MONASH University

Telehealth for Optimising Asthma Management during Pregnancy

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Doctor of Philosophy

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This thesis is dedicated to my parents.

For their endless prayers, love and encouragement

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Abstract

Background:

Evidence suggests that poorly controlled asthma during pregnancy is hazardous for both the mother and foetus. Some pregnant women with asthma may have few symptoms, but their lung function may be abnormal, putting the health of mother and foetus at risk. Forced expiratory volume in six seconds (FEV_6) has been shown to be equivalent to Forced vital capacity (FVC). Telehealth has the potential to improve asthma management through regular monitoring of lung function and/or asthma symptoms. This research aimed to develop and evaluate the application of a telehealth program for supporting asthma management in pregnant women.

Methods:

In phase 1, a systematic review of the literature was carried out to evaluate the non-pharmacological health care interventions for asthma management in pregnant women.

In phase 2, a prospective cohort study was conducted to investigate the changes in lung function and the role of objective measures of lung function (forced expiratory volume in one second [FEV_1], FEV_6 and FVC) for monitoring asthma during pregnancy in healthy (n = 20) and pregnant women with asthma (n = 20). Lung function (pre-bronchodilator) was measured three times at gestational weeks 11 – 20, 21 – 28, and 29 – 40. The results from phase 2 informed phase 3, which was a randomised controlled trial evaluating a telehealth program for asthma management

during pregnancy.

Phase 3 evaluated Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy (MASTERY©) compared to usual care in 72 pregnant women with asthma. The intervention group (MASTERY) was provided with the handheld COPD-6 device to measure lung function (FEV_1 and FEV_6) daily, *Breathe-easy*© application installed on a loaned mobile phone and an individualised written asthma action plan (WAAP). The control group (usual care) received standard antenatal care provided by their health care professionals. Both groups were followed prospectively and their asthma control scores were compared using Juniper's Asthma Control Questionnaire (ACQ) at 3 and 6 months.

Key findings:

Phase 1: Significant improvements in maternal asthma control (lung function and quality of life) and neonatal outcomes (birth weight) were found in those who received interventions involving progressive muscle relaxation (PMR) and Fraction of exhaled Nitric Oxide (FeNO) guided algorithm. Interventions that enable pregnant women to be monitored regularly using objective measures of lung function or asthma symptoms appear to be effective in reducing asthma exacerbations during pregnancy.

Phase 2: During pregnancy, lung function declined both in healthy women and women with asthma at weeks 21 – 28 (more markedly in those with asthma) but then improved at weeks 29 – 40 (more markedly in those with asthma). In those with asthma, asthma control scores increased, while quality of life scores declined at weeks 21-28; whilst at weeks 29 – 40 these changes were in the opposite direction. The

correlation between FEV_6 and forced vital capacity (FVC) in women with asthma was high (Pearson's $r = 0.88$, $p < 0.01$).

Phase 3: The demographic, maternal and clinical characteristics were similar in both groups at baseline. At 6 months, compared to the usual care group, the intervention (MASTERY) group had significantly greater improvement in their asthma control ($p = 0.02$) and asthma-related quality of life ($p = 0.002$) scores. At the end of the study, the MASTERY group had significantly higher proportion of participants with well controlled asthma, and more participants with an improvement in ACQ scores greater than 0.5, the minimum clinically important difference (MCID). There were no significant differences between the two groups in lung function, unscheduled healthcare visits, days off work/study, oral corticosteroid use and perinatal outcomes. No significant differences between groups were found at 3 months.

Conclusions:

The findings from this research confirm that asthma management involving regular monitoring of lung function and asthma symptoms is feasible and could potentially improve asthma control in pregnant women. In pregnant women with asthma, FEV_6 may be a suitable alternative to FVC. A telehealth program (*Breathe-easy*©) in conjunction with a handheld COPD-6 device for monitoring lung function (FEV_1 and FEV_6) and assessing asthma symptoms and a WAAP can promote asthma self-management during pregnancy and lead to better asthma control.

General Declaration (Part A)

Monash University

Declaration for thesis based or partially based on conjointly published or unpublished work.

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes **three** original papers published in peer reviewed journals, and **one** original paper revised and resubmitted to a peer reviewed journal. The core theme of the thesis is telehealth for optimising asthma management during pregnancy. The ideas, development and writing up of all papers in the thesis were the principal responsibility of myself, the candidate, working within the Centre for Medicine Use and Safety under the supervision of Dr Johnson George, A/Prof Kay Stewart and Prof Michael Abramson.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. In the case of **Chapters 3 to 6** my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent (%) of students contribution
3	The effectiveness of non-pharmacological healthcare interventions for asthma management during pregnancy: A systematic review	Published	80
4	A prospective cohort study of pulmonary function during pregnancy in women with and without asthma	Published	60
5	Study protocol for a randomised controlled trial evaluating the efficacy of a telehealth program – Management of Asthma with Supportive Telehealth of Respiratory Function in Pregnancy (MASTERY)©	Published	60
6	Telehealth to improve asthma control in pregnancy: a randomised controlled trial	Revised and Resubmitted	60

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] Date: 23 July 2015

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor signature: [redacted] Date: 23 July 2015

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Glossary of Terms and Abbreviations

Term / Abbreviation	Meaning
ACAAI	American College of Allergy, Asthma and Immunology
ACOG	American College of Obstetricians and Gynecologists
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ANZCTR	Australian New Zealand Clinical Trials Registry
APGAR	Appearance Pulse Grimace Activity Respiration
BTS	British Thoracic Society
CCHT	Care coordination home telehealth
CHF	Congestive heart failure
CI	Confidence Interval
CMUS	Centre for Medicine Use and Safety
COPD	Chronic Obstructive Pulmonary Disease
ED	Emergency Department
FDA	Food and Drug Administration
FeNO	Fraction of Exhaled Nitric Oxide
FEV_1	Forced expiratory volume in one second
FEV_6	Forced expiratory volume in six seconds
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GP	General practitioner
HbA_{1c}	Glycated haemoglobin
HTU	Home telemedicine unit
ICS	Inhaled corticosteroid
ICT	Information and communication technology
IDEATel	Informatics for Diabetes Education and Telemedicine project
IUGR	Intra-uterine growth restriction
LABA	Long-acting beta agonist
L	Litres
LDL	Low-density lipoprotein
LTRA	Leukotriene receptor antagonists
mL	Mililitres
MASTERY©	Management of Asthma with Supportive Telehealth of Respiratory Function in Pregnancy
MAMMA©	Multidisciplinary Approach to Management of Maternal Asthma
mAQLQ	mini Asthma Quality of Life Questionnaire
MCID	Minimum clinically important difference
MDI	Metered-dose inhaler
MUHREC	Monash University Human Research Ethics Committee
NAC	National Asthma Council of Australia
NHLBI	National Heart, Lung and Blood Institute

PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PMR	Progressive muscle relaxation
SABA	Short-acting beta agonist
SD	Standard Deviation
SE	Standard Error
SPSS®	Statistical Package for Social Sciences
TGA	Therapeutic Goods Administration
QoL	Quality of life
RCT	Randomised controlled trial
RWH	Royal Women's Hospital
VTA	Veteran health administration
WAAP	Written asthma action plan

List of Definitions

Term	Definition
APGAR test	An assessment of the physical condition of an infant immediately after birth created by Dr Virginia Apgar. The score is based on a combination of the heartbeat, respiration, skin colour, irritability, and muscle tone. The scores are added up to give a total score between 0 and 10 with 10 suggesting the healthiest infant; at one minute after birth. The assessment is repeated at five minutes after birth
COPD-6 device (model number 4000,Vitalograph Ltd., Ennis, Ireland)	It is a portable handheld spirometer electronic device measuring 11.3 cm high, 6.3 cm wide and 4.5 cm thick and weighs 55 g. It is powered by two disposable batteries and can measure FEV_1, FEV_6 and FEV_1/FEV_6 ratio. It is easy to use and has a large easy-to-read display and a comfortable design that allows it to be easily held by the patient.
FEV_1	Forced expiratory volume in one second; the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration expressed in litres
FEV_6	Forced expiratory volume in six seconds; the maximal volume of air exhaled in the six second of a forced expiration from a position of full inspiration expressed in litres
FVC	Forced vital capacity; the maximal volume of air exhaled with maximally forced effort for a maximal inspiration, i.e. vital capacity performed with a maximally forced expressed in litres
Foetus	An unborn baby from the eight week after fertilisation until delivery
Gestational age	The foetus age measured from the first day of the mother's last menstrual period; an average pregnancy lasts 280 days, or about 40 weeks, from that day
Gestational diabetes	Diabetes that arises during pregnancy; usually subsides after delivery
General practitioners	Doctors who do not specialise in a particular area of medicine but who attend to everyday medical needs of individuals within a community and refer to specialists when the management is beyond their scope of expertise
Low birth weight	Neonate weighing less than 2500g (5.5 lbs) at birth
Macrosomia	A condition in which a baby is considerably larger than normal
Miscarriage	The spontaneous loss of pregnancy before the foetus can survive outside the uterus; most common in the first trimester
Neonate	The newborn until 4 weeks of age
Preeclampsia	A complication involving high blood pressure, swelling and abnormal kidney function; occurs after the 20^{th} week and, left untreated, can lead to seizures and even death

Premature baby	A baby born before 37 weeks
Preterm labour	Labour that starts after 20 weeks but before the end of the 37th week
Singleton pregnancy	A singleton intrauterine pregnancy is a normal pregnancy with one foetus, developing in the uterus
Term	40 weeks (or thereabouts) from the first day of the last menstrual period
Vacuum extraction	The use of suction to help guide the baby's head out of the birth canal

Chapter 1
General Overview

1.1 Introduction

This thesis describes my research investigating application of a telehealth programme for managing asthma in pregnant women. Although much work has already been done to improve asthma management in the general population, limited work has focused on telehealth programmes for optimising asthma management, and none in pregnant women.

This introductory chapter provides general background information about the research topic and study populations. **Section 1.2** describes the burden of asthma globally and in Australia. **Section 1.3** outlines the epidemiology of asthma during pregnancy. **Section 1.4** provides a definition and details the types of telemedicine and telehealth. **Section 1.5** discusses gaps in the current knowledge that informed the direction of this research. **Section 1.6** delineates the aims and specific objectives of the research, including a brief overview of the projects comprising this thesis. **Section 1.7** summarises the thesis structure, with an outline of chapter content to guide further reading.

1.2 Burden of Asthma

Asthma is a chronic health condition affecting people of all ages across the world. When asthma is uncontrolled, the activities of daily living can be severely limited; sometimes asthma can even be fatal. According to estimates from the World Health Organization (WHO) and the Global Initiative for Asthma (GINA), as many as 300

million people of all ages and all ethnic backgrounds suffer from asthma. This number is expected to increase to 400 million by 2025. It is not just a public health problem for high-income countries, but occurs in all countries regardless of development levels [1-3]. Globally, 250,000 people die of asthma every year [3, 4]. In 2007, asthma accounted for 3,447 deaths in the United States of America (US), which equates to more than nine people every day [5]. Asthma deaths occurred more often among adults than children; the number of deaths was higher among women (2,173) than among men (1,274) [5]. In the United Kingdom (UK) asthma affecting around 10% of the adult population [6].

The prevalence of asthma in Australia is high by international standards and the reason for this unknown [7]. In 1999, Australian health ministers and the Commonwealth Government announced that asthma would be a National Health Priority Area (NHPA) [8]. About 10% of the population, or 2 million Australians, currently have asthma [9]. In 2010, 416 Australians died from asthma – many of these deaths were preventable [9, 10]. Asthma can be controlled with appropriate treatment. When asthma is well controlled, people should experience no more than occasional attacks or flare-ups; severe exacerbations should be rare [11].

1.3 Asthma and Pregnancy

Asthma is the most common obstructive airways disease affecting pregnant women and can cause complications during pregnancy [12, 13]. In the United States of America (US), the prevalence of self-reported asthma among pregnant women has been reported as between 8.4% and 8.8%, with 4.1% of all pregnant women having experienced an asthma attack during their pregnancy [14, 15]. Asthma prevalence

among pregnant women in the UK is around 8% [16, 17]. In Australia, asthma causing complications in 12% of pregnancies [12, 13, 18].

Pregnant women with asthma may experience more complications in their pregnancies than those without an asthma history. These complications include maternal and placental complications [19], pre-eclampsia [20-22], need for caesarean delivery [20], perinatal mortality [22-24], pre-term birth [20, 23], low birth weight or intrauterine growth restriction [20, 23, 25] and congenital malformations [22, 26, 27]. Asthma exacerbations during pregnancy may harm both foetus and mother [27-30]. Previous studies have shown that poorly controlled asthma during pregnancy increases the risk of poor maternal and neonatal outcomes [29-34].

Poorly controlled asthma may be the most easily remedied factor responsible for acute or chronic maternal hypoxia [35]. Asthma management goals in pregnant women are the same as for nonpregnant patients and include controlling asthma symptoms, maximising lung function, minimising drug side effects and preventing asthma exacerbations [11, 36-40]. Pregnant women with poorly controlled asthma should have a close liaison with their respiratory physician and obstetrician with early referral to critical care physicians for women with acute severe asthma [41, 42].

1.4 Telehealth and Telemedicine

Before examining the origins of telehealth research, this section will briefly define telehealth and telemedicine. The word ‘telemedicine’ began to be used in healthcare systems in the early 1990s. It originates from the ancient Greek prefix *tele-* meaning ‘far’, ‘at a distance’ or ‘remote’ [43]. The WHO defines telemedicine as:

‘The delivery of health care services, where distance is a critical factor, by

> all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities [44].'

In brief, the WHO describes four elements connected to telemedicine:

(1) its purpose is to provide clinical support;

(2) it is intended to overcome geographical barriers, connecting users who are not in the same physical location;

(3) it involves various types of information and communication technology (ICT); and

(4) its goal is to improve health outcomes [44].

By definition, telemedicine uses medical devices to evaluate, diagnose and treat patients remotely [45]. Telemedicine infrastructure has key components, including data storage devices, specialised application software, database management software and medical devices capable of electronic data collection, storage and transmission [45].

The terms 'telehealth' and 'telemedicine' are often used interchangeably in the scientific literature. According to the WHO, telemedicine refers to service delivery by medical practitioners only, whereas telehealth includes services provided by health professionals in general, including pharmacists and nurses [44]. In the twenty-first century, the term 'telemedicine' has been gradually replaced by 'telehealth', which describes this wider involvement of the healthcare team [43, 46]. The 2001 *Report to*

Congress on Telemedicine defines telehealth as 'the use of electronic information and telecommunications technologies to support long-distance clinical health administration' [45]. Two types of telehealth exist: 'live' (synchronous) or 'store and forward' (asynchronous) methods for transmitting data or broadcasting information [45, 47]. With live transmission, healthcare providers interact with the patient simultaneously across different locations while diagnostic information is being viewed, collected and transmitted to a facility e.g. giving advice by telephone, real-time consultation using video conferencing tools. Some telehealth programmes may use both methods [45]. The store and forward transmission method does not require both healthcare providers and patients to be present at the same time. The collected data can be viewed later (e.g. by storing two weeks of spirometry data) [45, 47].

The Australian Government Department of Health states that, broadly, telehealth services use advanced information and communication technology for delivering health services and transmitting health information over both long and short distances between providers (healthcare professionals) and receivers (patients) [48, 49]. Telehealth is concerned with transmitting data, images, spoken and other information that encompass the diagnostic, preventive (education), treatment and curative aspects of healthcare services between healthcare providers and patients [49]. Telehealth aims to remove some obstacles to accessing medical services for people who live in remote and rural areas or have limited access to specialists [50]. Telehealth applications can be used to deliver health services in remote areas, to enhance education and training through open learning services, and to improve health service organisation and administration [50]. An example of this would be electronic patient records [48, 51].

1.5 Statement of the Problem

Considering Australia's high prevalence of asthma, particularly in pregnant women, an efficacious and effective management approach should be identified to ensure appropriate treatment and monitoring for improved patient outcomes. Reducing asthma-related risks during pregnancy involves managing asthma actively during pregnancy, advising pregnant women about good asthma control and managing flare-ups during pregnancy [52]. Effective long-term management of asthma requires regular assessments of symptom control [52, 53]. Adequately controlled asthma during pregnancy is associated with little or no increased risk of foetal or maternal complications [54, 55].

Pregnant women with moderate to severe asthma should be more closely monitored. Appropriate adjustments in treatment may be required to maintain a level of lung function that ensures adequate oxygen supply to the foetus [39, 40]. As recommended in asthma guidelines [11, 38, 41, 52], regular monitoring of asthma symptoms, including objective measures of lung function, is essential to identify any changes in asthma during pregnancy. Accurate measurement of respiratory function is required to assess and manage asthma; spirometry is the lung function test of choice for diagnosing and assessing asthma control [56].

This research aimed to confirm the role of spirometry as an objective measure for monitoring asthma during pregnancy. I propose the application of measuring forced expiratory volume in one second (FEV_1), forced expiratory volume in six seconds (FEV_6) and the FEV_1/FEV_6 ratio for monitoring lung function in pregnant women with asthma. The novel use of FEV_6 as a substitute for forced vital capacity (FVC) in adults

with asthma is based on advice from the American Thoracic Society (ATS). This advice states that FEV_6 is equivalent to FVC [57]. The FEV_1/FEV_6 ratio has been demonstrated to be a valid alternative for FEV_1/FVC in measuring lung function in chronic obstructive pulmonary disease (COPD), particularly in elderly patients [57-59]. Performing FEV_6 is easier, more achievable, more reproducible and less physically demanding than FVC [57-61], for which reliable results cannot always be obtained, particularly in the elderly. As it is likely that women may experience shortness of breath during pregnancy, it was proposed that FEV_6 may be a more achievable and reliable measure in this population as well.

Telehealth not only provides greater accessibility and flexibility for patients. It also has other potential benefits, such as reduced waiting times to access healthcare services and reduced travel costs, earlier detection of worsening health conditions (e.g. exacerbations) and reduced healthcare visits/hospitalisations [62]. Many telehealth studies have been conducted in relation to managing patients with chronic diseases such as diabetes [63-66], congestive heart failure (CHF) [67, 68], hypertension [69-71] and pulmonary diseases [72, 73]. However, little information regarding the application of telehealth for asthma management during pregnancy exists, and the effectiveness of telehealth has been reported only rarely. Against this background, this research proposed a remote monitoring intervention to optimise the management of asthma during pregnancy and evaluated the efficacy of this telehealth intervention in this population. This was conducted on the assumption that, as the majority of pregnant women with asthma are young (18–45 years), they are likely to be willing to use mobile technology to assist in the management of their asthma.

1.6 Overview of the Research

1.6.1 Aims and objectives

As described in **Section 1.5**, several gaps exist in the literature regarding healthcare interventions for optimising asthma management during pregnancy. Firstly, limited information is available about the assessment of non-pharmacological interventions to improve asthma outcomes during pregnancy. Secondly, only a few studies have observed changes in lung function during pregnancy in both healthy and women with asthma and the role of objective measures (FEV_1 and FEV_6) for monitoring asthma during pregnancy is unknown. Finally, no evidence is available about the application of telehealth programmes for supporting asthma management during pregnancy. The research described in this thesis was conducted to address these knowledge gaps. The overall aim was to develop and evaluate the application of telehealth programmes for supporting asthma management in pregnant women.

The specific objectives were to:

1. evaluate non-pharmacological healthcare interventions for asthma management in pregnant women;
2. investigate the role of objective measures of lung function for monitoring asthma during pregnancy; and
3. develop, implement and evaluate a telehealth programme for asthma management in pregnant women.

1.6.2 Project scope

The research was conducted in three phases, each with specific objectives, as illustrated in **Figure 1.** The details for each phase are further discussed below and in the following chapters (see **Chapters 3 to 6**).

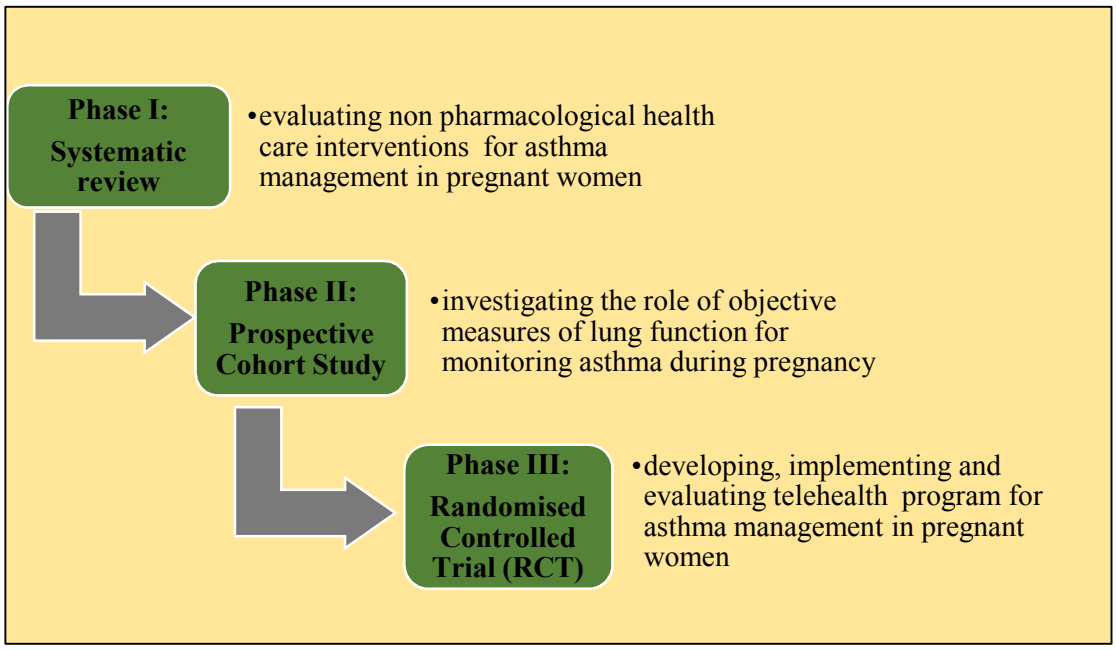

Figure 1. Project Scope

Phase 1 Systematic review

To assess evidence from non-pharmacological intervention studies for managing asthma in pregnant women.

Phase 2 Prospective cohort study

To observe changes in pulmonary function during pregnancy in both healthy and pregnant women with asthma.

Phase 3 Randomised controlled trial (RCT)

A randomised controlled trial was conducted to evaluate the feasibility and efficacy of a telehealth programme for monitoring and optimising asthma management during pregnancy.

1.7 Overview of Thesis Structure

This thesis by publications is presented in seven chapters. **Chapter 1** provides a general overview of the thesis, including the research aim and objectives. **Chapter 2** provides detailed background to the research, including a general review of the current literature on asthma management in pregnant women; the physiological changes during pregnancy and studies that have observed lung function changes during pregnancy; evidence from previous studies about asthma and pregnancy; and telehealth studies in the general population.

The subsequent chapters (3, 4, 5 and 6) present the three phases of the research in detail. **Chapter 3** describes the systematic review of non-pharmacological health interventions for asthma management during pregnancy. This chapter includes the manuscript published in BMC Pulmonary Medicine. **Chapter 4** discusses the role of spirometry for monitoring asthma during pregnancy and describes the changes in lung function during pregnancy in both healthy and women with asthma. **Chapter 5** describes the protocol for the RCT (Management of Asthma with Supportive Telehealth of Respiratory Function in Pregnancy [MASTERY©]) conducted to evaluate a telehealth programme and a written asthma action plan (WAAP) in pregnant women. **Chapter 6** presents the findings of the RCT. **Chapter 7** summarises and discusses the overall results of the research. This chapter also presents

recommendations to practitioners and researchers, discusses strengths and limitations of the studies, and proposes future research directions and implications for clinical practice.

Chapter 2
Literature Review

2.1 Introduction

As explained in **Chapter 1**, the research described in this thesis focuses on the application of a telehealth programme for monitoring asthma management during pregnancy. The rationale behind this will be further elaborated in this chapter. The purpose of this literature review is to provide a general overview to facilitate the understanding of asthma management during pregnancy, and to summarise the evidence from previous studies of telehealth applications and studies relating to the importance of managing asthma in pregnant women.

This chapter is divided into several sections. **Section 2.2** comprises a review of diagnosis and management of asthma in pregnancy. **Section 2.3** discusses the role of spirometry for monitoring asthma in pregnancy and explores studies that have observed lung function changes during pregnancy. **Section 2.4** explores the challenges of and current evidence for managing asthma in pregnant women. **Section 2.5** discusses the roles of telehealth in asthma and explores telehealth studies in the general population with asthma and other chronic diseases. **Section 2.6** provides a summary of the literature review.

2.2 Asthma in Pregnancy: Diagnosis and Management

2.2.1 Asthma diagnosis in pregnancy

The steps involved in the diagnosis of asthma in pregnant women are the same as for nonpregnant women (adults) [11]. The diagnosis of asthma in adults is based on: 1)

medical history and family history, 2) physical examination and 3) supportive diagnostic testing, including documentation of variable airflow limitation by spirometry [11, 52, 56]. The presence of one or more of the following symptoms suggestive of asthma: wheeze, cough, chest tightness or shortness of breath, along with fluctuation in symptoms (e.g. recurrent or seasonal, worse at night or in the early morning, triggered by irritants, allergies or viral infection, or exercise, and rapidly relieved by short-acting bronchodilators) [11, 56]. Descriptions of wheeze, chest tightness, shortness of breath and cough may vary among cultures and by age [11]. In older patients, the diagnosis may overlap with the features of chronic obstructive pulmonary disease (COPD), especially if there is a history of smoking or exposure to noxious gases or particles [52]. People with asthma may have a normal physical examination [11]; expiratory wheezing on auscultation is suggestive, although its absence does not exclude the diagnosis of asthma as other physical signs may be present [11, 56]. Crackles on chest auscultation indicate an alternative or concurrent diagnosis [56]. When the patient has a family history of asthma and allergy, examination for signs of allergic rhinitis is essential [11, 52]. When diagnosis of asthma relies on clinical examination alone rather than objective measurement, inappropriate diagnosis may occur. Inappropriate diagnosis leads to unnecessary or inappropriate asthma medication usage, increased healthcare costs and mislabelling of patients [74]. Studies have shown that patients with asthma often have been misdiagnosed or over diagnosed, a situation that is common, even in developed countries [74-77]. Performing objective testing such as spirometry to confirm the diagnosis is essential [74-77]. Spirometry is a physiological test of pulmonary function that measures how much an individual inhales or exhales volumes of air as a function

of time [78]. It is often measured before and after (i) the administration of bronchodilator agent(s) to assess reversibility, (ii) exercise to assess exercise-induced bronchoconstriction, or [79] inhalation of an agent that may reduce bronchospasm (e.g. mannitol, methacholine) to quantify airway reactivity [80]. Spirometry is able to show the excessive variation in lung function (i.e. variation in expiratory airflow that is greater than that seen in healthy people) [52].

