات الصيدلانية السريرية في وحدة العناية المكثفة الطبية" وهو بحث يجرى من قبل الطالبة في كلية الصحة العامة الدكتورالصيدلي اسيل خالد حوسو

ويهدف هذا البحث لتقييم الفوائد الاقتصادية للتدخل الصيدلاني السريري كجزء من فريق وحدة العناية المكثفة الطبية لحل المشاكل المتعلقة بالعلاج ، وتكمن أهمية هذا البحث في كونه يسهم في تحسين جودة رعاية المرضى من خلال تجنب حدوث مضاعفات دواءية لمرضى وحدة العناية المكثفة والتي تسبب معاناة غير ضرورية وتكاليف باهظة للمجتمع. وبالتالي جاءت الحاجة الملحة لإثبات أن خدمة الصيدلة الإكلينيكية في وحدة العناية المكثفة تنتج "عائد استثمار" فعليًا على مستشفياتنا وعلى المرضى.

المشاركة في هذا البحث اختيارية. ولن يخسر أي فرد أي منافع في حال تقرر عدم المشاركة أو التوقف عن المشاركة في أي وقت. وبمجرد الامضاء على هذه الموافقة، تقر\اي بأنك توافق\اي اختيارياً على المشاركة في هذا البحث، وأن المعلومات المدونة أعلاه قد شرحت شفهيا .

في حال وافقت على المشاركة في هذه الدراسة، سيبقى أسمك طي الكتمان. و لن يكون لأي شخص حق الاطلاع على ملفك الطبي باستثناء الطبيب المسؤول عن الدراسة ومعاونيه ولجان الاخلاق المهنية المستقلة .

لقد قرأت استمارة القبول هذه وفهمت مضمونها. تمت الاجابة على أسئلتي جميعها. وبناء عليه فأنني حر\اة مختار\اة أوافق على الاشتراك في هذا البحث واني أعلم أن الباحثة اسيل خالد حوسوستكون مستعدة للإجابة على أسئلتي، وأنه باستطاعتي التواصل معها عبر البريد الالكتروني. كما أعر ف بأنني حر/ة في الانسحاب من هذا البحث متى شئت حتى بعد التوقيع على الموافقة. وسأحصل على نسخة أصلية من هذا النموذج .

التاريخ ---------- اسم المشارك \اة---------- إمضاء المشارك\اة ----------

للمزيد من االستفسارات: aseelhouso@gmail.com توقيع الباحثة----------

:-شكراً على الاهتمام والاستعداد للمشاركة في هذه الد ارسة البحثية

Annex 7: Examples [MK6]on cases with high and medium P ADE Nesbit score

TRP category	Case	TRP	P ADE score	Intervention (accepted)	Pt status
Safety / safety regimen issue	71 yo female admitted with right-sided weakness for 2 hours Irregular vital sign, the patient was given Alteplase labetalol NPH However, after few hours, the patient had worsening level of consciousness. Brain CT showed left-brain hemorrhage.	Drug (Clexan 80MG SQ) initiated too early after massive stroke treated with tPA(anticoagulants) and complicated with hemorrhagic stroke	high	D/C Clexan, consider initiating after 14 days as no benefit has been shown with early initiation of anticoagulants after ischemic stroke due to AF	died
		Same as for other thinning blood drugs (aspirin , Plavix) that were discontinued	High	D/C Plavix and aspirin	
		Mannitol drug that was given to decrease intracranial pressure is contraindicated in this same case due to active intracranial bleeding	High	D/C mannitol	
Safety /dosage adjustment for renal failure	56 yo female Admitted to as a case of AKI. UTI, atypical chest infection	Dosage adjustment for renal failure for drugs (tazocin, clexan	medium	Adjust dose	alive

Annex 8: Case from control group

Patient information	
Weight (kg) 90	Admission Date Sep 28 at 22 pm
BMI = (Underweight/Normal/Overweight/**Obese** /Morbid obesity)	Discharge Date Oct 6 to MW
Date of Birth (dd/mm/yy) 58	APACHE 2 score. 16
Gender F	group: control

Case Summary (chief compliant and what happened to the patient during hospitalization)	**Cc: generalized weakness and fatigability of 3 days duration, hx of loss of appetite for 3 days and her son noticed that she became aggressive** **The patient reported black stool for 3 days duration but no vomiting** **RR 40m BP 125/65. HR 100 pH 7.08** **During dialysis the patient developed coffee ground vomiting** **Impression: AKI on top of CKD, uremia, metabolic acidosis, anemia, thrombocytopenia, UTI, UGIB, UTI**
Past Medical History/ Surgery	