2.2.2 Management of asthma during pregnancy – based on asthma guidelines

Guidelines for asthma management in pregnancy have been established by many national and international bodies. They include statements from the National Asthma Council of Australia (NAC), the British Thoracic Society [41], the National Heart, Lung, and Blood Institute (NHLBI), the American College of Obstetricians & Gynecologists (ACOG) and the American College of Asthma and Allergy (ACAAI), and the Global Initiative for Asthma (GINA) [11, 38, 41, 52, 81]. All these guidelines have emphasised the essentials needed to maintain asthma control and quality of life during pregnancy and for achieving normal maternal and foetal health outcomes [11, 38, 41, 52, 81]. The four key components of asthma management during pregnancy, based on National Asthma Education and Prevention Programme (NAEPP) panel report [38-40] are: 1) Monitoring and control of asthma during pregnancy, 2) Avoidance of triggers, 3) Patient education, and 4) Pharmacotherapy. Each of these factors will be further expanded below.

1. Monitoring and control of asthma during pregnancy

The fundamental goals of asthma management in pregnant women are to minimise chronic symptoms, have no limitations on physical activity, have no exacerbations,

minimise adverse effects of medication, maintain normal pulmonary function, prevent maternal and foetal complications and maintain quality of life [36-40]. There is an increasing awareness that current asthma control could be a predictor of future asthma exacerbations [82]. Asthma control refers to the extent to which the manifestations of asthma have been reduced or removed by treatment [82, 83]. The assessment of asthma control should include the current clinical control (e.g. symptoms, reliever use and pulmonary function) and future risk (e.g. exacerbations and pulmonary function decline) [11, 82]. The assessment levels of asthma control in pregnant women are similar to those in adult patients (**Table 1**) [11, 52, 84].

Table 1. Assessment levels of asthma control in pregnant women

Variable	Well controlled asthma	Asthma not well controlled	Very poorly controlled asthma
Frequency of symptoms	≤ 2 days/ week	> 2 days/week	Throughout the day
Frequency of night-time awakening	≤ 2 times/ month	1 – 3 times/week	≥ 4 times/week
Interference with normal activity	None	Some limitation	Extremely limited
Use of SABA for symptom control	≤ 2 days/ week	> 2 days/week	Several times/day
FEV_1 or peak flow (% predicted or personal best value)	> 80	60 – 80	< 60
Exacerbations requiring use of systemic corticosteroid (no.)	0 – 1 in the past 12 months*	≥ 2 in the past 12 months *	≥ 2 in the past 12 months*

***Notes:**
At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g. requiring urgent, unscheduled care, hospitalisation, or Intensive Care Unit (ICU) admission) indicate poorer disease control. For treatment purposes, patients who had ≥ 2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

SABA, short-acting beta-agonist; FEV_1, forced expiratory volume in 1 second
Source: Adapted from Namazy and Schatz, 2014 [84] and NAEPP panel report [38]

Pregnant women with persistent asthma should be evaluated periodically as needed with the aid of history (nocturnal asthma, exacerbations, symptoms frequency, interference with activities and medication usage), lung auscultation and lung function

testing [38]. Pregnant women with asthma may have minimal symptoms, yet have abnormal lung function tests and potentially impaired foetal oxygenation [85, 86]. An observational cohort study from US by Schatz *et al* [85] in 1739 pregnant women with asthma (873 mild asthma, 814 moderate asthma and 52 severe asthma) found a small but significant relationship between FEV_1 during pregnancy and an increased risks of low birth weight (< 2500 gram) and prematurity (< 37 weeks). This study also confirmed the importance of measuring pulmonary function (FEV_1) regularly in pregnant women with asthma, both as a prognostic factor for perinatal outcomes and as a measure of asthma control [85].

It is recommended to conduct spirometry in the initial assessment of all pregnant women being evaluated for asthma, and periodically as needed [40]. Regular monitoring can help early detection of asthma, early detection of asthma exacerbations, and indicate when asthma therapy needs to be adjusted [40]. Pregnant women with severe or uncontrolled asthma warrant increased surveillance, as the most common errors leading to adverse outcomes are underestimation of asthma severity and under-treatment of exacerbations [40]. Moreover, patients are instructed to be attentive to foetal activity throughout pregnancy. Serial ultrasound examinations starting at 32 weeks gestation may be considered for patients with moderate to severe persistent asthma [40]. Ultrasound examinations are also helpful after recovery from severe exacerbations [40]. Based on this evaluation, there is a possibility to step down the treatment if possible, or to increase if necessary [38, 41].

2. Avoidance of triggers

Eliminating adverse environmental exposures is critical in controlling asthma during

pregnancy [40]. Avoiding and controlling trigger factors including allergens (e.g. allergens from house dust, pets, cockroaches) and irritants (e.g. tobacco smoke, dusts, strong odours) and environmental pollutants (e.g. pollens, moulds) which contribute to asthma severity may lead to improved maternal well-being with less need for either preventer or reliever medications [39, 40].

Studies have shown an increased risk of poor neonatal outcomes due to maternal smoking during pregnancy and environmental tobacco smoke in women with asthma [18, 55, 87-90]. Maternal asthma, combined with cigarette smoking significantly increases the risk of severe exacerbations [87], preterm births [88], lower pulmonary function [89], wheezing and asthma during adolescence [89, 90]. Prenatal counselling, particularly about smoking cessation, should be provided, as the effects of asthma on poor perinatal outcomes may be greater among smokers than non-smokers [18, 87-90].

3. Patient education

Adequate asthma control is enhanced by ensuring access to education about asthma management skills including using medications correctly, self-monitoring, detecting and managing worsening asthma and continued adherence to long-term asthma management plans [39]. Pregnant patients should have a basic understanding of medical management during pregnancy (i.e. the correct use of inhalers and self-monitoring) [39, 40]. Individualised written asthma action plans (WAAP) based on an agreement between the healthcare provider and the patient about the goals of therapy should be provided [39].

Evidence has shown that limited asthma education (information only) does not

significantly reduce hospitalisations, unscheduled doctor visits or asthma medication use, although it may reduce symptoms and emergency department visits in high-risk patients [91]. However, education combined with self-management skills that involve self-monitoring by peak flow or symptoms, together with regular medical review and a WAAP leads to improvement of health outcomes (e.g. reduction in hospitalisations, unscheduled visits, days of work lost, episodes of nocturnal asthma and improvement in quality of life) for adults with asthma [92, 93]. A recent RCT study from Australia by Goeman *et al* [94] in community dwelling adults over 55 years (n = 123) showed that face-to-face delivered tailored education comprising inhaler device technique instruction and addressing any patient concerns demonstrated improvement in asthma control, quality of life, adherence to preventer medication and WAAP ownership in general population compared to usual care and brochure-only information.

4. Pharmacotherapy

Asthma medications can be divided into long-term controller medication (also known as preventers or symptom controllers) and rescue therapy (relievers). Long-term controller medications are used as maintenance therapy to prevent asthma manifestations and include inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), chromones, long-acting beta agonists (LABAs), theophylline and omalizumab [52, 84]. Rescue therapy most commonly involves short-acting beta agonists (SABAs) [11, 52]. Oral corticosteroids can be categorised either as rescue therapy after an acute asthma episode or chronic therapy to achieve adequate asthma control in patients with severe persistent asthma [84]. Oral corticosteroids are recommended, when indicated, for managing severe asthma during pregnancy [39].

The NAC and the Australian Government Department of Health's Therapeutic Goods Administration (TGA) have developed a categorisation system and database for the safety of prescribing asthma medication in pregnancy (**Table 2**) [52, 95]. The NAEPP "Working group report on managing asthma during pregnancy" recommends the following principles and stepwise approach to pharmacological management of asthma in pregnant women [39, 40, 96]. Salbutamol is preferred for use during pregnancy because it has an excellent safety profile and the most data related to safety during human pregnancy (Level C evidence from safety studies in pregnancy based on National Institutes of Health [NIH] scale) [38, 97]. The preferred long-term control medication is daily low-dose inhaled corticosteroid (Level C evidence from safety studies in pregnancy) [38, 97]. Budesonide is the preferred inhaled corticosteroid because more data are available on use of budesonide in pregnant women than other ICSs, and the data are reassuring (**Table 3**) [38, 39].

Table 2. Australian pregnancy safety categories for asthma medication

Category	Definition	Asthma medication
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.	Salbutamol sulfate (most formulations) Terbutaline sulfate Budesonide Methyl prednisolone Prednisolone Prednisone Adrenaline acid tartrate Adrenaline hydrochloride Aminophylline Theophylline
B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.	Salbutamol sulfate (*Airomir*) Montelukast sodium Sodium cromoglycate* Omalizumab
B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.	
B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.	Beclomethasone Ciclesonide Fluticasone propionate Budesonide/eformoterol* * Fluticasone/eformoterol Fluticasone /vilanterol Fluticasone /salmeterol
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details	Hydrocortisone sodium succinate
X	Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.	

** Intal Spincaps and Rynacrom formulations of sodium cromoglycate are Category A*
***Budesonide/eformoterol combination can also be used as a reliever*

Table 3. Stepwise approach for managing asthma during pregnancy and lactation

Classify severity: clinical features before treatment or adequate control			**Medications required to maintain long-term control**
	Symptoms/Day **Symptoms/Night**	**PEF or FEV_1** **PEF Variability**	**Daily medications**
Step 4 **Severe Persistent**	**Continual** **Frequent**	**≤ 60%** **> 30%**	• Preferred treatment: - High-dose ICS* AND - LABA AND, if needed, - Corticosteroid tablets or syrup long term (2 mg/kg per day, generally not to exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroid and maintain control with high-dose ICS*) • Alternative treatment: - High-dose ICS* AND - Sustained release theophylline to serum concentration of 5 – 12mcg/mL
Step 3 **Moderate persistent**	**Daily** **> 1 night/week**	**> 60% – <80%** **> 30%**	• Preferred treatment: EITHER - Low-dose ICS* and LABA or - Medium-dose ICS* if needed (particularly in patients with recurring severe exacerbations): - Medium-dose ICS* and LABA • Alternative treatment: - Low-dose ICS and either theophylline or leukotriene receptor antagonist** If needed: - Medium-dose ICS* and either theophylline or leukotriene receptor antagonist**
Step 2 **Mild persistent**	**> 2 days/week but < daily** **> 2 nights/month**	**≥ 80%** **20% – 30%**	• Preferred treatment: - Low-dose ICS* • Alternative treatment (listed alphabetically): cromolyn, leukotriene receptor antagonist OR sustained-release theophylline to serum concentration of 5 – 12mcg/mL
Step 1 **Mild intermittent**	**≤ 2 days/week** **≤ 2 nights/month**	**≥ 80%** **< 20%**	• No daily medication needed • Severe exacerbations may occur, separated by long periods of normal pulmonary function and no symptoms. A course of systemic corticosteroid is recommended

QUICK Relief **All patients**	• SABA: 2 – 4 puffs*** as needed for symptoms • Intensity of treatment will depend on severity of exacerbations; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroid may be needed. • Use of SABA > 2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term control therapy

Step down Review treatment every 1– 6 months; a gradual stepwise reduction in treatment may be possible	**Step up** If control is not maintained, consider step-up. First, review patient medication technique, adherence, and environmental control

Goals of therapy: asthma control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of inhaled SABA
- Minimal or no adverse effects from medications

Notes:

- The stepwise approach is meant to assist, not replace the clinical decision making required to meet individual patient needs
- Classify severity: assign patient to most severe step in which any features occurs (PEF is percent of personal best; FEV_1 is percent predicted)
- Gain control as quickly as possible (consider a short course of systemic corticosteroid), then step down to the least medication necessary to maintain control
- Minimise use of SABA (e.g. use of approximately one canister a month even if not using it every day indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy)
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g. allergens, irritants)
- Refer to an asthma specialist if there are any difficulties controlling asthma or if step 4 care is required. Referral may be considered if Step 3 is required

FEV_1, Forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; PEF, Peak expiratory flow; SABA, short-acting beta agonist

**There are more data on using budesonide during pregnancy than on using other inhaled corticosteroids*

***There are minimal data on using leukotriene receptor antagonists in humans during pregnancy although there are reassuring animal data submitted to Food and Drug Administration (FDA)*

****There are more data on using salbutamol during pregnancy than on using other SABA*

Source: Adapted from NAEPP Expert panel report managing Asthma during pregnancy: Recommendations for pharmacologic treatment - 2004 Update [39]

2.2.3 Management of acute asthma exacerbations in pregnancy

The American Thoracic Society / European Respiratory Society (ATS/ERS) statement distinguishes asthma exacerbations in clinical trials and in clinical practice [83] . In clinical trials, severe asthma exacerbations are defined as events that require medical intervention (e.g. unscheduled visits, hospitalisations, prescription of oral corticosteroids) for the patient to prevent a serious outcome, such as hospitalisation or even death from asthma [83, 98, 99]. In clinical practice, as the severity of exacerbations could vary from patient to patient, identifying changes in symptoms and/or reliever use and/or lung function from the patient's usual range of day-to-day asthma variations is essential [83].

The NAC, BTS and NAEPP have recommended the following steps for management of acute asthma in pregnancy [39, 41, 52]. Acute exacerbations during pregnancy should be treated aggressively in order to avoid foetal hypoxia [41, 52, 100]. Delivering high flow oxygen immediately is recommended to maintain saturation at 94 – 98% in order to prevent maternal and foetal hypoxia [41]. Drug therapy should be given as for non-pregnant patients with acute asthma, including nebulised beta agonists, oxygen and systemic glucocorticosteroids instituted when necessary [100]. Pregnant women with asthma should be taught to recognise early symptoms and signs of asthma exacerbations such as chest tightness, dyspnoea, cough, wheezing, or a 20% or more decrease in their personal best peak expiratory flow (PEF) rate [97]. A reduction in foetal movement may be one of the early manifestations of an asthma exacerbation [97]. Continuous foetal monitoring should be performed when asthma is uncontrolled or severe, or when foetal assessment on admission is not reassuring [11, 41, 52]. Early recognition of asthma exacerbations is crucial so that home rescue

treatment can be initiated to prevent maternal and foetal hypoxia [97]. The NAEPP recommends that home treatment begin with inhaled salbutamol (2 – 4 puffs every 20 minutes for up to 1 hour) [97]. A good response is described by the ability to resume normal activities, PEF rate > 80% of personal best and symptoms that are resolved or become subjectively mild [97]. Further medical attention is needed if the response is incomplete or if foetal movement is decreased (**Table 4**) [39, 97].

Table 4. Management of asthma exacerbations during pregnancy and lactation: home treatment

Assess Severity ➢ Measure PEF: Value < 50% personal best or predicted suggests severe exacerbation ➢ Note signs and symptoms: Degrees of cough, breathlessness, wheeze, and chest tightness correlate imperfectly with severity of exacerbation ➢ Accessory muscle use and suprasternal retractions suggest severe exacerbations ➢ Note presence of foetal activity* **Initial Treatment** ➢ SABA: up to 3 treatments of 2 – 4 puffs by MDI at 20 minutes intervals or single nebulizer treatment		
Good response	**Incomplete response**	**Poor response**
Mild Exacerbation PEF > 80% predicted or personal best No wheezing or shortness of breath Response to SABA sustained for 4 hours Appropriate foetal activity*	***Moderate Exacerbation*** PEF 50% – 80% predicted or personal best Persistent wheezing and shortness of breath Decreased foetal activity*	***Severe Exacerbation*** PEF < 50% predicted or personal best Marked wheezing and shortness of breath Decreased foetal activity*
Treatment	**Treatment**	**Treatment**
May continue SABA every 3-4 hours for 24 – 48 hours For patients on inhaled corticosteroid, double dose for 7 – 10 days	Add oral corticosteroid Continue SABA	Add oral corticosteroid Repeat SABA immediately If distress is severe and nonresponsive, call your clinician immediately and proceed to emergency department; consider calling ambulance or 911
Contact clinician for follow up instructions	**Contact Clinician urgently (this day) for instructions**	**Proceed to emergency department**

*Foetal activity is monitored by observing whether foetal kick counts decrease over time
MDI, metered-dose inhaler; PEF, peak expiratory flow, SABA, short-acting beta agonist
Source: Adapted from NAEPP Expert panel report managing Asthma during pregnancy: Recommendations for pharmacologic treatment–2004 Update [39]

2.2.4 Management of asthma during labour and delivery

Acute asthma attacks during labour are very rare, perhaps due to endogenous steroid production [41]. Women with asthma are advised to continue their usual medication in labour and they may safely use all forms of usual labour analgesia [41]. Careful foetal monitoring is essential when women with asthma are admitted in labour [40]. Intensive foetal monitoring is recommended for women who enter labour with uncontrolled or severe asthma [40]. This may be performed by either continuous electronic foetal heart rate monitoring or intermittent auscultation (every 15 minutes in the first stage of labour; every 5 minutes in the second stage of labour) [40]. In the absence of a severe acute asthma attack, Caesarean section is reserved for the usual obstetric indications [41]. Women receiving steroid tablets at a dose exceeding prednisolone 7.5 mg per day (or the equivalent) for more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6 – 8 hourly during labour [41].

2.3 Objective Measurements for Monitoring Asthma in Pregnancy

As mentioned in **Section 2.2**, diagnosis and monitoring of asthma need objective measures such as spirometry. Spirometry has been the preferred method of pulmonary function testing for the diagnosis of asthma and assessment of asthma control in response to treatment [56, 78]. Asthma symptoms may manifest for the first time during pregnancy, and the diagnosis may be confused with the physiological dyspnoea that is a common symptom during pregnancy [40, 101]. Dyspnoea may occur in early pregnancy in approximately 70% women. However this symptom is not associated with wheezing, chest tightness, cough or airway obstruction, which are characteristic

of asthma [97, 102]. Physical examination and spirometry can be used to distinguish physiologic dyspnoea from pathological dyspnoea [103].

FVC and FEV_1 are acceptable measures for diagnosing and assessing asthma control in adults [56]. PEF is another measurement that is sometimes useful in the diagnosis of occupational asthma and to monitor asthma control for some patients; but not a substitute for spirometry when diagnosing asthma [56]. During the prenatal visit, the clinician should collect the following information: medication usage, day and night symptoms and peak flow measures or spirometry readings [40].

Numerous studies have focused on observing changes in lung function during healthy pregnancy. Several of these have used longitudinal cohorts [104-108] with measurement of lung function during and after pregnancy, while others have addressed the issue from the point of gestational age and parity using less powerful cross-sectional [109-112] designs (**Table 5**).

Table 5. Summary of studies that have observed pulmonary function in healthy pregnancy

Authors; year; country	Aim/Question/Hypothesis	Study design; sample size	Outcome measure	Main findings
Alaily & Carrol [104]; 1978; UK	To describe pulmonary ventilation changes observed in normal pregnancy	Prospective longitudinal cohort n=38	FEV_1	No statistically significant change in FEV_1 during pregnancy and post-partum
Norregaard *et al* [109]; 1989; Denmark	To measure the effect of postural changes during pregnancy on pulmonary function and oxygenation	Cross-sectional n=39	FEV_1, PEFR	Significant reductions in FEV_1 and PEFR were observed as a result of postural changes
Puranik *et al* [105]; 1994; India	To observe the changes in pulmonary function test in each month of pregnancy in the same woman	Prospective longitudinal cohort n=50	VC, FVC, FEV_1	VC, FVC and FEV_1 remained unchanged during pregnancy. Slight variations observed were not statistically significant
Brancazio *et al* [106]; 1997; USA	To determine whether PEFR changes within pregnancy and with advancing gestation	Prospective longitudinal cohort n=57	PEFR	No significant difference in PEFR for the three trimesters and post-partum
Harik-khan *et al* [110]; 1999; USA	To examine the effect of parity on FEV_1 in a group of healthy volunteer women	Cross-sectional n=397	FEV_1, FEV_1%, FVC	Higher FEV_1 associated with parity in child-bearing age (18 – 50 years) in healthy women
McAuliffe *et al* [112] ; 2002; UK	To determine if changes in respiratory function during pregnancy in healthy women were greater in those with twin pregnancy than a singleton pregnancy	Cross-sectional n=230	FVC, FEV_1, PEFR	Respiratory function (FEV_1, PEFR, and FVC) of healthy women with twin pregnancies was not significantly different from those with singleton pregnancies
Harirah *et al* [107]; 2005; USA	To study the effect of gestational age and maternal position on PEFR	Prospective longitudinal cohort n=38	PEFR	PEFR declined significantly in all maternal positions throughout pregnancy. Supine PEFR was lower than sitting and standing positions.

Grindheim *et al* [108]; 2011; Norway	To record any physiological changes in pulmonary function during healthy pregnancies and evaluate the influence of parity	Prospective cohort n=100	longitudinal	FVC, FEV_1, PEFR	FVC and PEFR increased after 14-16 weeks of gestation and throughout pregnancy. FEV_1 remained unchanged during pregnancy
Siddiqui *et al* [111]; 2014; India	To identify changes in respiratory function during normal pregnancy and determine whether such changes are more pronounced in twin pregnancy than in singleton pregnancy	Cross-sectional n=150		FEV_1, FVC, FEV_1/FVC, PEFR	All respiratory parameters except FEV_1/FVC ratio were found to be lower in pregnant women than nonpregnant women. No significant differences between singleton and twin pregnancies.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; VC, vital capacity

Some methodological weaknesses were evident even in studies with prospective longitudinal designs, such as lack of clarity in the eligibility criteria for participants [104], no indication of when data were collected [106], small sample sizes [104, 107], and high attrition [106]. However, the longitudinal design allowed repeating measurements in the same women during pregnancy and post-partum to detect any minor changes in pulmonary function as other factors remain constant [108]. A cross-sectional study design can avoid the bias from a small number of patients, especially if there is complete follow-up [110, 112]. Nevertheless, since the measurement was done only once at a particular stage of pregnancy, any intra-subject changes in respiratory function during pregnancy would fail to be detected [111, 112].

Some studies in healthy pregnant subjects showed that FEV_1 and PEF remained unchanged [105, 106, 108] while others found significant changes during pregnancy and/or after delivery [107, 108]. Some circumstances that could account for differing results include differences in measuring times and methods, sample sizes, different methods and devices for measuring lung function (such as spirometry or portable peak flow meter), socioeconomic status and ethnicity [106-108]. The findings of Grindheim *et al* [108] and Alaily & Carrol [104] support the statement by the NHLBI of the National Institutes of Health (NIH), that FEV_1 remains unchanged in pregnancy. Therefore any alterations of FEV_1 during pregnancy in women with pulmonary disease might be due to the disease [40, 113]. Systematic reviews conducted by Hardy-Fairbanks *et al* [114] and Hanania *et al* [115] described the respiratory changes during pregnancy, as shown in **Table 6**.

Table 6. Normal respiratory physiological changes during pregnancy

Pulmonary capacity measurement	Description	Physiological changes
Functional residual capacity	Volume of air left in the lungs after a tidal breath out. The amount of air that stays in the lungs during normal breathing	Decreased
Respiratory rate	Number of breaths per minute	Unchanged
Residual volume	Amount of air left in the lungs after maximum exhalation	Slightly decreased
Tidal volume	Normal volume of air displaced between normal inhalation and exhalation with no extra effort	Increased
Expiratory reserve volume	Amount of additional air that can be pushed out after the end of expiratory level of normal breathing	Decreased
Minute volume/ventilation	Volume of air that can be inhaled and exhaled in 1 minute	Increased
FEV_1	Forced expiratory volume in 1 second	Unchanged
PEFR	Peak expiratory flow rate	Unchanged
FVC	Forced vital capacity	Unchanged
FEV_1/FVC	Forced expiratory volume in 1 second / Forced vital capacity ratio	Unchanged
FEV_6	Forced expiratory volume in 6 seconds	Unchanged

Source: Adapted from Hardy-Fairbanks et al [114] and Hanania et al [115]

Only a few studies have observed pulmonary function changes during pregnancy in women with asthma [116-119]**.** The findings from a cohort study by Sims *et al* [116] showed no indication that FEV_1 or FEV_1/FVC were affected by pregnancy in (n=27 with asthma and n=11 without asthma), either during exercise or at rest. Beckmann *et al* [117] tested the hypothesis that there was no difference in PEF by trimester in 43 pregnant women with asthma. The findings showed PEF tended to increase by trimester in pregnant women with asthma. Juniper *et al* [118] performed methacholine challenge in 16 women of child-bearing age in the second trimester and compared with four subjects preconception. FEV_1 and FEV_1/FVC showed no significant changes between the groups. White *et al* [119] conducted a prospective study to observe pulmonary function changes throughout pregnancy using a symptom questionnaire,

bronchodilator usage and daily peak flow measurements. Twenty-two women (60%) reported improvement in their asthma based on subjective measurement using a symptom questionnaire. With objective measurement using peak flow monitoring, only 10 subjects (34%) showed improvement [119]. The findings from White *et al* [119] support the argument that it is difficult to classify asthma changes during pregnancy based only on subjective measurement by patient perception [38, 40, 120].

Reliable objective measures of lung function are needed for monitoring asthma during pregnancy, since it is difficult for physicians and patients to differentiate breathlessness related to pregnancy based on subjective assessment alone [38, 40, 116]. There is uncertainty about changes in lung function during healthy pregnancy [108, 112, 121] and only a few studies have observed lung function during pregnancy in women with and without asthma [116-119]. This raises the question whether these objective measures, including FEV_1, FVC and PEF, have applications in asthma monitoring during pregnancy. Further study was justified to assess objective measures of pulmonary function in pregnant women with and without asthma.

2.4 Managing Asthma in Pregnant Women – Challenges and Evidence

Evidence has shown that the course of asthma during pregnancy changes unpredictably and is extremely variable. It may improve in one-third, worsen in one-third or remain unchanged in one-third of women [54, 122, 123]. The following statements are the contemporary evidence about progress of asthma during pregnancy. Asthma course changes during pregnancy in approximately 60% of women, with worsening more likely than improvement [124]. Asthma symptoms were shown to

worsen significantly during pregnancy compared with pre-pregnancy, both during day-time and night-time [125]. According to Guy *et al* [126], pregnant women with asthma are a high-risk population as pregnancy may alter the severity of asthma unpredictably, particularly in those with uncontrolled asthma since the beginning of pregnancy. Pregnant women who experienced asthma exacerbations during the first trimester had an increased risk of giving birth to an infant with congenital malformations, particularly in the respiratory, nervous (excluding spina bifida) and digestive systems [127, 128]. Research suggests that acute exacerbations should be treated as early as possible, and that effective control of asthma symptoms was needed during pregnancy [126-128]. Therefore pregnant women with asthma should be treated with appropriate medications and monitored carefully throughout pregnancy [122] .

The management of asthma in pregnancy may be affected by some concerns about the safety of asthma medications and their potential side effects to the foetus [129]. Existing evidence does not suggest that taking a regular preventive asthma medication during pregnancy is unsafe, as the incidence of adverse effects has been shown to be low and asthma preventive medications did not cause poor perinatal outcomes [30, 84, 130, 131]. Murphy *et al* [31] conducted a meta-analysis of cohort studies from 1975 to 2012, which showed no increased risk of congenital malformations, caesarean sections, or postpartum haemorrhages in pregnant women with asthma who used inhaled bronchodilators during pregnancy.

Kwon *et al* [14] found that women who had emergency department visits or hospitalisations prior to pregnancy were more likely to have taken their controller

medication during pregnancy (41%) and during the previous year (46%), compared to those who had not received emergency care (~16%). Despite the worsening asthma symptoms, over half of pregnant women had not taken their preventer medications regularly, either before or during pregnancy [125]. This might have led to asthma exacerbations [14, 125].

Guy *et al* [126] recommended that asthma management during pregnancy required close collaboration between obstetricians, primary care physicians, paediatricians and asthma-care specialists Education is one of the essential steps for managing asthma in pregnant women. Improving healthcare professionals' knowledge of asthma and the safety of asthma medications in pregnancy is also required, as there was a lack of confidence among them in managing deteriorating asthma in pregnant women [132, 133]. An RCT study from Australia in 58 pregnant women with asthma attending antenatal appointments at two tertiary maternity hospitals; showed that a multidisciplinary approach involving education and regular monitoring may be ideal for improving asthma control in pregnant women and could be implemented in clinical practice [134].

The use of Fractional exhaled nitric oxide (FeNO) in monitoring airway inflammation in patients with asthma is recommended by ATS but only low quality evidence is available [135, 136]. The role of utilising FeNO to tailor the dose of ICS cannot be routinely recommended for clinical practice at this stage since the evidence is limited and remains uncertain [137]. The individual (e.g. age, gender, height) and external factors such as cigarette smoking, virus infection, and certain food intake are clinically important confounding factors for FeNO measurements [136]. The application of

FeNO for monitoring asthma in pregnant women should be interpreted with caution due to the high long-term variability of FeNO [138, 139]. Considering the limited evidence to date about interventions for improving asthma management in pregnant women, further randomised trials are required to determine the most effective and safe interventions for this population [140, 141].

2.5 Telehealth

The terms and definitions of Telehealth and Telemedicine have been discussed in **Chapter 1** (section 1.4). This section presents the telehealth studies that have been conducted in general populations with chronic diseases. The basic concept of telehealth refers to a wide range of clinical applications and healthcare service, using ICTs including video conferencing, telephone, computer, fax, radio and internet to support the transmission of physiological and other clinical data. With the improvement of technology and global communications in the early 1990s, the application of telehealth to deliver healthcare services began to expand [45, 142]. The potential of telehealth for its feasibility and acceptability is the starting point for the development of intervention studies, particularly in chronically-ill patients [143, 144]. Most chronic diseases need long-term treatment, sometimes obstacles may lead to a delay in delivery of healthcare services. Over recent decades, several studies regarding the application of telehealth interventions in chronic diseases have been completed.

2.5.1 Telehealth studies in chronic diseases

A systematic review conducted by Weingarten *et al* [145] found that management of chronic illnesses can be improved by using interventions such as patient education, health provider feedback and patient reminders. Several studies comparing home

telemonitoring with usual care in patients with diabetes showed some improvements in clinical outcomes. An RCT of Informatics for Diabetes Education and Telemedicine project (IDEATel) compared telemedicine intensive nurse case management via a home telemedicine unit (HTU) to usual care in Medicare beneficiaries with diabetes aged ≥ 55 years (n = 1665) in the USA [64, 65]. The HTU components allowed participants to measure and monitor glucose and blood pressure readings, interact with an IDEATel nurse case manager, and access web-based educational material. The results showed greater clinical improvement in HbA_{1c}, LDL cholesterol and blood pressure in the intervention group than the control group at one and five year follow-ups [64, 65]. However, the IDEATel intervention-related costs were higher than the cost of a comparable telemedicine programme because of the size of the budget allocated to the operation and the installation of the HTU [146]. For the programme to be cost-effective, the intervention-related costs need to be reduced, while maintaining the clinical outcomes impact [146].

A nonrandomised controlled study was conducted in the USA to evaluate the effect of a Veterans Health Administration (VHA) care coordination home telehealth (CCHT) intervention compared to baseline in veterans with diabetes [66]. Administrative records (n = 445, mean age 68 years) were reviewed to compare healthcare service utilisation in the one year period before and after enrolment to the programme and also examined self-reported QoL at enrolment and one year later. The results showed a significant reduction in the proportion of hospitalised patients, emergency room admissions and the average number of bed days of care, and improvement in QoL [66] However, since this trial was a single-group before and after design, the results need to be interpreted with caution. A randomised controlled trial designed is warranted for

future research.

Telehealth has also been used in the diagnosis and management of cardiovascular conditions such as hypertension and CHF. The Telemonitoring and Self-Management of Hypertension Trial (TASMINH2) by McManus *et al* [147] assessed self-management of hypertension in patients (n = 527, mean age 66 years) with poorly controlled hypertension compared with usual care in 24 general practices in UK. The self-management consisted of self-monitoring of blood pressure and self-titration of antihypertensive drugs, combined with telemonitoring of home blood pressure. At 6 and 12 months follow-ups, there were significant differences in the reduction of systolic blood pressure from baseline between the groups, with the intervention group having larger reductions than the usual care group. Other studies using similar methods found that a telemedicine service transmitting data through telephone line or internet to assist blood pressure treatment, resulted in a significant improvement in blood pressure monitoring by patients with hypertension [69-71]. Improved clinical outcomes, such as reduction in unplanned ED visits or hospitalisations, better compliance with medication regimens, daily weight and blood pressure monitoring have been shown in the small groups of patients aged 50 – 81 years in US, who received home telehealth and a monitoring program or web-based compliance monitoring devices for CHF [67, 68]. Despite the successful outcomes of the telehealth studies in chronic diseases, more research data are required to provide a firm conclusion about the effectiveness of telehealth to support patients' self-management and improve clinical outcomes. The current evidence is mostly limited by the lack of generalisability and the cost of the telehealth interventions in comparison with usual clinical care settings.

2.5.2 Telehealth and Asthma

Telehealth can support asthma management through aspects such as patient education, screening, telephone follow-up, adherence support, screening and remote monitoring [148]. For instance, telehealth techniques such as videoconferencing can be used to deliver patient education [149] and improve adherence [150], while early detection of asthma exacerbation or better management of asthma exacerbations can be achieved by home telemonitoring in many other ways [151-154]. Recording daily symptoms continuously as a part of asthma management showed reduction in costs associated with unplanned hospitalisations and improved quality of life in asthma patients [150, 151, 154-156]. For optimising asthma management, it should be possible to carry out the essential interventions using telehealth techniques [148].

McLean and Sheikh [62] described the potential benefits associated with telehealth interventions as follows:

- Allows patients to be cared for in their preferred location i.e. typically at home.
- Videophone or web-based clinical consultations e.g. annual asthma or COPD reviews can replace routine visits for annual reviews.
- Proactive education and support e.g. through web forums, may facilitate self-management techniques and help prevent exacerbations.
- Telemonitoring of respiratory measures, such as peak expiratory flow and spirometry, can allow earlier detection of disease exacerbations, thereby facilitating timely management and support.
- Greater opportunities for continuity of care.
- Reduced costs to patients resulting from savings in time off work, and avoiding

transportation and parking costs.

Telephone follow-up, internet-based home monitoring and mobile-based monitoring with a web-based application or short-message-service (SMS) have been widely used in telehealth intervention studies. Pharmacists were the main providers of the telehealth intervention in two RCTs [149, 157] while the rest involved doctors or nurses [150, 151, 155, 156]. Bynum *et al* [149] conducted a study to evaluate the efficacy of telepharmacy counselling using interactive compressed video compared to written instructions on metered-dose inhaler (MDI) technique in adolescents (n = 36, aged 12 – 19 years) with asthma recruited from rural junior high and high schools in Arkansas, USA. The telepharmacy counselling group showed significantly greater improvement in MDI technique after 4 weeks than subjects in the control group ($p < 0.001$). Barbanel *et al* [157] carried out a self-management advice study with weekly telephone follow-up from a community pharmacy in adults with asthma (n = 24, mean age 45 years)cation techn in east London. After 3 months, the intervention group achieved a significantly better symptom score than the control group, who received no input from the pharmacist ($p < 0.001$).

2.5.3 Internet-based home monitoring of asthma

Several information and communication technologies implemented telehealth using internet-based home monitoring in patients with asthma. The characteristics of the studies are summarised in **Table 7**. In Copenhagen, Denmark, Rasmussen *et al* [155] conducted a RCT in 300 subjects divided into three levels of asthma care. During the six-month trial period, subjects were allocated to internet-based monitoring, specialist monitoring or general practitioner [158] monitoring and received two scheduled visits.

The internet-based group showed significantly greater improvement than the other two groups in asthma symptoms, asthma-related QoL, lung function (FEV_1) and airway responsiveness. The authors concluded that "when the physician and patients used an interactive internet-based asthma monitoring tool, better asthma control was achieved" [155]. It may be that telemonitoring enabled recognition of poor control with appropriate stepping up of treatment that might have improved compliance. Further analyses are needed to confirm whether the incorporated treatment algorithm needed to be adjusted accordingly to avoid any side effects of the higher doses of inhaled corticosteroid.

In Hawaii, Chan *et al*'s [150] project, "Asthma In-Home Monitoring", showed that after 52 weeks follow-up, the virtual group showed higher scores on metered-dose inhaler (MDI) technique than the control group (94% vs. 89%; $p < 0.05$) and better adherence to daily asthma symptom diary submissions (35% vs. 21% $p < 0.01$). Both groups experienced an increase in QoL scores and asthma knowledge from baseline. The study showed no significant differences in endpoints such as unplanned emergency department (ED) visits, hospitalisations and reliever use [150]. Poor adherence was found in the number of peak flow meter videos uploaded to the Web site by the virtual group and the use of asthma diaries in both the virtual and office-based groups. The poor adherence in the use of traditional (face-to-face care) or home-based monitoring raises concerns about their application in the clinical practice setting [150].

In Taiwan, Jan *et al'*s [151] study observed the effectiveness of the "Blue Angel for Asthma Kids" program. After 12 weeks, the intervention group had a significant

decrease in night-time and day-time symptoms compared to the control group, as well as improvement in morning and night PEFR, adherence rates for daily asthma diary entry and inhaled corticosteroids, well-controlled asthma, knowledge regarding self-management, and QoL scores [151]. However, this trial was not able to find group differences in the occurrence of ED visits or hospitalisations due to the short duration of the trial (12 weeks) and the small sample size.

In the Netherlands, Willems *et al* [156] conducted a study to evaluate a nurse-led telemonitoring program for patients with asthma compared to the regular care. The results show improvement of quality of life and asthma symptom scores in both groups at follow-up times, however no statistically significant differences were found between groups. No significant differences were observed among the types of asthma medication consumption from baseline and 12 months between groups. The participation rate of this study was relatively low (40%) with most of the patients having mild to moderate asthma. Having fewer patients with severe asthma may explain why there was no significant difference between groups in medication consumption. Although no significant differences were found, the nurse-led telemonitoring program seems feasible to support asthma self-management; shown by the low rate of drop-out throughout the study, high compliance and satisfaction regarding the system [159].

Another study by Van der Meer *et al* [160] also from the Netherlands, found that the internet-based group had improved asthma knowledge, inhaler technique use and self-reported medication adherence, but the improvements were not significantly different between groups. The internet-based group also showed greater improvement than the

usual care group from baseline to 12 months follow-up in asthma-related QoL, symptoms, lung function (FEV_1) and increased symptom-free days. However, the difference in changes of asthma control and QoL between the group were less than minimum clinically relevant improvement (< 0.5). The application of this program to reduce asthma exacerbations is unclear, as the study was not powered to detect a difference in asthma exacerbations in patients with mild-to-moderate persistent asthma.

Table 7. Characteristics of studies using internet-based home monitoring

Author; year	No. of participants; age ; country; setting	Study design	Interventions	Main outcomes	Follow-up
Rasmussen *et al [155]*; 2005	300 people with asthma;18 – 45 yr; Denmark; recruited directly from the community in Copenhagen	RCT with three parallel groups	Internet group: asthma specialist with the internet-based management tool (electronic diary + peak flow meter, an action plan for the patients, a decision support system for the physician) Specialist group: received treatment by asthma specialist in an outpatient clinic, peak flow meter and action plan GP group: received standard treatment from GPs in primary care	AQLQ score, asthma symptoms, lung function (FEV_1) at baseline and 6 months later; airway responsiveness to inhaled methacholine, ED visits, hospitalisations	6 months
Chan *et al* [150]; 2007	120 children with asthma; 6 – 17 yr; USA; Tripler Army Medical Centre, Honolulu, Hawaii	RCT	I: video conferencing to record their inhaler use technique and peak flow meter readings via the Web site (virtual visits) C: asthma visits in-person education and case management (office-based)	Adherence to treatment (patient's use of ICs), asthma control diary (e.g. use of relievers), PAQLQ, ED visits, hospitalisations, patient's technique when using an inhaler	12 months
Jan *et al* [151]; 2007	164 children with asthma; 6 – 12 yr; Taiwan; National Cheng Kung University Medical Centre in Tainan	RCT	I: internet-based multimedia asthma education with interactive asthma monitoring system: electronic diary, asthma action plan C: verbal information and booklet for asthma education with written asthma diary	PEFR weekly average (recorded in asthma diaries, morning and night), symptoms, childhood ACT at baseline and 12 weeks later), PAQLQ, caregiver's knowledge	12 weeks

Willems *et al* [156]; 2008	56 children with asthma aged ≥7 yr and 53 adults with asthma aged ≥18 yr; the Netherlands; the University Hospital in Maastricht	RCT	I: portable handheld device asthma monitor for home use in which spirometry test results, symptoms and medication use could be recorded C: regular outpatient care	PAQLQ, lung function (PEF and FEV_1), asthma symptoms and self-reported use of medication (recorded using patient diaries), ED visits, hospitalisations	12 months
Van der Meer *et al* [160]*;* 2009	200 adults with asthma; 18 – 50 yr; the Netherlands; 37 General practices and one outpatient clinic at Leiden University Medical Centre	RCT	I: internet-based self-management (weekly asthma control monitoring and treatment advice, online and group education, and remote Web communication) C: usual asthma care	Changes in AQLQ and ACQ scores, percentage of symptom-free days, response to 12-item Consumer Asthma Knowledge Questionnaire, , patient's inhaler technique use, number of changes in asthma medications per patient	12 months

ACQ, Asthma Control Questionnaire; ACT, Asthma Control test; AQLQ, Asthma Quality of Life Questionnaire; C, control; ED, emergency department; FEV_1, forced expiratory in one second; I, intervention; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PEFR, peak expiratory flow rate; RCT, randomised controlled trial

As most of the studies used internet-based home monitoring and required transmitting data using a portable spirometer over the internet, some challenges may have been encountered regarding the adoption of new technology by patients, which raises a question about the validity of the data submitted [161]. However, previous studies have shown that asthma patients, both children and adults, could perform the tasks successfully, including spirometry testing, submitting electronic diaries and conducting internet-based remote monitoring despite varied technology background and experience in using computers. The spirometry data obtained were comparable to those collected under the supervision of healthcare professionals and thus deemed to be valid [162-167].

Two clinical centres (one in Spain and one in London) assessed the feasibility of remote monitoring systems for patients with asthma (n = 33, aged 17 – 50 years) to be used in their own home [165]. The patients were remotely monitored by two respiratory research nurses for two weeks [165]. The results showed that remote internet-based monitoring programs seem feasible for asthma patients, as the compliance with monitoring in one study was relatively high (80%) and compliance in transmitting data through a modem was more than 50% after two weeks [165]. More than 90% of subjects found the equipment easy to use and said they would use it again in the future. Medical professional interventions occurred with only 48% of patients during the study [165]. A study from US by Bratton *et al* [168] evaluated user satisfaction with real-time telemedicine for monitoring vital signs in 18 patients and 11 physicians over eight weeks. The results showed different perspectives of satisfaction from patients and healthcare providers regarding real time telehealth for monitoring vital signs. The physicians were more uncertain about the benefits of the

services in assessing patients adequately, while patients felt more satisfied [168]. However, this study was done in a small sample; further studies with larger sample sizes are needed to confirm those findings. Mair and Witten [169] conducted a systematic review to evaluate the quality of evidence regarding patient satisfaction with telehealth or telemedicine from 32 studies. The review highlighted that most of the studies had not clearly specified the methodologies used for assessing satisfaction, making interpretation and comparisons of the results problematic [169]. Many studies had small sample sizes with some of them having unclear participant selection criteria and low response rates less than 50%; that may affect their reliability and validity [169]. Further analysis is required to design research tools to measure patients' satisfaction regarding the application of telehealth in asthma management. The instruments need to be tested rigorously to produce repeatable results accurately.

The findings from the above studies showed that internet-based home monitoring is an efficacious and increasingly accepted way to improve self-management and asthma outcomes. Compared to conventional asthma care, the internet-based home monitoring system has some advantages, such as the autonomous characteristics of the program and the interactive-feedback between patient and healthcare professionals that gives patients the confidence to manage and monitor their own asthma symptoms [150, 151, 156, 160]. It is an approach that may appeal to some patients, health care professionals and organisations and may be cost-effective. Participants in the control group in some studies received face-to-face care including education programs from health professionals (e.g. physicians, nurses or other case managers) for their asthma rather than usual care alone that may have resulted in no differences being detected between the intervention and control groups in terms of clinical outcomes such as ED

visits or hospitalisations [150, 151].

2.5.4 Scope for remote monitoring in asthma

Monitoring asthma patients regularly by telephone follow-up could be time consuming, and internet access may not always be available or convenient [70, 170-172]. Daily internet-based home monitoring has been criticised for high rates of attrition [70, 170, 173]. However the use of mobile phones is increasing globally. In the Asia-Pacific region, 90% of the overall and 80% of the rural population have access to a mobile network [174]. Mobile phone-based applications could support self-management of long-term conditions, although the evidence base for this technology is still very limited [174].

Mobile phone or mobile technology is increasingly being used as a part of telehealth interventions with wireless monitoring of health outcomes in disease management and delivery of health interventions [170]. Pinnock *et al* [175] explored opinions of people with asthma and clinicians in a qualitative study on the potential role of mobile phone technology in monitoring asthma. It was found that the mobile phone as part of asthma monitoring may have two roles: firstly, as an early phase of monitoring symptoms, supporting the process of diagnosis and controlling the asthma symptoms, and secondly, as an electronic medical record (i.e. spirometry or peak flow rates) that could enable patients and their clinicians to share data and seek advice and feedback remotely [175].

Fonseca *et al* [176] found that most people with moderate to severe asthma are willing and ready to use communication technology, such as mobile phones and the internet for managing their asthma. However, using a mobile phone as a device in monitoring

asthma may have some limitations too. It is not applicable for patients with hearing or vision impairments and some patients may have difficulty operating the application [161].

Mobile phone-based interventions to support asthma management have been tested in several studies. The characteristics of these studies are summarised in **Table 8.**

Table 8. Characteristics of the studies using mobile phone-based monitoring

Author; year; country	No. of participants; age ; setting	Study design	Interventions	Main outcomes	Follow-up
Anhoj and Moldrup [177] ; 2004; Denmark	12 people with asthma; 13 – 57 yr; recruited from the Danish website LinkMedica Asthma	Before and after	SMS asthma diary	The feasibility of SMS for asthma diary data collection from patient/user perspective,, response rates from SMS collection of asthma diary	2 months
Ostojic *et al* [72]; 2005; Croatia	16 adults with asthma; mean age 24 yr; respiratory clinic	RCT	I: weekly SMS instruction from an asthma specialist on adjustment therapy and recommended follow-up based on PEF values sent by SMS C: asthma diaries and peak flow meter	Lung function tests (PEFR, FEV_1 and FVC), patient's daily record of PEFR, symptoms and variability, use of asthma medication; cost and reliability of SMS (validated against patient's diaries)	16 weeks
Prabhakaran *et al* [178]; 2010; Singapore	120 adults with asthma; aged ≥ 21 yr; Tan Tock Seng Hospital	RCT	I: received SMS according to a structured workflow for symptom monitoring C: usual care without SMS support	ACT, reduction in nebulisations and ED visits	11 months
Strandbygaard *et al* [179]; 2010; Denmark	26 adults with asthma; 18 – 45 yr; recruited through an advertisement on local newspapers in Copenhagen	RCT	I: asthma education and SMS reminder to take their asthma medication C: asthma education and usual care	Adherence rate to inhaler use (% medicine actually taken by patients, calculated from dose-count and number of days between clinical examinations), reimbursement of asthma medication, change in FeNO levels, lung function (FEV_1, FVC) and airway responsiveness to inhaled methacholine	12 weeks
Liu *et al* [161]; 2011; Taiwan	89 adults with asthma; mean age 54 yr; outpatient clinics of Chang Gung Memorial Hospital, Linkou	RCT	I: mobile telephone-based interactive asthma self-care system C: asthma symptom diary booklet and action plan	Lung function (FEV_1, FVC), asthma symptom score (sleep quality, severity of coughing, difficulty in breathing and daily activities affected by asthma), unscheduled clinic visits, ED visits,	6 months

				hospitalisations	
Ryan *et al* [180]; 2012; UK	288 people with asthma; mean age 48 yr; 32 primary care practices in Norfolk and Yarmouth, East Kent, North England, Essex and Hertfordshire	RCT	I: mobile group monitoring and installed t+ Asthma application that enabled to record and transmit data of symptoms, drug use and PEFR readings twice daily C: paper based asthma diary to record symptoms, drug use and PEFR readings twice daily	*Asthma control* – ACQ *Self-efficacy* – KASE-AQ *Asthma related quality of life* – mAQLQ *Enablement* – mPEI	6 months

ACQ, Asthma Control Questionnaire; ACT, Asthma Control test; C, control; ED, emergency department; FEV_1, forced expiratory in one second; FeNO, fraction exhaled nitric oxide; I, intervention; KASE-AQ, Knowledge Attitude and Self-Efficacy Asthma Questionnaire; mAQLQ, mini Asthma Quality of Life Questionnaire; mPEI, modified Patient Enablement Instrument; PEFR, peak expiratory flow rate; RCT, randomised controlled trial; SMS, short message service

Sending regular SMS reminders about using asthma medications, obtaining peak flow readings, structured workflow and diary data collection have been carried out [72, 177-179]. The findings indicate that sending SMSs regularly may be feasible, affordable and convenient for self-monitoring asthma, in conjunction with a WAAP and standard follow-up [72, 177]. The effect of SMS reminders on clinical asthma outcomes was not investigated by Anhoj *et al* [177]. The short duration of the follow-up (16 weeks) and the small sample size (16 patients) in the Ostojic *et al* [72] study, made it unable to detect significant differences in the main clinical asthma outcomes such as lung function changes and daily consumption of inhaled corticosteroids. A study group of a minimum 40 patients was needed for follow-up to achieve 80% power within 95% confidence interval.

Prabhakaran *et al* [178] demonstrated improvement in Asthma Control Test (ACT) scores, reduction in nebulised bronchodilators and emergency visits in the study group compared to the control group. However, none of these outcomes were significantly different and there was no reduction in hospital admission rates in either group [178]. The Strandbygaard *et al* [179] study showed that adherence in the intervention group increased from week 4 to week 12 (77.9% to 81.5%) while the control group had a decreased adherence (84.2% to 70.1%). The absolute difference in mean adherence rate between the two groups was 17.8% ($p = 0.019$). However no significant differences were found between the groups in the changes in FeNO, lung function or airway responsiveness to inhaled methacholine. The validity of adherence measurement in this study was based upon participant credibility. Dose-dumping, where patients could empty their medicine device prior to the visit, was a possible

limitation [179].

Limitations of all these studies, including small sample sizes [72, 177] and short durations of follow-up [179] need to be considered when evaluating the results. Combining the SMS data collection system and traditional web page display may be useful for patients in managing their asthma [177].

Some telemedicine providers (e.g. Avalis Health Care Systems AG in Zurich, Switzerland) have created comprehensive disease management packages including asthma self-management kits [181]. For example, the "Go Asthma" application from Avalis Health Care allows patients with asthma to track and monitor their asthma through their personalised mobile phone, with internet availability and peak flow meter [181]. Similar systems from other telemedicine providers also have been offered, such as t+Medical Americas Inc ("t+Asthma"), TelehealthLink (asthma-monitoring package) and MedApps (through its mobile wireless health-monitoring systems) [181]. Portable devices, such as the PiKO peak flow meter (nSpire Health) and Asthma Monitor AM3® (Cardinal Health) are used together with these programs [180, 181].