Medication				
indication	**Drug Name, Generic and brand/Strength/Frequency/ Route**	**Start date**	**Stop date**	**time**
DM	**NPH 10*2 SC**	**On admission**	**Kept on transfer to MW**	**12 12**
UTI	**Meropenem 500 mg * 2**	**On admission**	**Kept on transfer to MW**	**12 12**
UTI	**Amikacin 500 mg EOD**	**Sep 28**	**Stopped on Oct 3**	**6 pm EOD**
UGIB	**Nexium IV infusion 8mg/hour**	**On admission**	**Stopped on Oct 3 at 11 AM**	
Thrombocytopenia, anemia	**PRBC(2 units) /FFP.(10 units) /Platelets (4 units)**	**On admission and**		
UBGI	**Nexium 40 mg *2 IV**	**Oct 3 at 11 AM**	**Kept on transfer to MW**	**6 6**

TRP BY DR **unnecessary drug therapy / step down / convert iv infusion Nexium to 4o mg iv twice daily**	**NEXIUM 40 MG VIAL = 22NIS**
CS **= (192 MG/DAY * 9 DAYS)– ((192MG /D * 5) + (NEXIUM 40 MG IV *2*4))** **=245.28 NIS**	

Consult Note

Sep 28

Disease

Assessment: (Treatment Related Problems)	**Plan**
Unnecessary drug therapy **Community acquired UTI** **Recent culture showed E. coli sensitive to meropenem**	**D/C amikacin**

Desired Outcomes and Goals	**Recommendation**
To protect the patient form being exposed to unnecessary medication	**As above**

Monitoring:

Efficacy target	**Toxicity sign**	**Counseling**
No worsening in inflammatory or infectious markers		

Annex 9: Case from intervention group

Patient information	
Weight (kg) 75	Admission Date Sep 9 at 21:25
BMI = (Underweight/**Normal**/Overweight/Obese /Morbid obesity)	Discharge Date Sep 15 at 2 PM
Date of Birth (dd/mm/yy) 65 y/o	APACHE 2 score 12
Gender M	group: interventional

Case Summary (chief compliant and what happened to the patient during hospitalization)	**CC: black tarry stool of 3 days duration plus diarrhea and nausea** **Fatigue a** **Upon standing and minimal activity, Hx of abdominal pain, during dialysis Hgb was found to be 6 so 2 unites of PRBCS were given and the patient was admitted to ICU, Hx of 30 Kg loss** **First Impression: UGIB** **+ for H. pylori**
Past Medical History/ Surgery	**End stage renal disease on hemodialysis**

Medication				
indication	**Drug Name, Generic and brand/Strength/Frequency/ Route**	**Start date**	**Stop date**	**time**
UGIB	**Nexium infusion (80 mg stat then 8mg/hour)**	**On admission**	**Continued for 72 hours Then dose made 40 mg* 2 IV until discharge**	
H. pylori	**Amoxicillin 500 mg* 2 PO (adjusted) Amoxicare**	**On Sep 14**	**After 14 days**	**8 Am 8 PM**
H. pylori	**Omeprazole (omepra 20 mg *2)**	**On Sep 14**	**After 28 days**	**6 AM 6 PM**
H. pylori	**Levofloxacin 500 mg * 1 initially then 250 mg Q 48 hours (adjusted)**	**On sep 14**	**After 14 days**	**12 MD**

Consult Note

Sep 14

Disease: H. pylori

Assessment: (Treatment Related Problems)	**Plan**
Untreated condition/ pylori	**Start Pylori regimen drugs** **Then continue on omeprazole 20 mg * 2 for 2 weeks**

Desired Outcomes and Goals	**Recommendation**
To eradicate Pylori and prevent recurrence of bleeding	**Start** **Amoxicillin 500 mg* 2 PO (adjusted) Amoxicare** **Omeprazole (omepra 20 mg *2)** **Levofloxacin 500 mg * 1 initially then 250 mg Q 48 hours (adjusted)** **For 2 weeks** **Then continue on omeprazole 20 mg * 2 for 2 weeks**

Monitoring:

Efficacy target	**Toxicity sign**	**Counseling**
Repeat Pylori after 6 weeks		

Physician Decision

Agree With Plan Recommended Proposed Modified Plan Disagree

Cost saving =- {amoxicare *2 + omepra *2} *2 + levox 500* 1} =-(1*2 + 1.5*2) *2 + 6.5*2*1 = - 23 nis	Amoxicre 5oomg tab = 1 nis Omepra 20 mg tab =1.5 nis Levox 250 mg tab =6.5 nis
Cost avoidance = 0.4* 750 = 300 nis	PADE MEDIUM CLINICALLY RELEVANT