Recently, a few studies have evaluated the combined use of mobile phone and web application or software to improve asthma control. In Taiwan, a prospective controlled study in an out-patient clinic was conducted by Liu *et al* [161] in 89 patients with moderate to severe asthma, who were randomly allocated to the intervention group with a mobile phone self-care interactive program. All subjects received asthma education and a self-management plan and were asked to record their daily PEFR and asthma symptoms in a diary. After six months, the intervention group had significantly

increased PEF rate (intervention: 382.7 L/min vs control: 343.5 L/min) and FEV_1% predicted (intervention: 65.2% vs control: 56.5%) compared to the control group ($p = 0.05$). The quality of life score in the intervention group was better after two months and throughout the study compared to the control group ($p < 0.01$) and they had fewer episodes of acute exacerbations and unplanned medical visits. Since the software application was compatible with the mobile phone and easy to use, good adherence with the program was achieved [161]. However, the study had several limitations including differences among the study groups, small sample size, and lack of generalisability as it was a single centre study [161].

Ryan *et al* [180] conducted an RCT in the UK primary care setting to compare mobile-phone with standard paper-based monitoring in improving asthma control in 288 patients with poorly controlled asthma, using the asthma control questionnaire (ACQ). The findings of this study contradicted those of Liu *et al* [161] as there were no significant differences in the ACQ or Knowledge Attitude and Self-Efficacy Asthma Questionnaire (KASE-AQ) scores between the groups. The numbers of patients with unplanned visits, steroid courses, acute exacerbations and healthcare cost were similar in both groups [180]. This study showed the intervention was not cost effective in improving asthma control or increasing self-efficacy compared to paper based-monitoring [180].

The results were not surprising as this study tested the impact of the mobile-phone based monitoring technology with the control group who received the same clinical care, but less intensive monitoring compared to the intervention group. The cost analysis of the intervention gave more effective results for reducing healthcare use

(e.g. unplanned visits and hospitalisation related to asthma) compared to usual care alone. The average ages in the intervention and control groups in this study were 47 and 52 years, respectively. The results might also have been different in younger people, who may be more adept at using mobile technology, or those with special circumstances, such as pregnant women with asthma. Moreover, the differences in the study settings between Liu *et al* [161] (tertiary care hospital) and Ryan et al [180] (primary care) might explain the differences in outcomes between the studies.

The Cochrane review (21 RCTs) and meta-analysis from nine included studies of telehealth care for asthma by McLean *et al* [182]; concluded that telehealth may produce small clinically relevant improvements in those with mild asthma, and may have a role in those with more severe asthma who are at high risk of hospital admissions. A recent meta-analysis of 6 RCTs by Zhao *et al* [183] concluded that the telemedicine or telehealth interventions do not result in an improvement of asthma symptom scores. However they may contribute to other factors such as the reduction of asthma exacerbations, unscheduled visits and hospitalisations that were not evaluated in the studies included.

2.6 Summary

It is difficult to conclude telehealth interventions are effective as most of the studies involving telehealth in chronic diseases were done as pilot studies with relatively small sample sizes, short durations of intervention, limited resources and some methodological flaws. To overcome the problem of low participation rates when testing a telehealth intervention over a longer period (> 6 months), a programme that is less time consuming, easy to follow, and that provides comprehensive care to

support asthma self-management may have attracted more participants. The level of asthma severity and asthma control of the targeted population also need to be considered when designing a telehealth intervention. Patients with severe asthma symptoms were confronted with more frequent asthma symptoms and medication use, and limitation in daily activity and therefore need to be monitored regularly. A telehealth intervention may not be significant in patients with well controlled asthma, but may offer significant benefits in those with poorly controlled asthma.

The GINA guideline supports the use of lung function data and asthma symptoms for assessing the level of asthma control. Previous studies had applied monitoring of lung function and asthma symptoms as part of their interventions [72, 151, 155, 156]. Portable handheld spirometers have been used in some studies for daily monitoring of lung function (FEV_1, PEFR) [161, 180]. Standardised questionnaires such as ACT, ACQ, and Asthma Quality of Life Questionnaire (AQL also have been used to measure asthma control and quality of life in some studies [150, 151, 156, 160, 178].

It can be seen that previous telehealth studies showed potential benefits for managing asthma in adults and children. Although only a few studies have shown significant clinical outcomes, such interventions may have clinical impacts in patients with asthma who need more intensive care. As described earlier, pregnancy may alter the severity of asthma unpredictably and that could affects both the mother and baby. Therefore, interventions that could optimise asthma management in pregnant women need to be developed and evaluated.

Chapter 3
Non-Pharmacological Healthcare Interventions for Optimising Asthma Management during Pregnancy: a Systematic Review of the Literature

3.1 Introduction

The previous chapter (**Chapter 2**) provided an overview of the literature regarding the challenges, current guidelines and evidence for managing asthma in pregnant women. **Chapter 2** demonstrated that there has been very limited research on healthcare interventions for improving asthma management in pregnant women. All asthma guidelines emphasise that it is safer for pregnant women with asthma to use regular asthma medications than to experience exacerbations during pregnancy. A few studies have reviewed the safety and efficacy of pharmacological therapy for asthma management in pregnant women. However, none of these have assessed the effectiveness of non-pharmacological healthcare interventions for optimising asthma management during pregnancy. Before designing an intervention for managing asthma in pregnant women, empirical evidence is needed to provide data about the effectiveness of such interventions. In this context, a systematic review was considered to give high-level research-based evidence.

Thus, this chapter presents a systematic review that investigated non-pharmacological healthcare interventions for managing asthma in pregnant women. The key objective of this systematic review was to identify non-pharmacological healthcare interventions for optimising asthma management during pregnancy and examine their

effects on maternal asthma symptoms and neonatal outcomes.

This systematic review has been published in *BMC Pulmonary Medicine* and is reproduced below.

3.2 Manuscript

3.2.1 Declaration (Part B) for Thesis Section 3.2.2

In the case of **Section 3.2.2**, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Conducted literature search; developed search strategy; identified relevant titles, abstracts and full texts; reviewed articles; undertook data extraction and synthesis; performed qualitative reviews; facilitated review meetings and prepared first draft of the manuscript and revised based on comments from co-authors and journal reviewers.	80

The following co-authors contributed to the work.

Name	**Nature of contribution**
Dr Johnson George	Assisted with the development of search strategy; , reviewed articles, assisted with data extraction, qualitative review and manuscript preparation
A/Prof Kay Stewart	Assisted with data review and manuscript preparation
Prof Michael Abramson	Assisted with data review and manuscript preparation

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

		Date
Candidate's Signature	[redacted]	**23 July 2015**
Main Supervisor's Signature	[redacted]	**23 July 2015**

3.2.2 Published manuscript: The effectiveness of non-pharmacological healthcare interventions for asthma management during pregnancy: a systematic review. *BMC Pulm Med* 2014; 14: 4

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BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

The effectiveness of non-pharmacological healthcare interventions for asthma management during pregnancy: a systematic review

Elida Zairina[1], Kay Stewart[1], Michael J Abramson[2,3] and Johnson George[1*]

Abstract

Background: While reviews have been published on asthma management in pregnant women, none has examined the effectiveness of non-pharmacological healthcare interventions for optimizing asthma management in pregnant women. This systematic review aims to identify non-pharmacological healthcare interventions for optimizing asthma management during pregnancy and to examine their effects on maternal asthma control and neonatal outcomes.

Methods: The Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library), MEDLINE, EMBASE, PsycINFO, CINAHL Plus and International Pharmaceutical Abstracts (IPA) were searched. Two reviewers independently assessed the identified studies against the eligibility criteria and extracted relevant information. The effects of the intervention were assessed qualitatively.

Results: Nine studies were identified, of which six were rejected according to the exclusion criteria. The three studies included in the final review described an education program, progressive muscle relaxation (PMR) and Fraction of exhaled Nitric Oxide (FeNO) guided management of asthma in pregnant women. The PMR and FeNO-guided interventions showed significant improvements in maternal asthma control (lung function and quality of life) and neonatal outcomes (birth weight).

Conclusions: Further evidence from well-designed studies evaluating non-pharmacological healthcare interventions for optimizing asthma management in pregnant women is required.

Keywords: Asthma, Non-pharmacological, Interventions, Management, Pregnancy

Background

Asthma is one of the most serious health problems affecting people of all ages throughout the world [1,2]. In the United States of America the prevalence of self-reported asthma among pregnant women was between 8.4% and 8.8% during the period 1997 to 2001, and 4.1% of all pregnant women had experienced an asthma attack in the previous year [3,4]. In Australia, asthma is the most common chronic disease affecting pregnant women, complicating one in eight pregnancies [5].

A prospective study conducted by Schatz et al. [6] of 366 pregnancies in 330 women with asthma, showed that during pregnancy, asthma improved in slightly more than a quarter of patients (28%), worsened in slightly more than a third of patients (35%) and remained unchanged in a third of patients (33%). More than half of women with asthma do not take their asthma preventer medications on a regular basis before and during pregnancy, leading to asthma exacerbations [3,7]. Good asthma control during pregnancy is important to reduce risks for both mother (e. g. pre-eclampsia, perinatal mortality, and need for cesarean delivery) and infant (e.g. low birth weight and prematurity) [8,9]. Therefore, pregnant women with asthma warrant additional support comprising education, ongoing monitoring and review of treatment [10].

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Many national and international bodies have developed guidelines for asthma management in pregnancy. They include the British Thoracic Society, National Heart Lung and Blood Institute (NHLBI), American College of Obstetricians & Gynecologists (ACOG) and the American College of Asthma and Allergy (ACAAI), National Asthma Council of Australia (NAC), and Global Initiative for Asthma (GINA) [11-15]. All these guidelines have emphasized the need to provide optimal therapy to maintain control of asthma throughout gestation for maternal health and quality of life as well as for normal fetal maturation. The Expert Panel Report of the Working Group on Asthma and Pregnancy – Updates in National Asthma Education and Prevention Program (NAEPP) – has recommended four critical components for managing asthma during pregnancy: (1) assessment and monitoring of asthma including objective measures of pulmonary function, (2) control of factors contributing to asthma severity, (3) patient education, and (4) a stepwise approach to pharmacological therapy [16]. Asthma management during pregnancy requires close collaboration among obstetricians, primary care physicians, and asthma-care specialists [17]. Better asthma control can be achieved if patients are involved in self-management, including self-monitoring of either symptoms or peak expiratory flow rates, maintaining regular contact with medical practitioners and following written asthma action plans [18].

While there are many published reviews of pharmacological asthma management in pregnant women [19,20], none has assessed the effectiveness of non-pharmacological healthcare interventions for optimizing asthma management in pregnant women. Most of the interventions in pregnant women have focused on the safety and efficacy of asthma medications in pregnant women [21,22]. General practitioners (family physicians) have reported a lack of confidence and/or knowledge in managing deteriorating asthma in pregnancy, although having a good understanding of the safety of asthma medications during pregnancy [23]. Despite being concerned about health outcomes, women are not well supported in managing asthma during pregnancy [24]. Empirical evidence on interventions to optimize asthma management during pregnancy, targeting both pregnant women with asthma and their health professionals, is needed. The aim of this review was to identify non-pharmacological healthcare interventions for optimizing asthma management during pregnancy and examine their effects on maternal asthma symptoms and neonatal outcomes.

Methods

Eligibility criteria

To be included, studies had to describe the effectiveness of non-pharmacological healthcare interventions for managing asthma in pregnant women using one of the following prospective study designs: randomized controlled trials (RCTs) controlled clinical trials (CCTs), or pre- and post- (uncontrolled before and after) studies. Studies of non-pharmacological healthcare interventions in pregnant women, including behavioral or educational interventions targeting patients, patient self-management programs, patient monitoring and follow-up of asthma management were eligible. Studies were excluded if they were not aimed at pregnant women with asthma, comprised only pharmacological interventions in the absence of intervention by a healthcare professional (e. g. drug trials), or only targeted healthcare professionals (e. g. education to improve prescribing). Studies needed to have measured at least one of the following primary or secondary outcomes at baseline and at follow-up:

Primary outcomes for the review

1. Asthma symptom scores measured using any validated instrument (e.g. Juniper's Asthma Control Questionnaire [ACQ] [25]).
2. Health-related Quality of Life (HRQoL) scores measured using any validated instrument (e.g. Asthma Quality of Life Questionnaire-Marks [AQLQ-M] [26]).
3. Asthma -related scheduled or unscheduled healthcare visits to emergency department (ED), general practitioner (GP), or hospitalization.

Secondary outcomes

1. Lung function measurements (e.g. Peak expiratory flow rate [PEFR], Forced expiratory volume in one second [FEV_1], Forced vital capacity [FVC]).
2. Asthma medication adherence (assessed using a valid instrument or objective data).
3. Neonatal outcomes (e.g. birth weight, survival, Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores, gestational age).

Information sources

A systematic search of the following databases was carried out using the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2013), Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, CINAHL Plus and International Pharmaceutical Abstracts (IPA). In addition to searching these databases, reference lists from previously published review articles were also searched. The final search was carried out in October 2013.

Search strategies

Professional librarians were consulted in developing the search strategy for each database. No language restrictions

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were used and searches were not limited to publication years. The broad terms asthma* AND pregnan* as (text word) were used. The following keywords were entered: asthma* OR wheez* OR, bronchoconstrict* OR bronchospas* AND pregnancy* OR pregnant OR maternal* in combination with clinical trials OR randomized controlled trials OR controlled clinical trials. Additional searches using the Medical Subject Headings (MeSH) 'asthma' and 'pregnancy' were performed in Medline and PubMed.

Study selection

One author (EZ) ran the search strategy described above. All studies identified were imported into an Endnote® library (version X6, Thomson Reuters). After removal of duplicates, the remaining titles and abstracts were reviewed by EZ to exclude studies that did not meet the inclusion criteria. Full texts of all studies that were considered relevant on the basis of review of title and abstract were retrieved, read and assessed independently by two reviewers (EZ and JG).

Data collection process and data items

Using an electronic data extraction form [27], one author (EZ) extracted the data from included studies, which were verified by a second author (JG). Any disagreements and uncertainties were identified and resolved in discussion with an adjudicating third author (KS). Given the clinical heterogeneity of the studies included, a qualitative assessment of the effects of the intervention was performed, based on the methodological quality and the study outcomes. The effects of the intervention were described by comparing the difference in outcome measures from baseline to end of the study between the groups. If more than one outcome was reported, priority was given to validated measures [28].

Results

Study selection

Figure 1 shows the process of selection of studies for the systematic review, based on PRISMA guidelines [29]. Overall, 2,387 references published until 9 October 2013 were identified in the preliminary search: Ovid MEDLINE (n = 636), Ovid EMBASE (n = 779), CINAHL Plus (n = 337), Ovid PsycINFO (n = 22), IPA (n = 137), Ovid CENTRAL (n = 143) and PubMed (n = 333). Screening of the reference lists of published articles resulted in identification of another 18 articles. After combining the results from each database and removal of duplicate titles from Endnote®, 1,717 unique studies remained. After further screening, 1,461 were removed due to irrelevant titles or abstracts, leaving 256 studies for further scrutiny; 247 studies were excluded after further review. Of the nine full-text articles obtained, one was a narrative review [30], one had a retrospective design [31], one had a cross-sectional design [32] and three were based on secondary analysis of other studies [33-35] leaving only three original studies for the final review [36-38].

Study characteristics

The characteristics and results of the three studies included in the final review are summarized in Table 1. These studies evaluated the following interventions in pregnant women: an education program [36], progressive muscle relaxation (PMR) [37] and management of asthma guided by Fraction of exhaled Nitric Oxide (FeNO) [38]. Heterogeneity in study design, setting, type of intervention, follow-up and outcome measures were found among the three studies. Two studies took place in the antenatal clinic of one Australian hospital [36,38] and another [37] in Germany. All three interventions were conducted in clinics or hospital settings.

Methodological quality

All three studies had methodological limitations. The education program in the uncontrolled pre- and post-test design study was delivered by the same personnel who were involved in outcome assessment and were not masked (blinded), thus observation/detection bias might have occurred [36]. Only one of the RCTs reported allocation concealment [38]. The outcomes of both trials [37,38] were assessed by masked investigators but only one reported masking of both the participants and personnel who were involved in the intervention [38]. Sample size calculation was described for both RCTs, but not in the pre- and post-test study [36]. Participation and attrition rates varied across the three studies. Only Powell et al. [38] gave reasons for participant withdrawal (11 from the trial group and 6 from the control group). None of the study protocols were published. One trial was registered with the Australian and New Zealand Clinical Trial registry [38].

Results of individual studies

Education program

Murphy et al. [36] conducted a study to implement asthma self-management skills through an education program in pregnant women with asthma in an antenatal clinic. The asthma self-management skills assessed were: medication adherence (inhaled corticosteroid [ICS] users only), knowledge about how the reliever and preventer medications worked and inhaler technique, possession of a written action plan, and self-monitoring. The medication adherence and knowledge were assessed by direct questioning, while the inhaler technique was demonstrated by the patient.

The study found that maternal and neonatal outcomes may be improved by asthma self-management education, which can be delivered in an antenatal clinic by a nurse with specific training in asthma education. Improvements

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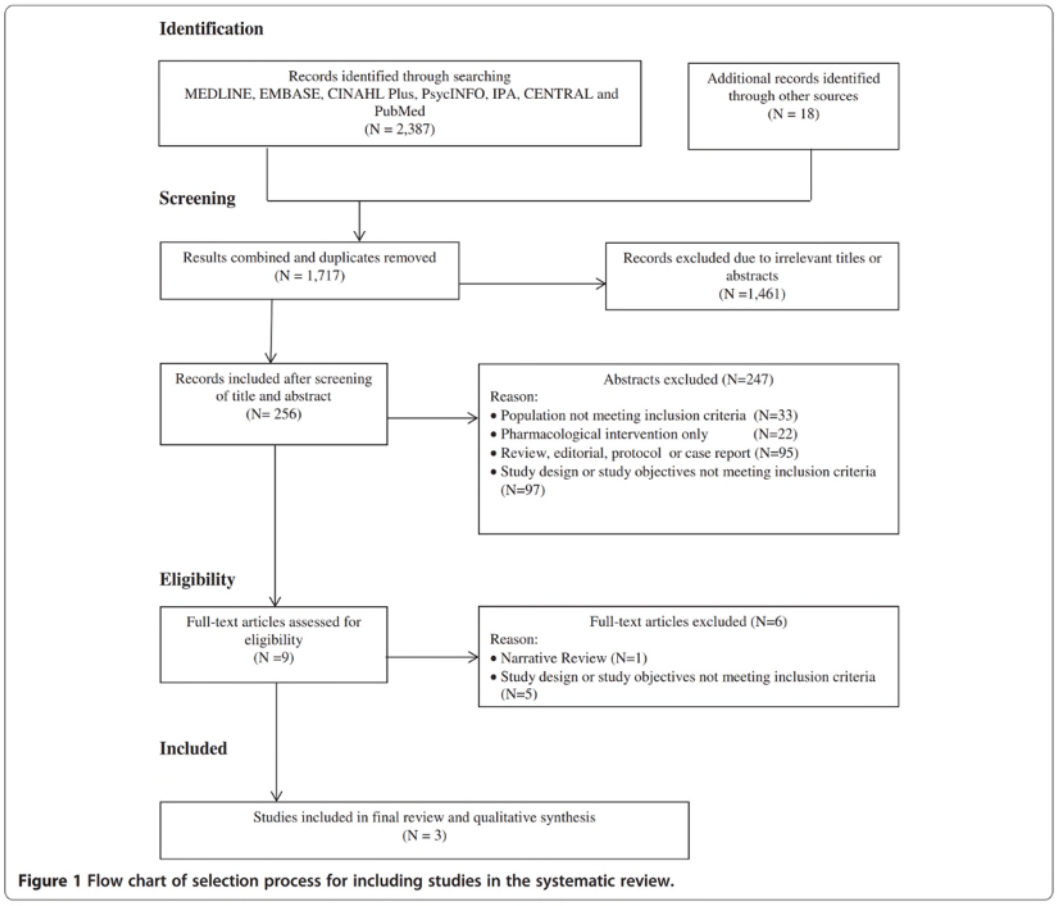

Figure 1 Flow chart of selection process for including studies in the systematic review.

in asthma medication adherence, knowledge and skills were associated with asthma education and should be considered as an important aspect of managing asthma in pregnant women [36]. There were some limitations of this study. The time elapsed (~3 months) between the two visits was identified by the authors as a potential confounder, as changes in asthma control could be influenced by gestation and seasonal changes [36]. Since there was no comparison group, it remained unclear if the asthma management skills improved because of the asthma education provided in the antenatal clinic, as a result of other factors, or spontaneously [36].

Progressive Muscle Relaxation (PMR)

This trial by Nickel et al. [37] examined the efficacy of progressive muscle relaxation (PMR) on changes in heart rate, systolic blood pressure (SBP), lung function and quality of life in pregnant women with asthma. The PMR procedures in this study required the participants to monitor and control their state of muscular tension. In the first step, the women deliberately applied tension to certain muscle groups and then released the tension and focused on how the muscle relaxed during the process [37]. This study claimed that the PMR intervention was inexpensive and demonstrated a potential benefit in pregnant women with asthma [37]. Inability to confirm that all the participants followed the instructions was a limitation acknowledged by the authors [37]. The short term follow-up of the study (8 weeks) may have contributed to the low drop-out rate [37]. Only immediate effects were measured after an active intervention. Hence it is unknown if PMR intervention would have had similar effects in the longer term and during asthma exacerbations [37].

FeNO-based algorithm

Powell et al. [38] carried out a double-blind parallel group RCT to test whether asthma control in pregnancy would

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Table 1 Key features of studies included in the final review

First Author, Year, study	Aim	Setting; country	Population	Study design	Interventions	Follow-up	Outcomes	Results
Murphy, 2005 [36] "Education program"	To determine the level of asthma self-management skills and knowledge, and to implement an asthma education program	Antenatal clinics; NSW, Australia	Pregnant women with a doctor's diagnosis of asthma (mild, moderate, severe) at ~ 20 weeks gestation	Pre-and post-	I: Received education about asthma control and self-management skills from a nurse (asthma educator) in two visits each consisting of a 30-60 min session (n = 211) C: no control group	~33 week s of gestation (last visit)	Self-reported nonadherence to ICS, lung function (FEV_1, FEV_1%, FVC, FEV_1/FVC), symptoms and reliever medication use.	Non-adherence to ICS decreased (p = 0.006). FEV_1(*l*) at first visit[1]: mild: 3.14 ± 0.05 moderate: 2.87 ± 0.08 severe: 2.87 ± 0.09 FEV_1(*l*) at last visit[1]: mild: 3.13 ± 0.08 moderate: 2.91 ± 0.12 severe: 2.95 ± 0.10. No significant difference in lung function, symptoms and reliever medication use between the two visits.
Nickel, 2006 [37] "Progressive Muscle Relaxation (PMR)"	To examine the efficacy of PMR in pregnant women	Psychosomatic clinics; Germany, Austria	Pregnant women with asthma who were regularly seen by an obstetrician/ gynecologist	RCT	I: 30 min PMR session, 3 times a week (n = 32) C: placebo (30 min sham training), 3 times a week (n = 32)	8 weeks from baseline	Lung function (PEF, FEV_1), QoL (SF-36)	FEV_1(*l*): initial[2]: I: 1.69 ± 0.6 C: 1.75 ± 0.5 final[2]: I: 2.22 ± 0.5 C: 1.75 ± 0.5 Difference in FEV_1[95%CI] = 0.5 (0.2 to 0.8) p = 0.005 Difference in SF-36 (mental health component)[95%CI] = 5.8 (1.4 to 10.2) p = 0.01
Powell, 2011 [38] "FeNO based Algorithm"	To test the hypothesis that a management algorithm for asthma in pregnancy based on FeNO and symptoms would reduce asthma exacerbations	Antenatal clinics; NSW, Australia	Non-smoking pregnant women (aged ≥ 18 years) with asthma, 12 – 20 weeks gestation and using asthma medications (e.g. inhaled therapy, $beta_2$-agonist) within the past year	Double-blind RCT	I: FeNO algorithm to adjust therapy: (1) FeNO concentration was used to adjust the dose of inhaled corticosteroids (2) ACQ score was used to adjust the dose of long acting $beta_2$-agonist (n = 111) C: ACQ- based clinical algorithm (n = 109)	monthly until delivery	Exacerbation types (unscheduled doctor visits, OCS use, hospital admission, ER/labor ward visits), QoL (SF-12 and AQLQ-M), Lung function (FEV_1 and FEV_1%), current treatment and perinatal outcomes	Significant reduction in unscheduled doctor visits for asthma (p = 0.002) and OCS use (p = 0.042), QoL (SF-12 mental health component) higher in FeNO group (p = 0.008) – remained significantly different after adjustment for baseline values (p = 0.037), AQLQ-M scores were low at the completion of the study and not different between the groups. FEV_1(*l*) at randomisation[3]: I: 3.05 (2.96 – 3.14) C: 3.06 (2.96 – 3.15) FEV_1(*l*) at end of study[3]: I: 3.09 (3.0 – 3.17) C: 3.01 (2.91 – 3.10) No significant difference in lung function.

Data are presented as [1]) mean ± SE, [2]) mean ± SD, [3]) mean [95% Confidence Interval].
ACQ = Asthma Control Questionnaire, AQLQ-M = Asthma Quality of Life Questionnaire-Marks, C = Control, FeNO = Fractional exhaled Nitric Oxide, FEV_1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, ICS = Inhaled corticosteroid, I = intervention, min = minute, *l* = liter, OCS = Oral corticosteroid, PEF = Peak expiratory flow rate, QoL = Quality of Life, RCT = Randomized Controlled Trial, SF-36 = Short Form 36, SF-12 = Short Form 12.

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be better using a FeNO-based treatment algorithm compared to an ACQ clinical algorithm in terms of reducing asthma exacerbations. FeNO helps to identify eosinophilic airway inflammation and to adjust the dose of ICS. The FeNO-based algorithm group had a sequential process: (1) FeNO concentration to adjust the dose of ICS; and (2) ACQ score to adjust the dose of long acting beta$_2$-agonist. The clinical algorithm was based on asthma control assessed with Juniper's ACQ questionnaire. The data collected included clinical symptoms, ACQ, quality of life questionnaires (AQLQ-M and SF-12), present treatment (ICS and β_2 agonist), FeNO and spirometry (FEV_1, FVC).

This trial showed that the FeNO group had a significantly lower rate of asthma exacerbations during pregnancy ($p = 0.001$) and unscheduled doctor visits due to asthma during pregnancy ($p = 0.002$) [38]. However the ACQ scores (symptom-free days) and the AQLQ-M scores of the two groups were not significantly different at the end of the study [38]. The mean daily ICS dose was lower in the FeNO group throughout the study. A higher median birth weight as well as a reduction in preterm deliveries and neonatal hospitalizations was also found in this group [38].

Discussion

This systematic review evaluated the effectiveness of non-pharmacological healthcare interventions for improving asthma management in pregnant women. The three studies included in the review assessed education, PMR and a FeNO-based algorithm, which were found to have some positive effects on asthma management in pregnancy. Firm conclusions however, cannot be drawn due to the limited number of reported studies, clinical heterogeneity of the interventions, variations in outcome measures and limitations in study designs.

Patient education is the cornerstone of asthma management during pregnancy as it promotes adherence and in turn, improves asthma control [16]. Gibson et al. [39] identified four components of an effective asthma education program: (1) information about asthma and its management, (2) self-monitoring of either symptoms or peak expiratory flow rate, (3) regular medical review for assessing asthma control, severity and medications, and (4) a written action plan to guide patient self-management of asthma exacerbations. Pregnant women with asthma should have a basic understanding of self-monitoring, how to use asthma medications correctly, how to manage worsening asthma and the importance of continued adherence to asthma management plans [16]. Asthma education programs and self-management skills have been proven to be effective in improving health outcomes in adults with asthma [18]. Both the studies of Murphy et al. [36] and Powell et al. [38] provided education to pregnant women on skills and knowledge to manage their asthma, leading to improvement in adherence to medication regimens and asthma action plans.

The 30-min PMR sessions three times a week showed a greater improvement in lung function compared to sham training [37]. A systematic review by Huntley et al. [40] concluded that muscular relaxation may improve lung function. However, there was no evidence for effectiveness on asthma symptoms in pregnant women with asthma. The effects of educational interventions and PMR on asthma at different stages of gestation remain unknown.

The outcomes measured varied among the three studies. Lung function (e.g. FEV_1, PEF) was measured as an outcome in all of the studies included. All three studies showed some improvement in FEV_1, although only one study demonstrated a significant improvement in FEV_1 as a result of the intervention [37]. During pregnancy, static lung function remains the same except for a reduction in functional residual capacity (FRC), expiratory reserve volume (ERV) and residual volume (RV) [41]. As the uterus enlarges, FRC decreases by 10% to 25% of the previous value due to a 35% to 40% decrease in chest wall compliance [42]. Normal pregnancy may have no significant effect on airway function. However in pregnant women with asthma, peak flow rate, FEV_1 and FVC may decrease particularly during acute exacerbations [43]. The study by Schatz et al. [44] observed that it is important to measure FEV_1 regularly during pregnancy, both as a prognostic factor for perinatal outcomes and as a measure of asthma control. Monitoring lung function using spirometry is recommended in the initial assessment of all pregnant women with asthma and periodically as needed [45], although lung function is typically impaired only in severe asthma and during acute exacerbations. Further studies are needed to confirm the efficacy of healthcare interventions in pregnant women with asthma over different trimesters, as pulmonary function changes throughout pregnancy in asthmatic women [6,43,46].

Powell et al. [38] reported a significant reduction in the rate of unscheduled doctor visits for asthma and oral corticosteroid use in patients receiving FeNO-guided management. Reduced asthma exacerbations leading to improvements in both maternal and neonatal outcomes were also reported [38]. The application of FeNO as a biomarker of airway inflammation for the adjustments of ICS treatment to guide asthma management has been widely studied, however the results are as yet inconclusive. Several studies have shown that FeNO-guided asthma management is no more effective in reducing asthma exacerbations than current asthma guidelines and conventional pulmonary tests using spirometry [47-50]. Daily FeNO monitoring has been shown to be of no added value compared to daily symptom monitoring. Moreover, FeNO measurements are not routinely available in most clinical settings [11].

The American Thoracic Society [51] recommends FeNO for monitoring airway inflammation in patients with asthma. However, there is insufficient evidence to support more widespread use. Various confounders, including sex, age, height, measurement technique, exhalation flow rate, smoking, anti-inflammatory medications and even what the patient ate for breakfast, may affect FeNO results [51]. A cross-sectional study by Tamasi et al. [32] showed that in pregnant women with asthma, FeNO levels are elevated compared to healthy pregnant women and they correlate with the level of asthma control. Further studies comparing FeNO-guided asthma management with simple implementation of asthma guidelines in conjunction with conventional lung function monitoring, especially in pregnant women, are required to confirm any advantage of FeNO monitoring over traditional monitoring/self-management.

Strengths and weaknesses of this review

This is the first systematic review of the effectiveness of non-pharmacological healthcare interventions for managing asthma and improving health outcomes in pregnant women with asthma. Unpublished studies were not included in this review. A meta-analysis was not possible because of the clinical heterogeneity of the data and study designs.

Practice and research implications

A clinical algorithm for asthma management based on objective measures and asthma symptoms could potentially reduce asthma exacerbations during pregnancy. The goals of asthma management in pregnant women are the same as in non-pregnant patients, which are to control asthma symptoms, maximize lung function, minimize medication side effects and prevent asthma exacerbations. These goals need to be considered when designing interventions, in addition to pharmacological treatment, to improve health outcomes in pregnant women with asthma. The cost-effectiveness of interventions and satisfaction of patients and health professionals also need to be assessed before implementation of such interventions in clinical practice. Further evidence is needed from well-designed prospective controlled studies in pregnant women with asthma investigating the effectiveness of interventions that incorporate patient education, patient self-management and periodic follow-up with health professionals.

Conclusions

Our review suggests that non-pharmacological healthcare interventions including education, self-management, progressive muscle relaxation and periodic follow-up may optimize asthma management in pregnancy. Interventions that enable pregnant women to be monitored regularly using objective measures of lung function or asthma symptoms appear to be more effective in improving health outcomes during pregnancy.

Abbreviations

ACQ: Asthma control questionnaire; AQLQ-M; AQLQ-M: Asthma quality of life questionnaire – marks; FeNO: Fraction of exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; ICS: Inhaled corticosteroid; PEF: Peak expiratory flow rate; PMR: Progressive muscle relaxation; SF- 12: Short form-12; SF-36: Short form-36.

Competing interests

JG and MA hold an investigator-initiated grant from Pfizer for unrelated research. The other authors declare that they have no conflicts of interest.

Authors' contributions

EZ searched the literature and selected the studies. She also extracted and assessed the relevant data, working with JG and KS. EZ drafted the manuscript and developed it with input from all the authors. All authors approved the final manuscript.

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3.3 Discussion and Summary

The systematic review identified only a few non-pharmacological healthcare interventions for managing asthma in pregnant women. The three studies included in the final review assessed an education programme, progressive muscle relaxation (PMR) and a FeNO-based algorithm. All three interventions were found to have some positive effects on asthma management during pregnancy. However, a meta-analysis was not possible because of the clinical heterogeneity of the data and the study designs. Despite the clinical heterogeneity of the interventions and variations in outcome measures, some similarities among the studies included were found. Self-monitoring of lung function and education on asthma management by health professionals were components of both the education programme and FeNO-based algorithm. All three studies used lung function (FEV_1) as one of the study outcomes to measure the effect of the interventions. Monitoring asthma symptoms and asthma–related QoL using standardised tools, e.g. ACQ and AQLQ, were outcome measures in the included studies. This review suggested that a non-pharmacological healthcare intervention that involves regular monitoring using objective measures such as lung function or asthma symptoms may result in better asthma control during pregnancy and better health outcomes. These findings informed the design of the next phase of the PhD project as described in Chapter 4.

Chapter 4
The Role of Objective Measures of Pulmonary Function for Monitoring Asthma Management in Pregnant Women

4.1 Introduction

The findings reported in **Chapter 3** highlighted the important role of objective measures for monitoring pulmonary function during pregnancy. Spirometry is considered the best method for diagnosing and monitoring pulmonary function in asthma. Uncertainty still exists regarding objective measures such as FEV_1 and FVC for monitoring asthma during pregnancy. Previous studies that observed changes in pulmonary function during pregnancy were limited by aspects of study design. Several studies used a cross-sectional design, which is not suitable for observing changes in pulmonary function during pregnancy because of the hormonal, metabolic and physiological effects of pregnancy. No previous studies have prospectively observed changes in pulmonary function in both healthy and pregnant women with asthma. No studies have investigated the role of the novel measure FEV_6 as a surrogate for FVC to monitor pulmonary function in pregnant women with asthma.

Thus, this chapter describes a study to observe changes in pulmonary function during pregnancy, in women with and without asthma.

The key objectives of this study were to:

- compare changes in pulmonary function during pregnancy between healthy women and those with asthma;
- determine the relationship between changes in pulmonary function and asthma-related quality of life in pregnant women with asthma; and
- investigate the application of FEV_6 in monitoring asthma during pregnancy.

A prospective cohort study was conducted to observe pulmonary function changes in pregnant women with and without asthma. Pulmonary function changes were measured by spirometry (pre-bronchodilator) performed three times during pregnancy (prior to 20 weeks, 21–28 weeks and 29–36 weeks gestation).

This prospective cohort study has been published in *Journal of Asthma* and is reproduced below.

Appendices relevant to this chapter are appendix 4, 6, 7, 11, 13, 20 and 21.

4.2 Manuscript

4.2.1 Declaration (Part B) for Thesis Section 4.2.2

In the case of **Section 4.2.2**, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Reviewed literature, designed methods, developed study materials, carried out participant recruitment and data collection, entered and analysed data, and prepared first draft of the manuscript and revised based on comments from co-authors.	60

The following co-authors contributed to the work.

Name	**Nature of contribution**
Dr Johnson George	Advised on study design and assisted with manuscript preparation
A/Prof Kay Stewart	Advised on study design and assisted with manuscript preparation
Prof Michael Abramson	Advised on study design and assisted with manuscript preparation
Prof Christine McDonald	Advised on study design and assisted with manuscript preparation
Eldho Paul	Assisted with data analysis and manuscript preparation
Prof Susan Walker	Advised on study design and with manuscript preparation
Peter Rochford	Assisted with interpretation of spirometry and with manuscript preparation
Gary Nolan	Assisted with interpretation of spirometry and with manuscript preparation

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

		Date
Candidate's Signature	[redacted]	**23 July 2015**
Main Supervisor's Signature	[redacted]	**23 July 2015**

4.2.2 Published manuscript: A Prospective Cohort Study of Pulmonary Function during Pregnancy in Women with and without Asthma. *J Asthma*. 2015; 1 - 9

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ORIGINAL ARTICLE

A prospective cohort study of pulmonary function during pregnancy in women with and without asthma

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Abstract

Background and objective: Pregnancy alters the severity of asthma unpredictably. Uncertainty still exists about longitudinal changes in pulmonary function during pregnancy in both healthy and asthmatic women. This study aimed to compare pulmonary function changes during pregnancy in healthy and asthmatic women and to determine the relationship between pulmonary function and asthma-related quality of life during pregnancy. A secondary aim was to investigate the application of forced expiratory volume in 6 s (FEV_6) for monitoring asthma during pregnancy. *Methods*: Pregnant women with ($n = 20$) and without asthma ($n = 20$) had pulmonary function tests at 8–20, 21–28 and 29–40 weeks gestation. Those with asthma also completed the Asthma Control Questionnaire (ACQ) and mini Asthma Quality of Life Questionnaire (mAQLQ) at each visit. *Results*: Pulmonary function declined in both groups at follow-up #1 (more markedly in those with asthma) but then improved at follow-up #2 (more markedly in those with asthma). In those with asthma, ACQ scores increased, while mAQLQ scores declined at follow-up #1; whilst at follow-up #2 these changes were in the opposite direction. FEV_6 and forced vital capacity (FVC) were highly correlated ($r = 0.88$, $p < 0.01$) in asthmatics. *Conclusions*: Pulmonary function changes during second and third trimesters were more pronounced in asthmatics than in healthy women. FEV_6 monitoring may assist pregnant women and their health professionals in optimizing asthma management. The changes in pulmonary function in women with asthma were not significantly associated with changes in asthma control or asthma-related quality of life.

Keywords

Asthma, pregnancy, pulmonary function, spirometry

History

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Introduction

Uncertainty still exists about the longitudinal changes in pulmonary function during pregnancy in both healthy women and those with asthma. During pregnancy asthma improves in nearly a third of patients, worsens in slightly more than one-third, and remains unchanged in one-third [1]. Some pregnant women with asthma may have few symptoms, but their pulmonary function may be abnormal, putting the health of mother and fetus at risk [2]. Since pregnancy alters the severity of asthma unpredictably, patients should be monitored closely so that any changes in asthma control can be matched with appropriate changes in management. Regular objective monitoring in conjunction with assessment of asthma-related quality of life (QoL) and asthma control might help early detection of worsening asthma by patients and health professionals, enabling changes in management.

Spirometry is still the best means of monitoring and assessing asthma severity [3]. For pregnant women with asthma, spirometry should be conducted early in pregnancy and periodically, as needed [4]. Forced expiratory volume in 6 s (FEV_6) has been shown to be equivalent to forced vital capacity (FVC) in consecutive patients referred to a New Zealand tertiary hospital respiratory laboratory for spirometry [5]. Performing FEV_6 is easier, more achievable, more reproducible and less physically demanding than FVC [5–7]. FEV_6 has the advantage that at the end of a spirometry measurement, the result is more explicitly defined and easier to achieve compared to FVC [8]. However, FEV_6 has not been used in prospective evaluation of lung function during pregnancy.

This study aimed to: (i) compare changes in pulmonary function during pregnancy between healthy women and those with asthma; (ii) determine the relationship between changes

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in pulmonary function and asthma-related QoL in pregnancy and (iii) investigate the application of FEV_6 in monitoring asthma during pregnancy.

Methods

Subjects

Pregnant women with a singleton pregnancy aged ≥18 years and able to communicate in English were recruited when attending scheduled antenatal visits at the Mercy Hospital for Women, Melbourne, Australia. The healthy group had no history of asthma and none of the participants in either group had a history of hypertension or cardiovascular disease. Pregnant women who self-reported asthma at the time of booking their first antenatal clinic visit and had used any asthma medication (anti-inflammatory or bronchodilator) during or in the 12 months before the current pregnancy were eligible for inclusion. The study was approved by the Human Research Ethics Committees of Monash University and the Mercy Hospital for Women. Written informed consent was obtained from all participants.

Design

A prospective cohort study was conducted to observe changes in pulmonary function. Pulmonary function (pre-bronchodilator) was measured, seated; three times (gestational weeks 8–20, 21–28, and 29–40) in the Respiratory Laboratory, Austin Health, using a spirometer (Jaeger MasterScreen, Carefusion, Hoeschberg, Germany). All spirometry variables were reported to American Thoracic Society/European Respiratory Society (ATS/ERS) 2005 standards [9]. Spirometry was not performed if participants self-reported respiratory infection at a particular visit to avoid compromising the quality of the maneuver due to coughing or sneezing and to reduce infection control hazards.

Study outcomes

Pulmonary function parameters measured or calculated at the three time points included FEV_1, FEV_6, FVC, FEV_1/FEV_6 and FEV_1/FVC. FEV_1 and FVC were also expressed as percentage (%) predicted values using the National Health and Nutrition Examination Survey (NHANES III) reference equations. A standard ethnicity correction 0.88 for non-Caucasian subjects was applied as suggested by ATS/ERS 2005 guidelines [10].

Asthma control and asthma-related QoL were assessed prior to spirometry using the Asthma Control Questionnaire (ACQ) 7 questions [11] and mini Asthma Quality of Life Questionnaire (mAQLQ) [12], respectively. An ACQ score of ≥1.5 suggested that asthma was not well controlled; and a change in ACQ score by ≥0.5 was regarded as clinically significant [minimum clinically important difference (MCID)] [13]. The mAQLQ measures the functional (physical, emotional, occupational and social) problems that concerned patients with asthma. The maximum score on mAQLQ was 7, which meant there was no impairment due to asthma [12].

Neonatal characteristics including Activity Pulse Grimace Appearance Respiration (APGAR) scores at 1 and 5 min, gestational age, birth weight, length and head circumference were recorded at delivery. Birth weight centiles were calculated using www.gestation.net/grow-au.aspx, which adjusted for maternal characteristics including height, weight, ethnicity, parity and fetal gender.

Statistical analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC) and SPSS version 19.0 (IBM SPSS Statistics for Windows, Armonk, NY). Differences in demographic characteristics, and maternal and fetal outcomes were examined using χ^2 tests, unpaired t-tests or Mann–Whitney U-tests where appropriate. Univariate correlations were determined using Pearson's r and Spearman's ρ. All reported p values were two-sided and not adjusted for multiple comparisons. A $p<0.05$ indicated statistical significance.

Pulmonary function parameters were the main outcome measures. A longitudinal analysis was performed using the PROC MIXED procedure in SAS with patients treated as random effects. Models were fitted using main effects for group (asthma versus healthy), time (baseline, follow-up visits #1 and #2) and an interaction between group and time to ascertain if the groups behaved differently over time. To account for any baseline imbalances, baseline values of outcomes were included as potential covariates in these models. The PROC MIXED procedure uses a restricted maximum likelihood algorithm that enables specific modeling of the within-patient covariance structure. Using an Akaike information criterion (AIC) to determine goodness of fit, an auto regressive (order 1) covariance structure was found to produce the best fit to data. All observed data were considered for analysis, with the mixed-effects models treating missing values as being missing at random. *Post hoc* pairwise comparisons were performed to assess between group differences at follow-up visits and within group differences between follow-up visits.

Results

The flow of participants through the study is illustrated in Figure 1. Forty pregnant women (20 healthy, 20 with asthma) were recruited between 11 and 19 weeks of gestation. All participants completed baseline spirometry including FEV_6 measurement prior to 20 weeks gestation. The characteristics of the sample are summarized in Table 1. There were no significant differences in demographic or maternal characteristics between women with and without asthma. Twelve (60%) women with asthma used short-acting beta agonists (SABA) as needed only, while the rest also used an inhaled corticosteroid (ICS) or an ICS long-acting beta agonist (LABA) combination. None of the women with asthma self-reported any comorbidities.

Changes in pulmonary function

When the pulmonary function parameters were analyzed with the mixed-effects models, significant group × time interaction effects were found for FEV_1 ($p=0.04$), FEV_1% predicted ($p=0.042$) and FEV_1/FVC% predicted ($p=0.01$). Changes in pulmonary function during pregnancy were similar in both

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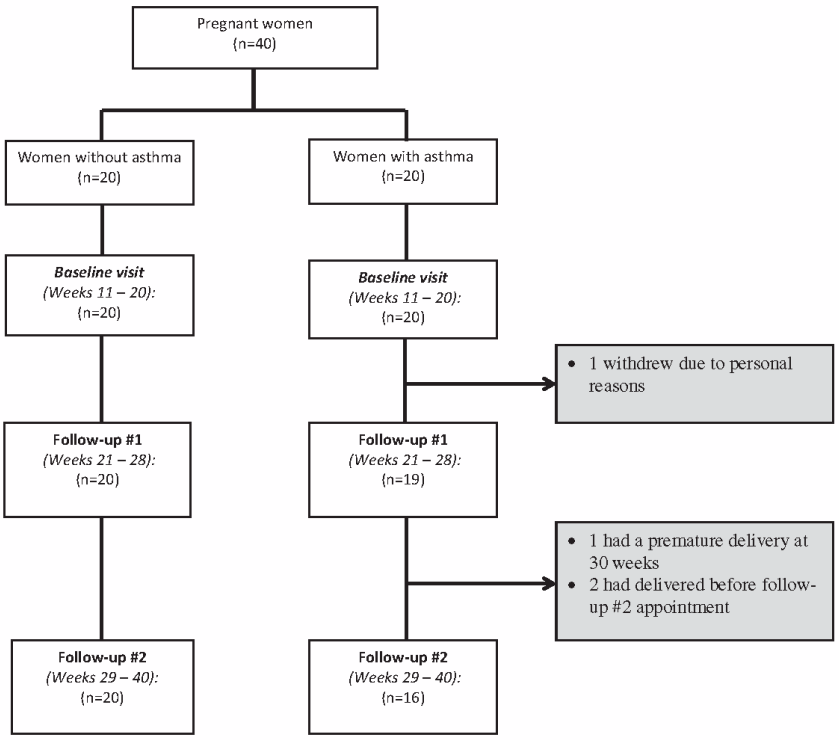

Figure 1. Flow of study subjects through the study.

groups. At baseline, there were no statistically significant differences in pulmonary function between groups (Table 2). At follow-up #1, pulmonary function declined in both groups, but women with asthma had a greater reduction. At follow-up #2, both groups showed improvement in pulmonary function compared to follow-up #1. FEV_1, FEV_1% predicted (both $p = 0.02$) and FEV_1/FVC% predicted ($p = 0.01$) values were significantly different between healthy and asthmatic groups at follow-up #2. These changes are also illustrated in Figure 2.

The within group differences in FEV_1, FEV_6, FVC, FEV_1% and FEV_1/FVC% predicted at the first and second follow-ups compared to baseline are presented in Table 3. In the healthy group, mean baseline FEV_1 dropped by 101 and 43 ml at follow-ups #1 and #2, respectively. On the other hand, women with asthma had a mean reduction in baseline FEV_1 of 139 ml at follow-up #1, which subsequently increased by 51 ml to higher than baseline levels at follow-up #2.

Changes in ACQ and mAQLQ

In women with asthma, the decline in pulmonary function at follow-up #1 was also marked by a reduction in asthma control (i.e. increase in ACQ score) and QoL (i.e. decline in mAQLQ score). At follow-up #2 these changes were in the opposite direction, suggesting improvement in pulmonary function, better asthma control and QoL (Figure 3). At follow-up #1 ACQ score increased >0.5 (MCID) in 58% of the asthmatic group, decreased in 21%, and remained unchanged in 21%. At follow-up #2 ACQ score increased in 19%, decreased in 56% and remained unchanged in 25%. A strong inverse correlation was found between ACQ and mAQLQ at follow-ups #1 ($r = -0.74$; $p < 0.01$) and #2 ($r = -0.75$; $p < 0.01$). However, correlations between pulmonary function parameters and both ACQ and mAQLQ were very weak.

Correlations between FEV_6 and FVC

At follow-up #1, compared to non-asthmatics, women with asthma had a greater decline in FEV_6 and the decrease of FEV_6 in the asthmatic group was also followed by the reduction in FVC (Table 3). However, at follow-up #2 the differences in reductions of FEV_6 and FVC from baseline between the groups were not significant. There were strong, positive correlations between changes in FEV_6 and FVC from baseline to follow-up #1 ($r = 0.88$, $p < 0.01$) and from follow-up #1 to follow-up #2 ($r = 0.85$, $p < 0.01$).

Maternal and neonatal characteristics

Pregnant women with asthma delivered slightly shorter babies ($p = 0.02$) with lower APGAR scores at one minute ($p = 0.01$) compared to those without asthma (Table 1). Nevertheless,

Table 1. Demographic, maternal and neonatal characteristics of the study participants.

	Without asthma ($n=20$)	With asthma ($n=20$)	p Value
Demographic characteristics	n (%)	n (%)	
Race			0.34
Caucasian	16 (80)	19 (95)	
Asian	4 (20)	1 (5)	
Past smoker	8 (40)	6 (30)	0.51
Gravidity			0.74
Primigravid	6 (30)	7 (35)	
Multigravid	14 (70)	13 (65)	
Maternal characteristics	Mean ± SD	Mean ± SD	
Age (year)	33.2 ± 5.0	32.3 ± 3.1	0.47
Height (cm)	165.8 ± 6.7	162.1 ± 6.6	0.08
BMI (kg/m^2) at baseline*	24.7 (21.9–27.0)	26.1 (22.7–30.5)	0.30
Weight (kg) at			
Baseline	70.7 ± 15.8	74.2 ± 20.0	0.56
Follow-up #1	72.9 ± 14.7	78.3 ± 19.5	0.34
Follow-up #2	79.5 ± 15.0	80.9 ± 19.1	0.79
Gestational age (weeks) at*			
Baseline	16 (16–17)	15.5 (13.3–17)	0.28
Follow-up #1	24 (22–26)	25.5 (24–27)	0.15
Follow-up #2	35 (34–36)	35.5 (34.3–36.8)	0.65
Duration of asthma (years)*	–	24.5 (18.5–29.8)	–
Asthma severity	–		–
Intermittent to mild		12 (60%)	–
Moderate to mevere		8 (40%)	–
Asthma medications			
SABA only	–	12 (60%)	–
ICS + SABA	–	1 (5%)	–
ICS/LABA + SABA	–	7 (35%)	–
Neonatal characteristics	Median (interquartile range)	Median (interquartile range)	
Gestational age	39.9 (38.6–40.5)	39.4 (39–40.7)	1
Mode of delivery [n (%)]			
Vaginal delivery	16 (80)	11 (55)	0.09
Emergency cesarean	2 (10)	5 (25)	0.41
Elective cesarean	2 (10)	2 (10)	1.00
Forceps/vacuum	0 (0)	2 (10)	0.48
Birth weight (gm)	3600 (3339–3745)	3400 (3118–3523)	0.13
Birth weight percentile <10th [n (%)]	2 (10%)	2 (10%)	1.00
Birth length (cm)	51.5 (51–52)	50.3 (47.4–51)	0.02
Head circumference (cm)	34.5 (34.4–36)	34.25 (33.6–35)	0.33
APGAR scores at 1 min	9 (9–9)	9 (6.25–9)	0.01
APGAR scores at 5 min	9 (9–9.75)	9 (9–9)	0.24

*Median (interquartile range).

Table 2. Pulmonary function parameters during pregnancy in women with and without asthma.