تحليل تكاليف وفوائد تداخلات الصيدلي السريري في قسم العناية الطبية المركزة :دراسة متابعة وتدخل

اعداد : اسيل خالد محمود حوسو

اشراف :البروفيسور الدكتور معتصم حمدان

ملخص

الخلفية: توسعت خدمات الصيدلة السريرية في قسم العناية الطبية المكثفة بشكل كبير، إذ انتقلت من صرف الأدوية إلى التدخلات الصيدلانية السريرية الاستباقية ذات التأثير الإيجابي من الناحية السريرية والإنسانية والاقتصادية على رعاية وصحة المرضى والمؤسسات الصحية.

مشكلة وتبرير الدراسة: يتم تنفيذ القليل من خدمات الصيدلة السريرية في فلسطين وخاصة في اقسام العناية الطبية المكثفة. ولا يتلقى العديد من مرضى العناية المكثفة الفوائد المرجوّة من علاجهم بسبب المشاكل المتعلقة بالعلاج التي تسبب معاناة لا داعي لها وتكاليف مالية ضخمة بسبب عدم توفر صيدلاني سريري ضمن فريق العلاج.

الهدف من الدراسة: : تهدف الدراسة إلى تقييم توفير التكلفة لتدخلات الصيدلي السريري في حل المشاكل المتعلقة بالعلاجات المقدمة لمرضى العناية الطبية المكثفة.

طرق البحث: أجريت دراسة متابعة و تدخل في قسم العناية الطبية المكثفة في مجمع فلسطين الطبي –رام الله على مدى أربعة شهور. تم اختيار وتوزيع المرضى على مجموعتين، مجموعة تدخل ومجموعة مراقبة من قبل الصيدلاني السريري المعالج. تم تحديد المشاكل المتعلقة بالعلاج في كلتا المجموعتين، ولكن تم تقديم التدخلات الصيدلانية العلاجية فقط لمجموعة التدخل. كان إجمالي الفوائد الاقتصادية على النحو التالي:

(أ) التوفير في التكاليف نتيجة تدخل الصيدلي السريري.

(ب) تجنب التكاليف المتعلقة بالآثار الجانبية للعقاقير الممكن تجنبها.

وكانت مقاييس النتائج الأولية هي صافي التكلفة مع تدخلات الصيدلي السريري والتي تم حسابها باستخدام منهجيات منشورة سابقًا وتم تعديلها لتلائم السياق الفلسطيني. تم تحليل قبول الأطباء لتلك التدخلات لبيان الأثر العلاجي للتدخلات الصيدلانية السريرية.

نتائج البحث: خلال فترة الدراسة التى استمرت أربعة أشهر، تم إدخال ١١٧ مريضًا إلى وحدة العناية المكثفة، وتم إدراجهم جميعًا في الدراسة، منهم ٦٦ مريضًا لمجموعة التدخل و٥١ مريضًا لمجموعة المراقبة. خلال فترة الدراسة، نتج عن تدخل الصيدلي السريري توفير مباشر في التكاليف المالية بمبلغ يقدر ب ١٦١٩٥.٣٢ شيقلًا ، وتجنب تكلفة بمبلغ مقداره ٢٢٠٨٧ شيقلًا ، . وبلغ مجموع التوفير ٢٣٢ شيقلا لكل تدخل وتوفير بمقدار ٥٨٠ شيقلا لكل مريض.

من خلال مقارنة الفوائد الاقتصادية ٣٨٢٨٢.٨٢ شيقلًا الى التكلفة **٦٥. ١٩,٨٧٧** بلغ صافي التوفير ٤٠٥ ,١٨ شيقلًا وبلغت نسبة الفوائد إلى التكلفة ١.٩٣.

الخلاصة: على الرغم من استخدام منهج محافظ في جميع التصورات المحتملة، فإن إدماج الصيدلي السريري في فريق العناية الطبية المكثفة كان ذا فائدة اقتصادية من حيث توفير التكلفة المباشرة، وتجنب التكاليف غير المباشرة. ومن المتوقع أن يكون هناك فائدة اقتصادية أعلى من ذلك إذا ما تم اعتماد خدمة الصيدلة السريرية في المستشفيات بشكل رسمي، وتوظيف الصيدلي السريري كعضو بفريق العناية الطبية المكثفة.