	Baseline		Follow-up #1		Follow-up #2	
Test	Without asthma $n=20$	With asthma $n=20$	Without asthma $n=20$	With asthma $n=19$	Without asthma $n=20$	With asthma $n=16$
FEV_1 (L)	3.18 ± 0.03	3.17 ± 0.03	3.08 ± 0.03	3.04 ± 0.03	3.14 ± 0.03	3.24 ± 0.03*
FEV_6 (L)	3.87 ± 0.03	3.87 ± 0.03	3.80 ± 0.03	3.71 ± 0.03	3.83 ± 0.03	3.85 ± 0.03
FVC (L)	3.91 ± 0.03	3.90 ± 0.03	3.85 ± 0.03	3.77 ± 0.04	3.87 ± 0.03	3.86 ± 0.03
FEV_1%	100.37 ± 0.90	100.00 ± 0.90	96.92 ± 0.90	95.75 ± 0.92	99.07 ± 0.90	102.13 ± 0.99*
FVC %	103.20 ± 0.86	103.14 ± 0.86	101.25 ± 0.86	99.41 ± 0.88	102.35 ± 0.86	102.15 ± 0.96
FEV_1/FVC	81.97 ± 0.84	81.12 ± 0.84	80.47 ± 0.84	81.72 ± 0.84	80.92 ± 0.84	83.80 ± 0.93
FEV_1/FVC% predicted	97.37 ± 0.70	96.19 ± 0.73	95.57 ± 0.70	94.36 ± 0.72	96.12 ± 0.70	98.71 ± 0.78*
FEV_1/FEV_6	82.53 ± 0.55	81.65 ± 0.55	81.42 ± 0.55	81.16 ± 0.57	82.41 ± 0.55	83.69 ± 0.61
ACQ score	–	0.5 (0.3–1.2)	–	1.43 (1–1.6)	–	0.7 (0.4–1.4)
mAQLQ score	–	6.1 (5.6–6.5)	–	5.3 (4.9–6.2)	–	6.2 (5.3–6.6)

FEV_1%, FEV_1 expressed as a percentage of the predicted value; FVC%, FVC expressed as a percentage of the predicted value. Pulmonary function data are presented as mean ± SE; ACQ and mAQLQ scores as median (interquartile range).
Significantly different from healthy *$p<0.05$.

there were no differences noted in 5 min APGAR or customized birth weight centile which are better measures of acute and chronic fetal compromise due to placental insufficiency, respectively. Two women in the asthma group reported symptoms in Weeks 21–28 and were prescribed prednisolone 50 mg daily for 2 weeks; one of them presented to the emergency department due to asthma exacerbation and was hospitalized. Only 55% women in the asthma group had a

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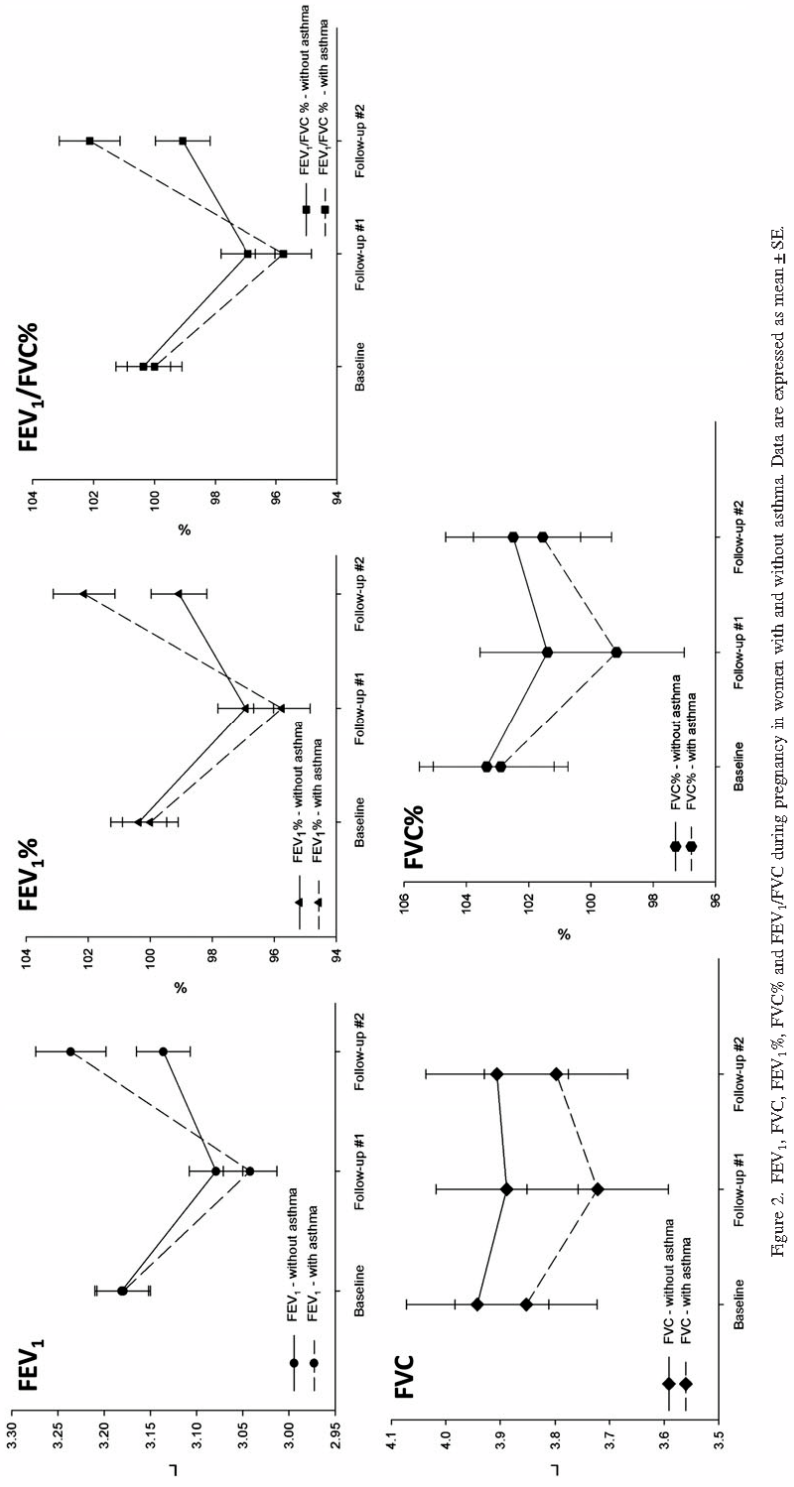

Figure 2. FEV_1, FVC, FEV_1%, FVC% and FEV_1/FVC during pregnancy in women with and without asthma. Data are expressed as mean ± SE.

Table 3. Changes from baseline in pulmonary function, asthma control score and asthma-related QoL in women with and without asthma.

	Mean difference (95% CI)			
	Without asthma		With asthma	
Test	Follow-up #1	Follow-up #2	Follow-up #1	Follow-up #2
FEV_1 (ml)	101 (29,172)	43 (−28,115)	139 (65,212)	−51 (−130, 28)
FEV_6 (ml)	71 (−5,147)	47 (−29,123)	159 (8, 237)	46 (−37,129)
FVC (ml)	52 (−34,138)	34 (−52,121)	134 (45, 222)	58 (−36, 153)
FEV_1%	3.20 (0.98,5.41)	1.05 (−1.17, 3.26)	4.55 (2.27, 6.83)	−1.73 (−4.20, 0.74)
FVC%	1.92 (−0.14, 3.98)	0.82 (−1.24, 2.88)	3.74 (1.63, 5.86)	1.35 (−0.92, 3.62)
FEV_1/FVC	0.92 (−1.11, 2.95)	0.47 (−1.56, 2.50)	0.12 (−1.93, 2.17)	−2.05 (−4.31, 0.21)
FEV_1/FVC% predicted	1.02 (−0.65, 2.69)	0.47 (−1.20, 2.14)	2.88 (1.14, 4.62)	−1.56 (−3.41, 0.29)
FEV_1/FEV_6	0.51 (−0.78, 1.79)	−0.49 (−1.77, 0.79)	1.25 (−0.08, 2.58)	−1.37 (−2.80, 0.05)
ACQ scores			−0.36 (−0.44, 0.30)	−0.14 (−0.65, 0.56)
mAQLQ scores			0.29 (−0.32, 0.43)	0.02 (−0.69, 0.71)

FEV_1%, FEV_1 expressed as a percentage of the predicted value; FVC%, FVC expressed as a percentage of the predicted value. There were no significant differences between the groups at baseline.

Values represent mean difference (CI) compared with baseline. Positive means values lower than baseline (decrease) and negative means values higher than baseline (increase).

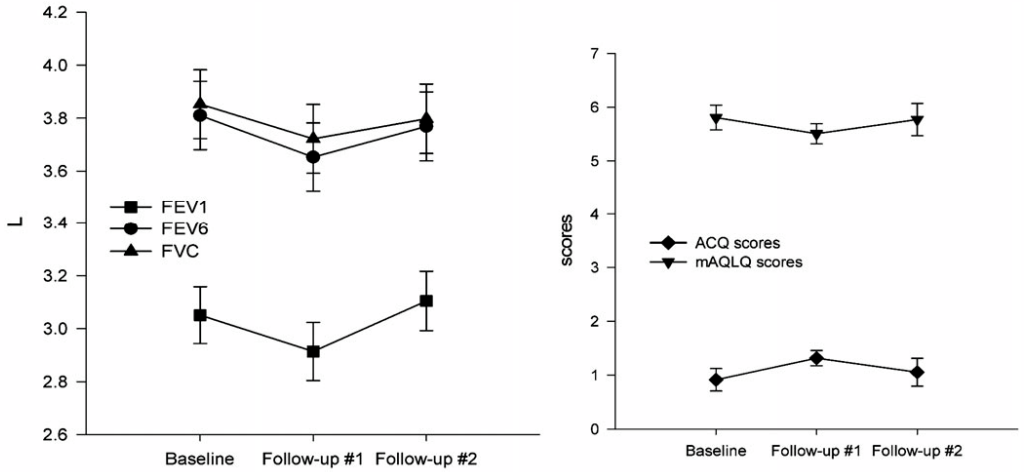

Figure 3. Pulmonary parameters, ACQ and mAQLQ scores in women with asthma.

normal vaginal delivery compared to 80% in those without asthma ($p = 0.09$).

Discussion

Changes in spirometry during pregnancy differed significantly between women with and without asthma. Compared to their counterparts, women with asthma showed a greater reduction of FEV_1 from baseline at follow-up #1, but had better pulmonary function at follow-up #2, the latter result being consistent with a previously described reduction in bronchial hyper responsiveness later in pregnancy [14]. The majority of the asthmatic group (60%) had mild asthma, as reflected by their use of only occasional SABA and the overall well preserved interval lung function, as is commonly seen in people with intermittent or mild persistent asthma [15].

Shortness of breath, often referred to as ''physiologic dyspnea'', is a common symptom during pregnancy [16]. Physical examination and spirometry can be used to distinguish physiologic dyspnea from pathologic dyspnea [17]. Physiologic dyspnea often occurs while at rest or with mild exertion; but when accompanied by other symptoms such as wheezing or cough is possibly due to asthma [17]. White et al [18] showed that some women with infrequent-mild asthma felt subjectively better during pregnancy when they were asked to self-report symptoms using diary cards, although no improvements were found in pulmonary function. Ideally, monitoring asthma changes during pregnancy should not rely on subjective patient perceptions alone; spirometry and

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Table 4 Summary of pulmonary function parameters in our study and previous studies during pregnancy.

	Our findings*		Sims [24]		Grindheim [20]	Nørregard [21]	Puranik [22]	Siddiqui [23]
Tests	Without asthma $n=20$	With asthma $n=20$	Without asthma $n=12$	With asthma $n=27$	Without asthma $n=100$	Without asthma $n=39$	Without asthma $n=50$	Without asthma $n=60$
Gestational age: 8–20 weeks								
FEV_1(L)	3.18 ± 0.03	3.17 ± 0.03	–	–	3.18 ± 0.44	–	2.00 ± 0.09	–
FVC (L)	3.91 ± 0.03	3.90 ± 0.03	–	–	3.89 ± 0.48	–	2.19 ± 0.25	–
FEV_1%	100.37 ± 0.90	100.00 ± 0.90	–	–	98.2 ± 11.10	104.0 ± 12.00	–	–
FVC%	103.20 ± 0.86	103.14 ± 0.86	99.3 ± 12.20	96.90 ± 9.50	–	–	–	–
FEV_1/FVC	81.97 ± 0.84	81.12 ± 0.84	81.40 ± 4.40	83.30 ± 6.10	–	–	–	–
FEV_1/FVC%	97.37 ± 0.70	96.19 ± 0.73	–	–	–	–	92.60 ± 5.01	–
Gestational age: 21–28 weeks								
FEV_1(L)	3.08 ± 0.03	3.04 ± 0.03	–	–	3.16 ± 0.39	–	2.07 ± 0.25	–
FVC (L)	3.85 ± 0.03	3.77 ± 0.04	–	–	3.96 ± 0.51	–	2.10 ± 0.28	–
FEV_1%	96.92 ± 0.90	95.75 ± 0.92	–	–	99.1 ± 11.40	96.0 ± 12.00	–	–
FVC%	101.25 ± 0.86	99.41 ± 0.88	101.20 ± 12.10	82.60 ± 6.80	–	–	–	–
FEV_1/FVC	80.47 ± 0.84	81.72 ± 0.84	83.40 ± 4.40	82.60 ± 6.80	–	–	–	–
FEV_1/FVC%	95.57 ± 0.70	94.36 ± 0.72	–	–	–	–	98.63 ± 3.54	–
Gestational age: 29–40 weeks								
FEV_1(L)	3.14 ± 0.03	3.24 ± 0.03	–	–	3.21 ± 0.43	–	2.15 ± 0.21	2.17 ± 0.25
FVC (L)	3.87 ± 0.03	3.86 ± 0.03	–	–	4.00 ± 0.53	–	2.21 ± 0.27	2.47 ± 0.29
FEV_1%	99.07 ± 0.90	102.13 ± 0.99	–	–	99.3 ± 11.30	96.0 ± 19.00	–	88.64 ± 5.62
FVC%	102.35 ± 0.86	102.15 ± 0.96	102.20 ± 11.2	95.50 ± 13.10	–	–	–	86.48 ± 4.37
FEV_1/FVC	102.35 ± 0.86	102.15 ± 0.96	84.4 ± 3.5	82.80 ± 3.10	–	–	–	85.52 ± 2.32
FEV_1/FVC%	96.12 ± 0.70	98.71 ± 0.78	–	–	–	–	97.51 ± 4.04	–

Values are mean ± SDs except for *mean ± SEs.

validated asthma questionnaires may identify clinically significant changes in asthma [14,18,19].

Previous studies

Previous studies have not observed consistent changes in pulmonary function during healthy pregnancy. Table 4 compares the pulmonary parameters in our study to previous studies. While our study showed that FEV_1 and FVC decreased significantly at Weeks 21–28 in healthy subjects, Grindheim et al. [20] did not find a change in FEV_1 but showed that FVC increased significantly after Week 23, which was maintained at 6 months post-partum. Norregaard et al. [21] showed that FEV_1 decreased slightly during second and third trimesters, but then increased postpartum. The study by Puranik et al. [22] found that FEV_1 and FVC remained unchanged throughout normal pregnancy. Siddiqui et al. [23] demonstrated that pulmonary function parameters were not significantly different between healthy singleton and twin pregnancies in the last trimester (36 weeks gestation); while the values were lower in healthy pregnant women (singleton or twin pregnancy) than in non-pregnant women.

Sims et al. [24] measured FVC and FEV_1 in 27 pregnant women with asthma and 11 healthy pregnant women. The groups were not matched except for age. The asthmatic group had lower values at all-time points compared to controls. This study was not able to show significant longitudinal changes in FEV_1 and FEV_1/FVC between pregnancy and the non-pregnant state [24]. It also showed no indication that FEV_1 or FEV_1/FVC were affected by pregnancy either during exercise or at rest [24].

Our study sample was different from previous studies. Grindheim et al. [20], Norregaard et al. [21] and Sims et al. [24] studied European populations, while Puranik et al. [22] and Siddiqui et al. [23] studied Indian populations. The differences in subjects' ethnicity, sample size, medication use, data analysis methods, spirometer and measurement position (e.g. standing, sitting or supine) may account for differing results.

FVC versus FEV_6

We confirmed that FEV_6 and FVC are significantly correlated in pregnancy. FEV_6 and FEV_1/FEV_6 have been widely studied as surrogates for FVC and FEV_1/FVC, respectively [7], but have not previously been applied prospectively to monitor asthma in pregnancy. FEV_6 can be used as a substitute for FVC and has been shown to be equivalent to FVC in adults with asthma [5]. Longitudinal changes in FEV_6 and FVC during pregnancy in the asthmatic group were in the expected direction with changes in asthma control and asthma-related QoL, further supporting the potential use of FEV_6 for monitoring asthma in pregnancy.

A descriptive cross-sectional study by Nwagha et al. [25] in 172 healthy women with varying gestational ages [40 non-pregnant and 132 pregnant comprising 30 (<14 weeks), 48 (14–27 weeks) and 54 (>27 weeks)] showed that FVC and FEV_6 values were lower while the FEV_1/FVC and FEV_1/FEV_6 were higher as pregnancy progressed. Our study has confirmed longitudinal changes in FVC and FEV_6 in both women with and without asthma at various stages of pregnancy.

Our participants represented women attending major Australian maternity hospitals [26,27]. Although this study is limited by a small sample size, it is still sufficient to describe the longitudinal changes of pulmonary function during pregnancy in healthy women and those with asthma as they relate to gestational age. Statistically significant changes in pulmonary function may be meaningful to researchers, but of little clinical importance to patients [10]. The small

changes in FEV_1 and FVC observed in women with asthma in this study were possibly the result of restriction rather than obstruction as FEV_1/FVC did not change, suggesting asthma was not the major contributor to the pattern of pulmonary function changes in this group. The majority of studies in both adults and children have found no significant correlation between objective measures such as FEV_1/peak expiratory flow (PEF) and clinical asthma symptoms [3].

We observed some significant differences in pulmonary function between groups; hormonal, metabolic and physiological changes during pregnancy may alter the mechanics of breathing and pulmonary function in pregnant women. Pulmonary function changes during pregnancy are mediated initially by hormonal changes and later by the enlarging uterus [28]. In healthy women, there is usually adequate maternal compensation for the increase in oxygen demands, with the increases in tidal volume leading to a significant fall in partial pressure of carbon dioxide (pCO_2) [28]. The process appears to be mediated by rising levels of progesterone and augmented by a decrease in residual volume [28]. Progesterone and cortisol may affect the respiratory center [29]. Progesterone levels rise progressively in the first trimester and remain elevated until delivery resulting in stimulation of the respiratory center and smooth muscle relaxation [30]. Cortisol also rises sharply throughout pregnancy potentially leading to increased pulmonary glucocorticosteroid receptor interactions and effects causing smooth muscle relaxation [1,30].

Asthma symptoms may improve or worsen during pregnancy; hence appropriate management should be tailored to changes in pulmonary function. Various factors may contribute to poor QoL in pregnant women with asthma. Asthma changes unpredictably during pregnancy, and asthma symptoms usually worsen during the second and third trimesters, especially the sixth month, with improvement in the last 4 weeks [1,31]. Women who have poorly controlled asthma from the beginning of the pregnancy are likely to have more asthma symptoms throughout pregnancy; therefore they should be treated with appropriate medications and monitored closely [31]. Concerns about medication safety during pregnancy may prompt women to stop taking their medication without consulting their healthcare professionals leading to worsening symptoms and QoL [27,32]. However, in this study we did not assess asthma medication adherence at each visit.

Asthma self-management programs for pregnant women, involving regular monitoring of FEV_1 and FEV_6 in conjunction with assessment of asthma symptoms, should be evaluated in larger prospective studies for their ability to optimize health outcomes in women with varying severities of asthma. Future studies may also benefit from including longitudinal markers of inflammatory change in serum and possibly in exhaled condensate given the changes present at follow-up #1. A larger study with groups matched for body mass index (BMI), age, height and gestational age with more severe cases of asthma may also be beneficial.

In summary, we have demonstrated that pulmonary function declined during second trimester, then improved in the final weeks of gestation in both groups, but larger changes were found in women with asthma. Although the changes in pulmonary function were statistically significant in the asthma group, they were modest. The changes in pulmonary function in women with asthma were not significantly associated with changes in asthma control or QoL. FEV_6 can be substituted for FVC for monitoring during pregnancy. Regular monitoring of FEV_1 and FEV_6, along with assessment of symptoms and medication adherence, may assist pregnant women and their health professionals in optimizing asthma management.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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4.3 Discussion and Summary

Changes in lung function during pregnancy differed significantly between women with and without asthma. In the asthma group, changes in lung function parameters (FEV_1, FVC and FEV_6) were also marked by changes in ACQ and mAQLQ scores. There was a strong inverse correlation between ACQ and mAQLQ, however only weak associations were found between lung function parameters and both ACQ and mAQLQ. This study also confirmed that FEV_6 and FVC were significantly correlated in pregnancy. The longitudinal changes in FEV_6 and FVC in the asthma group were in the expected direction and in line with changes in ACQ and mAQLQ scores. The changes in lung function, ACQ and mAQLQ scores observed in the asthma group were in agreement with the literature that asthma symptoms change unpredictably during pregnancy (they may improve, worsen or remain the same). Although we found statistically significant changes in lung function during pregnancy in the asthma group, they were modest. However, as lung function changes throughout pregnancy it is essential to use it as part of the monitoring tools and outcomes measurements when designing an intervention particularly a telehealth intervention. These findings underline the importance of designing appropriate interventions for asthma management involving regular monitoring using objective measures such as lung function (FEV_1 and FEV_6) and asthma symptoms. It is suggested that FEV_6 can be substituted for FVC in pregnant women with asthma.

Chapter 5
Management of Asthma with Supportive Telehealth of Respiratory Function in Pregnancy (MASTERY©) – Study Protocol for a Randomised Controlled Trial

5.1 Introduction

Chapters 3 and **4** highlighted the importance of regular monitoring of lung function and asthma symptoms during pregnancy to optimise asthma management. Mobile phone-based self-monitoring is feasible for monitoring asthma control in adults and children with asthma (**chapter 2**)**.** Previous studies in pregnancy (**chapter 3**) have confirmed that when patients were involved in self-management (e.g. Education program, FeNO based-algorithm) better asthma outcomes were achieved. However, intervention involving FeNO-based algorithm was not used as not only was it costly, but also not widely available in clinics for routine use. The findings presented in **Chapter 3** highlighted that healthcare interventions involving regular monitoring of pulmonary function and asthma symptoms may contribute to improved asthma control and reduction in asthma exacerbations during pregnancy. An intervention that involving pregnant women to do self-monitoring from their home rather than have an extra visit to healthcare professional for managing their asthma is needed.

Chapter 4 demonstrated that the decline in lung function during pregnancy was more pronounced in women with asthma; this was also marked by deterioration of asthma control and asthma-related quality of life. Monitoring lung function (FEV_1; FEV_6)

daily is useful to detect any changes in lung function and these objective measures could be used in the individualised algorithm and asthma action plan to guide management. This ensured that any changes in lung function were detected on the same day and appropriate changes in management were recommended. Chapter 4 also highlighted the potential role of FEV_6 as a replacement for FVC to monitor asthma in pregnant women.

These results helped guide the development of an intervention for supporting asthma management in pregnant women developed involving regular self-monitoring of asthma using lung function and symptoms to assist self-management. The details of the intervention are described in the published protocol, which is presented in the next section (**section 5.2.2**). This chapter presents the protocol for the randomised controlled trial, known as MASTERY© (Management of Asthma with Supportive Telehealth of Respiratory Function in Pregnancy), to assess the efficacy of the intervention.

The key objectives of this study were to:

- develop and implement a telehealth programme for remotely monitoring pulmonary function and asthma symptoms during pregnancy;
- explore the feasibility of asthma self-management using a telehealth programme for regular monitoring of pulmonary function and asthma symptoms; and
- evaluate the efficacy of a telehealth intervention supported by a handheld respiratory device and a written asthma action plan (WAAP) for improving asthma control during pregnancy.

The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12613000800729). The protocol of this study has been published in *BMC Pulmonary Medicine* and is reproduced below.

Appendices relevant to this chapter are appendix 5, 9, 10, 12, 14 and 22.

5.2 Manuscript

5.2.1 Declaration (Part B) for Thesis Section 5.2.2

In the case of **Section 5.2.2**, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Reviewed literature, designed trial, developed *Breathe-easy*© application and algorithm, carried out participant recruitment and baseline data collection, entered and analysed data, prepared first draft of the manuscript and revised based on comments from co-authors and journal reviewers.	60

The following co-authors contributed to the work.

Name	**Nature of contribution**
Dr Johnson George	Conceived idea, advised on study design, was in charge of product purchases and assisted with manuscript preparation
A/Prof Kay Stewart	Advised on study design and assisted with manuscript preparation
Prof Michael Abramson	Advised on study design and assisted with manuscript preparation
Prof Christine McDonald	Advised on study design and participant's written asthma action plan and assisted with manuscript preparation
Eldho Paul	Conducted statistical analysis on primary outcomes and assisted with manuscript preparation
Prof Susan Walker	Advised on study design and assisted with manuscript preparation
Dr Jonathan Li	Assisted with *Breathe-easy*© development, and provided technical support during the trial
Thanuja Dharmasiri	Assisted with *Breathe-easy*© development, and provided technical support during the trial

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

		Date
Candidate's Signature	[redacted]	**23 July 2015**
Main Supervisor's Signature	[redacted]	**23 July 2015**

5.2.2 Published manuscript: Study Protocol for a Randomised Controlled Trial Evaluating the Efficacy of a Telehealth Program – Management of Asthma with Supportive Telehealth of Respiratory Function in Pregnancy (MASTERY)©. *BMC Pulm Med*. 2015; 15:8-4

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BMC Pulmonary Medicine

STUDY PROTOCOL Open Access

Study protocol for a randomised controlled trial evaluating the efficacy of a telehealth program – management of asthma with supportive telehealth of respiratory function in pregnancy (MASTERY©)

Elida Zairina[1], Michael J. Abramson[2,3], Christine F. McDonald[4], Jonathan Li[5], Thanuja Dharmasiri[5], Kay Stewart[1], Susan P. Walker[6,7], Eldho Paul[2,8] and Johnson George[1*]

Abstract

Background: Telehealth has the potential to improve asthma management through regular monitoring of lung function and/or asthma symptoms by health professionals in conjunction with feedback to patients. Although the benefits of telehealth for improving asthma management have been extensively studied, the feasibility of telehealth for supporting asthma management in pregnant women has not been investigated. This study aims to evaluate the use of telehealth for remotely monitoring lung function and optimising asthma control during pregnancy.

Methods: A randomised controlled trial comparing usual care with a telehealth program (MASTERY©) has been conducted. The intervention comprised a mobile application – *Breathe-easy*© supported by a Bluetooth-enabled handheld device (COPD-6®), which was used for self-monitoring of lung function (FEV_1, FEV_6) twice daily, and recording asthma symptoms and medication usage weekly; and a written asthma action plan (WAAP). The primary outcome measure is change in asthma control measured using the Asthma Control Questionnaire (ACQ). Secondary outcomes include changes in mini-Asthma Quality of Life Questionnaire (mAQLQ) score, lung function, asthma-related health visits, days off work/study, and oral corticosteroid use. Outcome data were collected at baseline, 3 months and 6 months by a research assistant masked to group allocation. Maternal and neonatal outcomes were also collected post-partum.

Discussion: This is the first study to evaluate the application of telehealth to optimize asthma management in pregnant women. If effective, this telehealth program could improve asthma self-management by pregnant women which may reduce the maternal and fetal risks of poorly controlled asthma during pregnancy.

Trial registration: Australian New Zealand Clinical Trials Registry (ACTRN 12613000800729) 17 July 2013

Keywords: Asthma, Pregnancy, Telehealth

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Background

Asthma is the most common obstructive pulmonary disease that occurs during pregnancy and may complicate pregnancy [1–4]. Previous studies have demonstrated that asthma during pregnancy improves in slightly more than a quarter of patients, but worsens in slightly more than one-third, and remains unchanged in one-third [5]. Poorly controlled asthma increases the risk of poor outcomes such as pre-eclampsia, fetal growth restriction, preterm birth and need for caesarean delivery [6–9]. Given the lifelong health decrements associated with these outcomes, an approach to optimise monitoring and treatment of asthma could have major short and long term public health benefits.

Education and regular monitoring by a pharmacist-led multidisciplinary team has been shown to improve asthma control during pregnancy [10]. Asthma management programs for pregnant women which involve regular monitoring of lung function and assessment of asthma symptoms appear to be effective in reducing asthma exacerbations [11, 12]. However, further studies are required to determine the most effective and safe interventions for managing asthma in pregnancy to improve maternal and neonatal outcomes [12].

Better asthma control can be achieved if patients are involved in self-management. This includes self-monitoring of asthma symptoms or lung function and following written asthma action plans while maintaining regular contact with their health professionals [13]. Telehealth supports asthma management through patient education, adherence support, telephone follow-up and remote monitoring [14]. Telehealth interventions have shown significant clinical improvement and potential benefits in patients with asthma, including: reduced time to access healthcare services and reduced cost linked to travelling; earlier detection of worsening asthma (e.g. exacerbations), and reduced healthcare visits/hospitalisations due to asthma [15–18]. Lung function data derived from telehealth assessment studies were comparable to those collected under supervision by healthcare professionals and thus valid [19, 20]. Telehealth programs also appeared to be feasible for asthma patients, as compliance with monitoring was high and most patients found the equipment easy to use [21].

Telehealth studies show potential benefits for asthma management in the general population [22]. However the feasibility of telehealth for supporting asthma management in pregnant women has not been investigated to date. Pregnant women with asthma are young and are likely to be willing to use new technology to assist self-management of their asthma. Hence, the present study will examine the potential for enhanced asthma management in pregnancy through a telehealth program.

The study aims to evaluate the efficacy of a telehealth intervention supported by a handheld respiratory device and a written asthma action plan (WAAP) for management of asthma in improving asthma control during pregnancy. We hypothesised that the telehealth intervention group will have better asthma control as measured by the Asthma Control Questionnaire (ACQ) score changes than the control group at three and six months from baseline.

Methods

Study setting

Participants were recruited when attending scheduled antenatal visits at two large maternity hospitals in Melbourne, Australia (Mercy Hospital for Women and The Royal Women's Hospital); each hospital has approximately 6000 births per year.

Study design

The study was designed as a prospective multi-centre single-blinded randomised controlled trial (RCT) with outcome assessors masked to group allocation at follow-up assessments. The flow of participants is illustrated in Fig. 1. The total duration of the intervention was 6–8 months depending on timing of the first antenatal visit and enrolment in the study. Both groups were followed up throughout pregnancy and the outcomes are being compared at three and six months from baseline to evaluate the efficacy of the intervention.

Inclusion and exclusion criteria

Eligibility for this trial included pregnant women with asthma who had used any inhaled bronchodilator or anti-inflammatory agent for asthma within the previous 12 months, were attending antenatal clinics in first or second trimester, aged 18 years or older and able to communicate in English. Those under specialist care for severe/difficult asthma were excluded. Women who are not already in possession of or have not used a smart mobile phone were considered ineligible to participate. This was confirmed by directly asking pregnant women about their mobile phone usage.

Trial recruitment

The following methods of identification and recruitment of participants were used:

1. One of the researchers (EZ) or research staff searched the outpatient files and screened the medical records of pregnant women with asthma scheduled to have a clinic visit on the following day by reviewing GP referral letters and/or notes from previous clinic consultations. Eligible women were approached for recruitment after clinic visit completion. On each day the researcher/research staff also searched for potential participants by

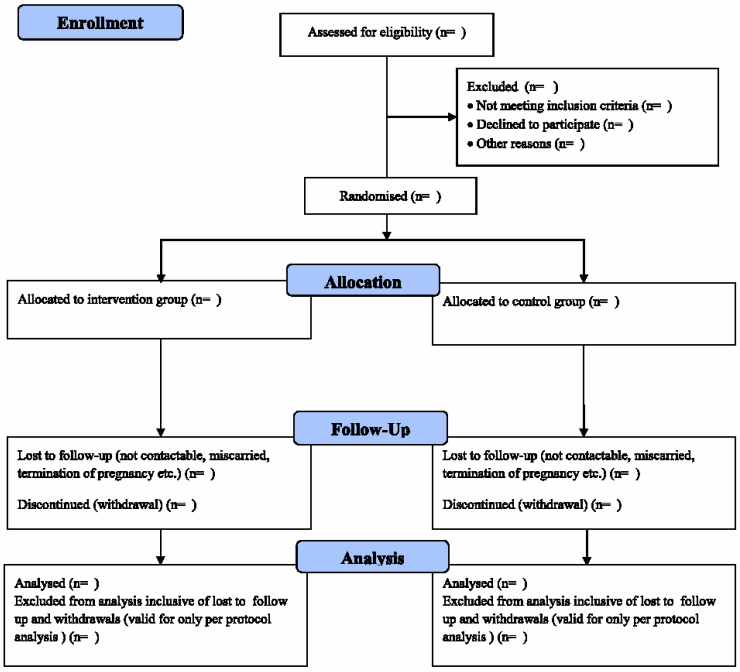

Fig. 1 Participant flow diagram

screening medical records of women who were reviewed by the midwives or medical staff in the antenatal clinics.

2. At one of the sites (the Mercy Hospital for Women), a letter of invitation including a brief explanation of the study together with their antenatal appointment letter was posted to all pregnant women newly registered with the antenatal clinic. At their first clinic visit, the researcher approached each eligible woman and sought interest in participation.
3. Advertising posters about the study were placed in the antenatal clinics of participating hospitals and on the websites of the National Asthma Council and the Asthma Foundation of Victoria. Participant explanatory statements and expression of interest forms were also made available. Potential participants had access to the information and were asked to leave their contact details to allow one of the researchers to contact them.

If the woman agreed to participate, written informed consent was sought.

Group allocation

Recruited participants were allocated to intervention or control groups on a 1:1 basis, stratified by their asthma severity. Asthma severity was assessed in accordance with the National Asthma Council Australia (NAC) Asthma Handbook classification based on their current asthma medications and symptoms [23]. Participants were classified into two groups: 1) Intermittent – mild asthma: using relievers only (e.g. salbutamol); 2) moderate – severe asthma: using any regular inhaled corticosteroids/ preventers/ symptom controllers or their combinations.

Allocation was concealed using the sealed opaque envelope technique. Random blocks of four and six were chosen and random numbers were generated using a random allocation software program [24] by an external researcher not involved in the study. The allocation sequence was known to this researcher only. At the time of recruitment, the investigator (EZ) opened the numbered envelope and allocated each participant to the control (usual care) group or the intervention (MASTERY) group. The outcome assessors were masked to the participant group allocation at follow-up assessments.

Control and intervention group

Intervention: MASTERY group

The trial evaluated an intervention involving a telehealth program supported by a Bluetooth-enabled handheld spirometer COPD-6® (model number 4000, Vitalograph

Ltd, Ennis, Ireland) and a WAAP. Women allocated to the intervention group were provided with a COPD-6® and a loaned smart mobile phone with the specifically designed *Breathe-easy*© application installed on it. Each participant measured their lung function (FEV_1 and FEV_6) daily using the COPD-6® device and recorded asthma symptoms and asthma medication usage in the *Breathe-easy*© application weekly. The daily lung function data were uploaded to a central server where the researchers, participants and their health professionals had secure access to the data. The participants' health professionals were contacted by one of the researchers, a trained asthma educator (EZ), if any medication changes or unscheduled asthma-related visits were needed.

A WAAP consistent with NAC guidelines was designed for each participant based on information obtained at baseline. The WAAP contained instructions on which medications to take when feeling well, how to recognise worsening asthma, what to do when symptoms are getting worse and what to do in the event of an acute attack, including a first aid plan. Each participant received an automated weekly message regarding their asthma status based on the *Breathe-easy*© algorithm that was designed based on NAC [23] and Global Initiative for Asthma (GINA) guidelines [25] (Additional file 1: Table S1). An automated weekly message of overall asthma control status was displayed as 'well-controlled' (score 0, green zone), or 'not well controlled' (score 5, yellow zone and score 6, orange zone) to encourage participants to follow their agreed asthma action plan and/or contact their health professional the next working day if there was no improvement. If the asthma control status was displayed as 'very poorly controlled' (score 7–15, red zone), patients were prompted to follow their agreed asthma action plan and contact their health professional on the same day. The flow of the study is described in Fig. 2 and the details of the intervention are illustrated in Fig. 3.

Control: usual care group

Women allocated to the control group received the usual medical care provided by the antenatal clinics and/or their health professionals. This included their regular weekly to monthly antenatal visits depending on their trimester and other complications. If during follow up, it was apparent that their asthma control deteriorated since prior assessment (for example; using their reliever three or more times a week, needing to increase their preventer dose), the participant was advised by the research team to contact their health professionals. The control group was also given a summarised version of the "Asthma and Pregnancy" brochure from the NAC which explained about asthma in pregnancy including first aid and emergency assistance number to use for any concerns regarding their asthma.

Outcome measures

The primary outcome measure was change in asthma control as measured by the Juniper Asthma Control Questionnaire (ACQ - 7) [26]. Secondary outcomes included changes in Juniper's mini Asthma Quality of Life Questionnaire (mAQLQ) score [27], lung function (FEV_1 and FEV_6), self-reported exacerbations (symptoms requiring bronchodilators), asthma-related health visits, days off work/study related to asthma, and oral corticosteroid use. Lung function testing (pre-bronchodilator) was performed by trained research assistants using EasyOne™ Worldspirometer (ndd Medizintechnik AG, Zurich, Switzerland). Maternal and neonatal outcomes data collected are the gestational age of the baby at delivery, development of any antenatal complications such as gestational diabetes, hypertensive disorders of pregnancy, fetal growth restriction, antepartum hemorrhage, and delivery details. Neonatal outcomes collected at delivery include birth weight centile, birth length, head circumference, and Appearance Pulse Grimace Activity and Respiratory (APGAR) scores at 1 and 5 min after delivery. Birth weight centiles were calculated using www.gestation.net/grow-au.aspx, which adjusted for maternal characteristics including height, weight, ethnicity, parity and fetal gender.

Data collection and follow-up

ACQ, mAQLQ scores, asthma-related health visits, asthma-related days off work/study, and oral corticosteroid use were collected at baseline, 3 months and 6 months from baseline to allow comparisons. Identical data collection forms were used for both groups. Maternal and neonatal outcomes data were collected shortly after delivery by reviewing medical records. The assessors responsible for collecting outcome data at three and six months were masked to the participant group allocation.

Sample size

A sample size of 28 per arm is sufficient to detect the minimum clinically important difference in ACQ score of 0.5 or more between treatment groups using a standard deviation of 0.66 [10, 28, 29]. We estimate, conservatively, that by 3 months, there will be an improvement of at least 0.5 in the ACQ score in the intervention arm and that the control arm could exhibit a very small improvement or no improvement at all in the ACQ score. If these improvements are sustained at 6 months, then with 28 evaluable subjects in each arm, and assuming an independence model for measurement variation, and an intraclass correlation of 0.5 (equivalent to a within patient variance of 0.218 when the total variance is $0.66^2 = 0.436$), the F-test, conducted at the 5 % significance level will have at least 80 % power to detect a treatment by time interaction effect. If these conjectured

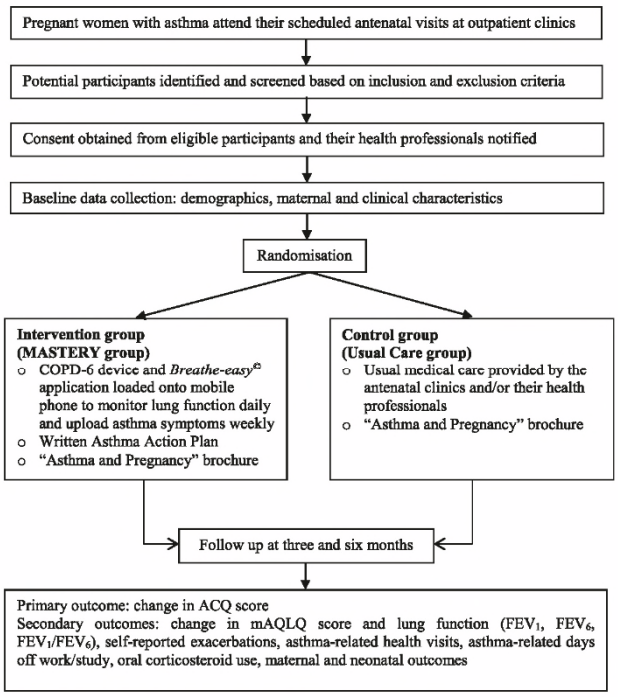

Fig 2 Flow chart of the study

Fig 3 The MASTERY© trial design

improvements by month 3 are not durable and the scores return, on average, to their baseline levels at 6 months, then both the F-test for the interaction and the two-sided *t*-test comparing the two arms at month 3 at the 5 % level of significance will continue to have at least 80 % power. To allow for approximately 25 % attrition, the target sample size has been inflated from 28 per arm to 36 participants per arm. The study is, however, not powered to detect differences in the secondary outcomes.

Data analysis

All analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 19.0 (IBM SPSS Statistics for Windows, Armonk, NY). The baseline characteristics of the two groups will be compared using Student's *t*-test for normally distributed continuous variables, Mann-Whitney 'U' test for non-normally distributed continuous variables and chi-square or Fisher's exact test as appropriate for categorical variables. The primary analysis will be performed according to the intention to treat (ITT) principle on the "full analysis set".

Primary inferential analyses will be conducted using a mixed effects model for the ITT population. This model will include treatment group and time as fixed effects with an interaction between treatment and time to ascertain if the groups behave differently over time. All observed data will be included in the analysis, with the mixed-effects models, fitted by residual maximum likelihood (REML) assuming non-informative dropout such that the probability of dropout may depend on a participant's previous response but not on current or future responses. In supportive analyses, changes in the primary outcome from baseline to 3 and 6 months will be compared between groups using linear regression modelling adjusting for baseline scores. Baseline demographic and clinical factors that appear to be different will be included as potential covariates in all regression models.

We will also compare the proportion of participants whose ACQ score improves more than 0.5 (MCID) over the study period, the proportion in whom asthma remained "not well controlled' (ACQ score 1.5 or greater) and those whose asthma was "well controlled" (ACQ score less than 1.5) at each time point [26]. Secondary outcomes will be summarised using descriptive statistics and analyses will be performed using the methods described above.

Ethical aspects

The study has been approved by the human research ethics committees of Monash University, Mercy Hospital for Women and The Royal Women's Hospital. All participants provide written informed consent at the time of enrolment. The study has been registered with the Australian New Zealand Clinical Trials Registry: ACTRN12613000800729.

Discussion

Innovative solutions are needed to support self-management and to improve asthma control during pregnancy. The MASTERY trial is designed to evaluate a telehealth program aimed at helping pregnant women with asthma to monitor their lung function and better manage their asthma during pregnancy. The Vitalograph COPD-6® is designed to enable the lung function data to be transmitted automatically via a Bluetooth connection to another enabled device (e.g. phone, computer). In our study, the Breathe-easy© application installed on a smart phone acquires the data and transmits via internet to a secure website, which can be accessed only by patients and other authorized personnel.

Automatic transmission can minimise the risk of errors when data are entered/reported manually. The *Breathe-easy©* application has been developed to record lung function data, asthma symptoms and medication usage and provides a user-friendly interface through a smart mobile phone. Recording symptoms as part of asthma management is known to reduce costs associated with unplanned hospitalisation and improved quality of life in asthma patients [13, 27, 28].

Daily recording of lung function and weekly assessment of asthma symptoms could allow women to recognize early worsening of their asthma control. Participants in the intervention group were provided with a WAAP as it was part of the algorithm of the telehealth intervention (MASTERY). The automated messages sent to each participant in the intervention group contained feedback regarding their asthma control/condition and asked them to refer to their individualised WAAP for further management. The individualised WAAP designed for each woman provided clear guidelines in terms of actions to be taken in case of worsening asthma. Although the WAAP alone may be effective in achieving asthma control, the telehealth (Breathe-easy©) app had additional features for monitoring and recording symptoms and lung function to give instant feedback to participants about their asthma status using an algorithm based on an individualized WAAP.

The proposed intervention has the potential to identify worsening asthma control early and prevent asthma exacerbations during pregnancy by regularly monitoring lung function and asthma symptoms. This may translated to reduce health care costs through fewer asthma-related unplanned medical and emergency department visits. If the intervention is efficacious, this could potentially influence clinical practice and health policy. The *Breathe-easy©* application could be made widely

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Table 1 The *Breathe-easy*© algorithm

Symptoms	Night-time awakening	Interference with normal activity	SABA for symptom control (not prevention of exercise-induced bronchoconstriction	FEV_1	Total Score	Asthma Control Zone	Levels of asthma Control
≤2days/week (0)	0/week (0)	None (0)	≤2 days/week (0)	>80% predicted/ personal best (0)	0	Green	Well-controlled
>2 days/week (1)	1-3x/week (1)	Some limitation (1)	>2 days/week (1)	70-80% predicted/ personal best (1)	5	Yellow	Not well-controlled
>2 days/week (1)	1-3x/week (1)	Some limitation (1)	>2 days/week (1)	60-69% predicted/ personal best (2)	6	Orange	
Throughout the day (3)	≥4x/week (3)	Extremely limited (3)	Several times per day (3)	<60% predicted/ personal best (3)	7 - 15	Red	Very poorly controlled

Categories		Message/Feedback
0	*Well-controlled*	Your asthma seems to be well-controlled. Continue your current asthma management including any medications you are currently using.
1-5	*Not well-controlled*	Your asthma seems to be getting worse, refer to your asthma action plan and make any changes in management as recommended.
6		Your asthma seems to be getting worse, refer to your asthma action plan and make any changes in management as recommended. If still no improvement, your asthma needs to be reviewed by a health professional.
7 - 15	*Very Poorly Controlled*	Follow the Asthma First Aid Plan and call an Ambulance if there is no improvement in your symptoms. Your asthma needs to be reviewed by a health professional.

1

5.3 DISCUSSION AND SUMMARY

The MASTERY© trial was informed by the MAMMA© trial by Lim *et al* [134] , which evaluated an educational intervention in similar number of participants at the same settings. The main change was the use of the *Breathe-easy*© application as part of the intervention. The pilot testing was done but restricted to the testing of the *Breathe-easy*© application. The pilot testing focused on ensuring that the *Breathe-easy*© application worked with the mobile phone (Android system), was easy to use by adults with asthma, and integrated well with the MASTERY portal. Individual patient randomisation was used as alternative methods of randomisation such as cluster randomisation were not suitable given the pilot nature of the study and the limited number of sites (n = 2).

The intervention group was required to record lung function daily and asthma symptoms weekly. Asthma symptoms were recorded in line with GINA/NAC guidelines. This included: the frequency of day and night symptoms, interference with normal activity, and the use of reliever medication in the previous week. Recording symptoms daily in addition to lung function may be too much for patients and would not be consistent with the guidelines.

General Practitioners (GPs), respiratory physicians, and obstetricians all had secure access to the telemonitoring system and were able to access data for their patients. Each health professional was provided with a user name and a password that allowed him/her to log in any time to monitor the asthma status of patients. However, many health professionals did not make use of this feature due to their busy schedule. Nevertheless, GPs were involved when any changes regarding patients' asthma action

plan were essential during the trial. The researcher, who is also a trained asthma educator, was in-charge of the telemonitoring system in the pilot/feasibility trial. If the proposed intervention is adopted more widely, I would anticipate an asthma educator, practice nurse or practice pharmacist to be in-charge of the telemonitoring system, especially if the GP is not available to undertake this role.

Standardised questionnaires like the Nathan's Asthma Control Test (ACT)) [184], the Juniper's ACQ [185], the Vollmer's Asthma Therapy Assessment Questionnaire (ATAQ) control index [186], and others have been developed and approved by GINA to facilitate and standardise the assessment or monitoring the impairment domain of asthma control [187]. Many instruments such as Juniper's mAQLQ [188], Marks and Katz's AQLQ[189] have also been developed and tested to assess the quality of life among people who have asthma in all age groups. ACQ and mAQLQ were also used in the study by Powell *et al* [190] (FeNO-based algorithm) and Ryan *et al* [180](the CYMPLA trial) as described in the systematic review in chapter 3 and MASTERY trial in **chapter 6**. Therefore, ACQ and mAQLQ scores were chosen as study outcomes in this trial.

Chapter 6
Management of Asthma with Supportive Telehealth of Respiratory Function in Pregnancy (MASTERY©) – Findings of a Randomised Controlled Trial

6.1 Introduction

An intervention for optimising asthma management during pregnancy was developed, incorporating a telehealth programme, regular self-monitoring of pulmonary function and asthma symptoms, and a Written Asthma Action Plan (WAAP). The efficacy of the intervention was evaluated in a RCT. The study protocol for the MASTERY© trial was described in the previous chapter **(Chapter 5).** This chapter presents the key findings from the MASTERY© trial.

There were no significant changes to the study protocol as published in chapter 5 during the course of the trial.

A manuscript has been revised and resubmitted to *Respirology* and is reproduced below.

Appendices relevant to this chapter are appendix 5, 9, 10, 12, 14 and 22.

6.2 Manuscript

6.2.1 Declaration (Part B) for Thesis Section 6.2.2

In the case of **Section 6.2.2**, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Reviewed literature, designed trial, developed *Breathe-easy*© application and algorithm, carried out participant recruitment and baseline data collection, entered and analysed data, and prepared first draft of the manuscript and revised it based on comments from the other authors.	60

The following co-authors contributed to the work.

Name	**Nature of contribution**
Dr Johnson George	Conceived idea, advised on study design, was in charge of product purchases and assisted with manuscript preparation
A/Prof Kay Stewart	Advised on study design and assisted with manuscript preparation
Prof Michael Abramson	Advised on study design and assisted with manuscript preparation
Prof Christine McDonald	Advised on study design and participant's written asthma action plan and assisted with manuscript preparation
Eldho Paul	Conducted statistical analysis on primary outcomes and assisted with manuscript preparation
Prof Susan Walker	Advised on study design and assisted with manuscript preparation
Dr Jonathan Li	Assisted with *Breathe-easy*© development, and provided technical support during the trial
Thanuja Dharmasiri	Assisted with *Breathe-easy*© development and provided technical support during the trial

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

		Date
Candidate's Signature		**23 July 2015**
Main Supervisor's Signature		**23 July 2015**

6.2.2 Revised and resubmitted manuscript: Telehealth to Improve Asthma Control in Pregnancy: a Randomised Controlled Trial

Revised and resubmitted to *Respirology.*

Telehealth to improve asthma control in pregnancy: a randomised controlled trial

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Abstract

Background and objective: Poorly controlled asthma during pregnancy is hazardous for both mother and fetus. Better asthma control may be achieved if patients are involved in regular self-monitoring of symptoms and self-management according to a written asthma action plan (WAAP). Telehealth applications to optimise asthma management and outcomes in pregnant women have not yet been evaluated. This study evaluated the efficacy of a telehealth program supported by a handheld respiratory device in improving asthma control during pregnancy.

Methods: Pregnant women with asthma (n=72) from two antenatal clinics in Melbourne, Australia were randomised to one of two groups: 1) intervention – involving a telehealth program (Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy [MASTERY©]) supported by a handheld respiratory device and an Android smart phone application (*Breathe-easy*©) and WAAP; or 2) control – usual care. The primary outcome was change in asthma control at 3 and 6 months (prenatal). Secondary outcomes included changes in quality of life, lung function, and perinatal/neonatal outcomes.

Results: At baseline, participants' mean (±SD) age was 31.4±4.5 years and gestational age 16.7±3.1 weeks. At six months, the MASTERY group had better asthma control (p=0.02) and asthma-related quality of life (p<0.01) compared to usual care. There were no significant differences between groups in lung function, unscheduled healthcare visits, days off work/study, oral corticosteroid use or perinatal outcomes. Differences between groups were not significant at three months.

Conclusions: Telehealth interventions supporting self-management are feasible and efficacious to improve asthma control and asthma-related quality of life during pregnancy.

Keywords: asthma control, pregnant women, quality of life, telehealth

Trial registration:

Australian New Zealand Clinical Trials Registry (ACTRN 12613000800729) 17 July 2013.URL: www.anzctr.org.au.

INTRODUCTION

Asthma is the most common lung condition that affects and complicates pregnancy.[1, 2] Managing asthma in pregnant women is an integral part of asthma guidelines,[3-5] however, poorly controlled asthma during pregnancy still remains a major problem. Poorly controlled asthma increases the risks of pre-eclampsia, fetal growth restriction, pre-term birth and need for caesarean delivery.[6-9]

Better asthma control can be achieved if patients are involved in self-management, visit medical practitioners regularly and possess (and follow) a written asthma action plan (WAAP).[10] Recording daily symptoms continually as a part of asthma self-management reduces unplanned hospitalizations and improves quality of life in asthma patients.[11-14]

Early detection of exacerbations and better management of asthma exacerbations can be achieved by home telemonitoring.[11-14] Internet or mobile phone-based healthcare interventions have been reported to have potential benefits in adults[11, 14] and children[13] with asthma when compared with usual care. Mobile phone-based interventions to support asthma management have been evaluated in several studies.[14-16] However, telehealth applications to optimise asthma management and outcomes in pregnant women have not yet been evaluated.

The aim of this study was to evaluate the efficacy of a telehealth program, supported by a handheld respiratory device, in improving asthma control during pregnancy. We hypothesised that the intervention group (Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy [MASTERY©]) would have better asthma control compared to the control group (usual care).

METHODS

Study design and participants

A prospective multi-centre single-blinded randomised controlled trial (RCT) was conducted in the antenatal clinics of two large maternity hospitals in Melbourne, Australia. The study was registered (ACTRN 12613000800729) and was approved by the human research ethics committees of Monash University, Mercy Hospital for Women and the Royal Women's Hospital. All participants provided written informed consent at the time of enrolment.

Pregnant women with asthma aged ≥18 years, up to 20 weeks gestation and able to communicate in English were approached. Those who self-reported use of any inhaled bronchodilator or anti-inflammatory agent for asthma within the previous 12 months were included. Women under specialist care for brittle/difficult asthma[17] or who were not in possession of or have not used a "smart" mobile phone were excluded. All women in the intervention group were loaned an Android phone with *Breathe-easy*© application installed.

Randomisation and group allocation

The detailed protocol has been published elsewhere.[18] In brief, all consenting participants were stratified by asthma severity based on their current asthma medications and symptoms into two groups: intermittent-mild or moderate-severe asthma.[3] Participants were randomised to intervention (MASTERY) or control (usual care) with 1:1 allocation in

random blocks of four and six using a random allocation software[19] by an independent researcher. Randomisation results were concealed using the sealed opaque envelope technique. Participation of the women in the study is summarised in Figure 1.

Intervention and control group

Intervention: MASTERY group

The flow of the study is described in Figure 2. Participants allocated to MASTERY were provided with a COPD-6® (Vitalograph Ltd, Ennis, Ireland) to measure their lung function (FEV_1 and FEV_6) daily and a specifically designed *Breathe-easy*© application installed on a loaned "smart" mobile phone to record asthma symptoms and asthma medication usage weekly. Participants were also prompted to follow an individualised WAAP specifically developed by the study team as part of the intervention package. Each participant received an automated weekly feedback message on the phone regarding her asthma status based on the *Breathe-easy*© algorithm that was based on National Asthma Council[3] and Global Initiative for Asthma (GINA) guidelines.[5] An automated weekly message of overall asthma control status was displayed as 'well-controlled', or 'not well controlled' to encourage participants to follow their agreed WAAP and/or contact their health professionals the next working day if there was no improvement. If the asthma control status was displayed as 'very poorly controlled', patients were prompted to follow their agreed WAAP and to contact their health professional on the same day. All data were transmitted automatically to a central server to which the researchers, participants and their health professionals had secure access. Participants' health professionals were contacted by one of the researchers, a trained asthma educator (EZ), if any medication changes or unscheduled asthma-related visits were needed.

Control: Usual care group

Control group received usual medical care from the antenatal clinics and/or their health professionals including regular weekly to monthly antenatal visits depending on pregnancy stage and presence of any complications. A summary of the "Asthma and Pregnancy" brochure from the NAC, which explained asthma in pregnancy, including first aid and an emergency assistance number to call for any concerns regarding asthma was given to participants in both groups.

Outcome measures

The primary outcome measure was change in asthma control as measured by the 7-item Asthma Control Questionnaire (ACQ-7) at 3 and 6 months.[20] Secondary asthma-related outcomes were changes in Juniper's mini Asthma Quality of Life Questionnaire (mAQLQ) score,[21] lung function (FEV_1 and FEV_6), self-reported exacerbations, asthma-related health visits, days off work/study related to asthma and oral corticosteroid use. All these measures were conducted prenatally.

Perinatal outcomes were development of any antenatal complications such as gestational diabetes, hypertensive disorders of pregnancy, postpartum haemorrhage, and foetal growth restriction, mode of delivery and gestational age of baby at delivery.

Neonatal outcomes included birth weight centile, birth length, head circumference, and Appearance Pulse Grimace Activity and Respiratory

(APGAR) scores at 1 and 5 minutes after delivery. Birth weight centiles were calculated using www.gestation.net/grow-au.aspx, which adjusted for maternal characteristics including height, weight, ethnicity, parity and foetal gender.

Data collection and follow-up

ACQ and mAQLQ scores, asthma-related health visits, asthma-related days off work/study, oral corticosteroid use were assessed at three and six months from baseline to allow comparisons. Perinatal outcomes data were collected shortly after delivery by reviewing medical records. The outcome assessors doing follow-ups at three and six months were masked to participant group allocation.

Sample size

Using a standard deviation in ACQ score of 0.66,[22, 23] we estimated that a sample size of 28 in each arm would have 80% power with a two-sided 5% significance level to detect the minimal clinically important difference (MCID) in ACQ score of 0.5 or more between groups.[20] To allow for 25% attrition, 36 participants were required in each arm.

Data analysis

The primary analysis was performed according to the intention to treat (ITT) principle. Baseline characteristics were compared using Student's t-test or Mann-Whitney U test as appropriate for continuous variables and chi-square or Fisher's exact test as appropriate for categorical variables. For the primary analysis, linear regression models were fitted to compare changes in ACQ scores between groups at three and six months adjusting for baseline scores. We also compared the proportion of participants whose ACQ score improved more than 0.5 (MCID) over the study period, and the proportions in whom asthma remained "not well controlled" (ACQ score 1.5 or greater) or "well controlled" (ACQ score less than 1.5) at each time point.[24] Secondary outcomes were summarised using descriptive statistics and analyses performed as described above. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 19.0 (IBM SPSS Statistics for Windows, Armonk, NY).

RESULTS

Seventy two pregnant women with asthma, mean (±SD) age 31.4±4.5 years, were enrolled in the study. The groups had similar characteristics at baseline (Table 1). The mean (±SD) gestational age (in weeks) at baseline, 3 months and 6 months was 16.7±3.1, 27.4±1.3 and 36.5±0.6. No significant difference in gestational age was observed between the groups. The majority had moderate to severe asthma (58%). Inhaled corticosteroid/long-acting beta agonist (ICS/LABA) combinations were the regular asthma medication for almost half of them. The mean ACQ scores and mAQLQ scores for MASTERY and usual care groups matched well. FEV_1, FEV_1% predicted and FEV_1/FEV_6 were lower in the MASTERY group than the usual care group, but these differences were not significant.

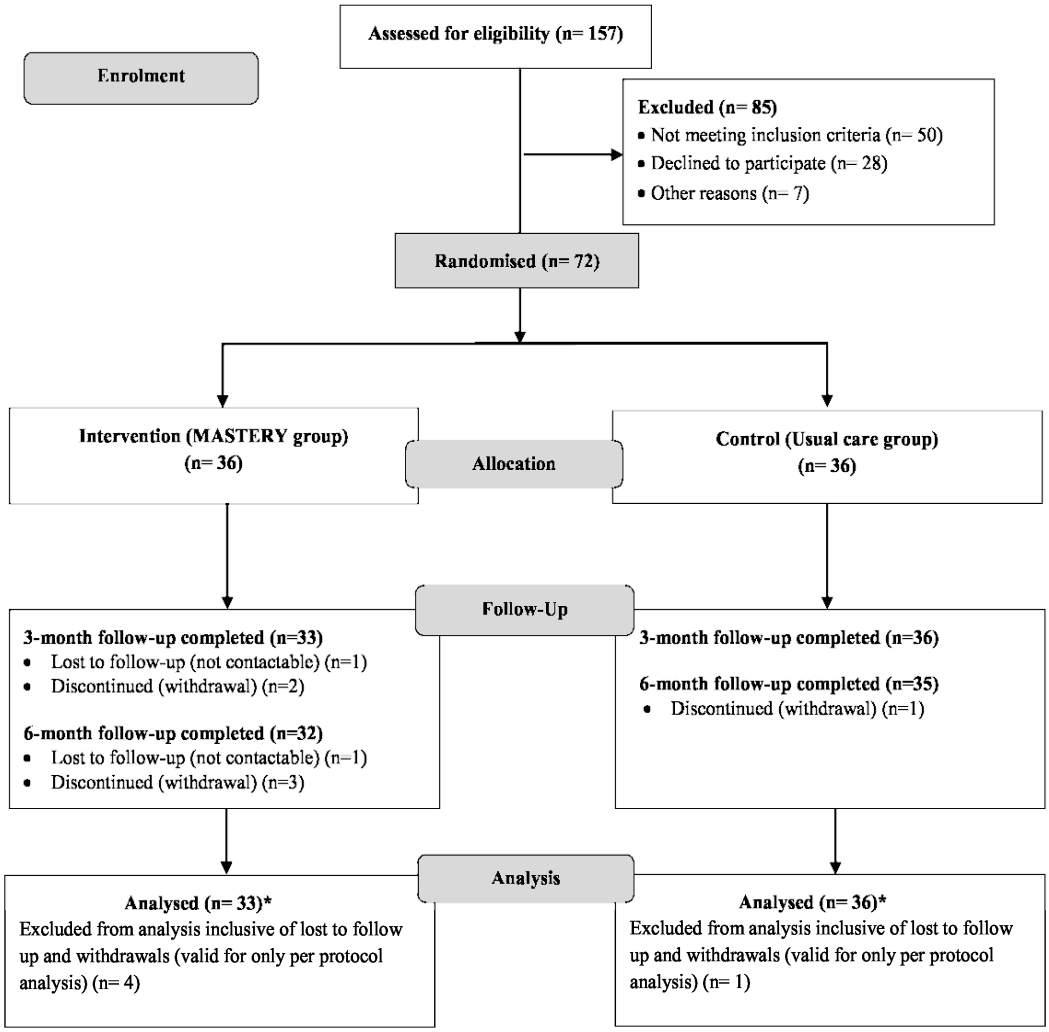
Changes in ACQ score from baseline to 3 months (mean ±SE) for MASTERY and usual care groups were 0.01±0.11 and -0.16±0.09, respectively. At six months, the changes in ACQ score in the two

groups from baseline were 0.30±0.11 and -0.06±0.10, respectively; and the mean difference between groups was significant (p=0.02) (Table 2). Participants in the MASTERY group also had clinically significant improvements (MCID > 0.5) in their quality of life at six months than the usual care group (p=0.002) (Table 2). Changes in FEV_1, FEV_1% and FEV_1/FEV_6 from baseline to both three and six months between the groups were not significant (Table 2).

Figures 3(A) and 3 (B) show changes in ACQ and mAQLQ scores, respectively, in the two groups between baseline and both three and six months. At six months, the MASTERY group had a higher proportion of participants with well-controlled asthma (ACQ <1.5) than the control group (82% vs 58%, p=0.03). Compared to the control group, MASTERY group also had more participants with a clinically significant (i.e. change in scores greater than the MCID) improvement in ACQ (39% vs 19%, p=0.07) and mAQLQ scores (36% vs 19%, p=0.12), but the differences were not statistically significant.

At 6 months, the MASTERY group self-reported fewer asthma symptoms requiring a reliever in the previous three months (MASTERY [n=1] vs control [n=18], p<0.001). Only one control participant had any unscheduled health visit related to asthma. One participant from the MASTERY and two from the control group were prescribed an oral corticosteroid. One participant in each group reported days off work/study related to asthma.

The perinatal outcomes including neonatal outcomes, delivery data and complications at the end of the study were similar in both groups (Table 3). Small differences between the groups in normal vaginal delivery (MASTERY=58%, usual care=47%; p=0.39) and emergency caesarean (MASTERY=12%, usual care=17%; p=0.74) did not reach statistical significance. No significant differences in neonatal outcomes or pregnancy complications were observed between the groups either.



**ITT analysis: participants who had at least one follow-up were included in the primary analysis*

Figure 1. CONSORT diagram of participant flow

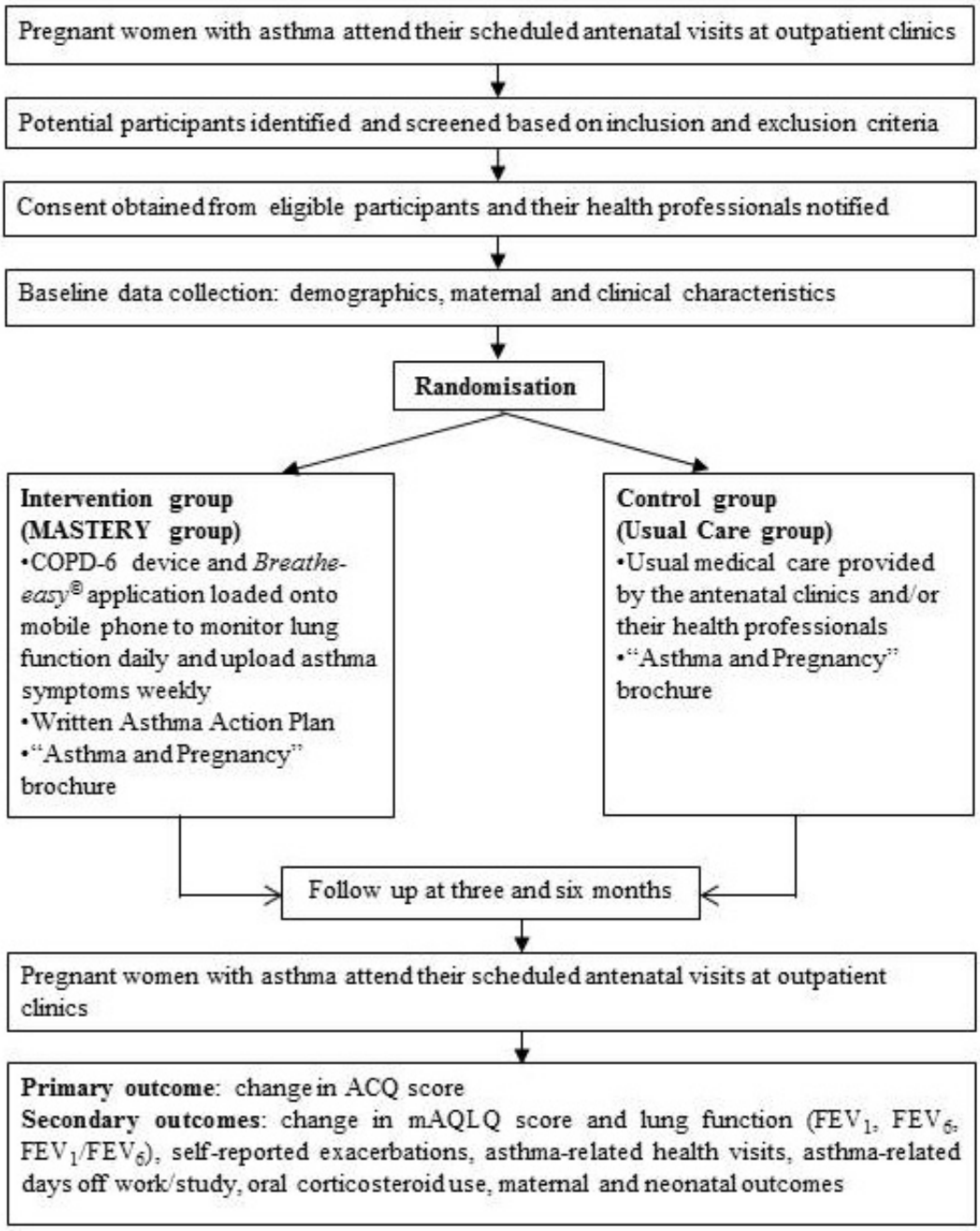


Figure 2. Flow chart of the study

Table 1. Demographic, maternal and clinical characteristics of the study population at baseline

	MASTERY group (n=36)	Usual care group (n=36)
Demographic characteristics		
Race		
Caucasian	30 (84)	30 (84)
Asian	3 (8)	3 (8)
Other	3 (8)	3 (8)
Australian/New Zealander	30 (83)	30 (83)
Married	27 (75)	29 (81)
Full time employment	17 (47)	18 (50)
Health care/concession card holder	5 (14)	4 [7]
Possessed current asthma action plan	2 (5)	1 (3)
Level of education		
High school graduate	5 (14)	4 [7]
University graduate	6 (16)	11 (31)
Postgraduate or advanced degree	15 (42)	13 (36)
Other	10 (28)	8 (22)
Smoking status		
Never	25 (69)	23 (64)
Quit pre-pregnancy	8 (22)	11 (30)
Quit during pregnancy	1 (3)	1 (3)
Currently smoking	2 (5)	1 (3)
Maternal characteristics		
Age (years)[1]	31.1± 4.7	31.8 ± 4.3
Height [1]	164.0 ± 5.4	161.7 ± 7.1
Weight (kg)[1]	78.9 ± 21.6	70.8 ± 11.1
BMI (kg/m^2)[1]	29.3 ± 7.4	27.6 ± 3.9
Gestational age (weeks)[1]	16.5 ± 2.9	16.2 ± 2.9
Primigravid	16 (44)	15 (42)
Other medical conditions		
Anxiety/depression	10 (28)	10 (28)
Thyroid disorder	4 [7]	2 (6)
Clinical characteristics		
Duration of asthma [years][2]	26.5 [20.50 – 30]	25.5 [20 – 30]
Asthma severity		
Intermittent to Mild	15 (42)	15 (42)
Moderate to Severe	21 (58)	21 (58)
Asthma medications		
SABA only	15 (42)	15 (42)
ICS + SABA	3 (8)	2 (6)
ICS/LABA + SABA	18 (50)	19 (52)
FEV_1 in litres[3]	2.7 ± 0.1	2.9 ± 0.1
FEV_1% predicted [3]	89.1 ± 2.3	91.6 ± 0.1
FEV_1/FEV_6 (%)[3]	80.1 ± 1.1	81.5 ± 1.0
ACQ score[3]	1.1 ± 0.1	1.2 ± 0.1
mAQLQ score[3]	5.5 ± 0.2	5.5 ± 0.2

ACQ, Asthma Control Questionnaire; BMI, Body Mass Index; mAQLQ, mini Asthma Quality of Life Questionnaire;FEV_1, Forced expiratory volume in 1 second; FEV_1%, FEV_1 expressed as a percentage of the predicted value; FEV_6, Forced expiratory volume in 6 seconds; ICS, inhaled corticosteroid; LABA, long-acting beta agonist, SABA, short-acting beta agonist. Values are presented as numbers (percentages) unless specified. [1]mean ± SD, [2] median [interquartile range], [3]mean ± SE.

Table 2. Mean (±SE) change of ACQ, mAQLQ score and lung function from baseline at 3 and 6 months and the difference in mean change between groups adjusted for baseline

	Change within group		Difference between groups adjusted for baseline		
Change in outcome	***MASTERY group (n=33)***	**Usual care group (n=36)**	**Mean difference**	**95% CI**	***p* value**
ACQ					
3 months	0.01± 0.11	-0.16 ± 0.09	-0.17 ± 0.14	-0.45 to 0.12	0.26
6 months	0.30 ± 0.11	-0.06 ± 0.10	-0.36 ± 0.15	-0.66 to -0.07	**0.02**
mAQLQ					
3 months	-0.09 ± 0.14	0.17 ± 0.13	0.27 ± 0.19	-0.09 to 0.64	0.15
6 months	-0.51 ± 0.16	0.22 ± 0.15	0.72 ± 0.22	0.29 to 1.16	**0.002**
FEV_1					
3 months	0.12 ± 0.05	0.08 ± 0.05	-0.03 ± 0.06	-0.16 to 0.09	0.63
6 months	0.11 ± 0.06	0.07 ± 0.05	-0.04 ± 0.08	-0.19 to 0.11	0.57
FEV_1%					
3 months	6.04 ± 1.69	1.75 ± 1.57	-4.29 ± 2.32	-8.84 to 0.25	0.07
6 months	4.27 ± 1.86	1.54 ± 1.72	-2.72 ± 2.54	-7.71 to 2.27	0.29
FEV_1/FEV_6					
3 months	3.43 ± 1.17	0.14 ± 1.09	-3.29 ± 1.61	-6.44 to 0.14	0.05
6 months	1.53 ± 1.07	-0.56 ± 0.98	-2.08 ± 1.46	-4.94 to 0.78	0.16

ACQ, Asthma Control Questionnaire; mAQLQ, mini Asthma Quality of Life Questionnaire;FEV_1, Forced expiratory volume in 1 second; FEV_1%, FEV_1 expressed as a percentage of the predicted value; FEV_6, Forced expiratory volume in 6 seconds. Values are presented as mean ± SE. Positive mean change of ACQ score suggests that asthma control improved from baseline and vice-versa. Negative mean change of mAQLQ score suggests that QoL improved from baseline and vice-versa.

Figures 3(A) and 3 (B) show changes in ACQ and mAQLQ scores, respectively, in the two groups between baseline and both three and six months. At six months, the MASTERY group had a higher proportion of participants with well-controlled asthma (ACQ <1.5) than the control group (82% vs 58%, p=0.03). Compared to the control group, MASTERY group also had more participants with a clinically significant (i.e. change in scores greater than the MCID) improvement in ACQ (39% vs 19%, p=0.07) and mAQLQ scores (36% vs 19%, p=0.12), but the differences were not statistically significant.

At 6 months, the MASTERY group self-reported fewer asthma symptoms requiring a reliever in the previous three months (MASTERY [n=1] vs control [n=18], p<0.001). Only one control participant had any unscheduled health visit related to asthma. One participant from the MASTERY and two from the control

group were prescribed an oral corticosteroid. One participant in each group reported days off work/study related to asthma.

The perinatal outcomes including neonatal outcomes, delivery data and complications at the end of the study were similar in both groups (Table 3). Small differences between the groups in normal vaginal delivery (MASTERY=58%, usual care=47%; p=0.39) and emergency caesarean (MASTERY=12%, usual care=17%; p=0.74) did not reach statistical significance. No significant differences in neonatal outcomes or pregnancy complications were observed between the groups either.

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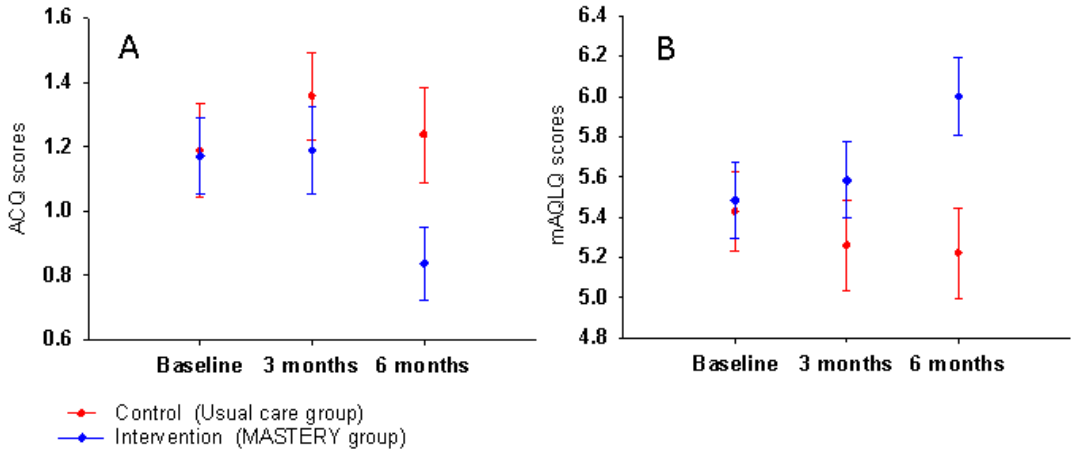

Figure 3. (A) Changes in ACQ scores (B) Changes in mAQLQ scores. Data are expressed as mean ± SE

Table 3. Perinatal outcome data and the comparison between the groups

	MASTERY group (n=33)	Usual care group (n=36)
Outcome		
Neonatal Data		
Male	16 (49)	21 (58)
Birth weight (g)[1]	3434 ± 555	3447 ± 547
Length [1]	49.9 ± 2.7	50.3 ± 2.3
Head circumference [1]	34.3 ± 1.7	34.8 ± 2.8
APGAR score[2]		
At 1 minute	9 [8-9]	9 [7.25 – 9]
At 5 minutes	9 [9-9]	9 [9-9]
Gestational age (weeks)[1]	39.1 ± 1.4	39.3 ± 1.2
Admission to NICU or SCN	1 (3)	2 (6)
Premature (< 37 weeks)	1 (3)	2 (6)
Low birth weight (<10th centile for gestational age)	4 (12)	7 (19)
Delivery Data		
Mode of Delivery		
Vaginal delivery	19 (58)	17 (47)
Assisted delivery	4 (12)	7 (19)
Elective caesarean	6 (18)	6 (17)
Emergency caesarean	4 (12)	6 (17)
Complications		
Gestational diabetes	3 (9)	6 (17)
Hypertensive disorders of pregnancy	2 (6)	2 (6)
Postpartum haemorrhage	1 (3)	2 (6)
Macrosomia	2 (6)	5 (14)
IUGR	1 (3)	0 (0)

APGAR, Activity Pulse Grimace Appearance, Respiration; NICU, Neonatal Intensive Care Unit; SCN, Special Care Nursery; IUGR, Intra Uterine Growth Restrictions.
Values are presented as numbers (percentages) unless specified. [1]mean ± SD, [2] median [interquartile range]

DISCUSSION

A telehealth intervention supported by a mobile application, self-monitoring device and use of an individualized WAAP improved self-management of asthma in pregnancy. Change in asthma control was statistically significant in the MASTERY (telehealth) group at 6 months, but the mean change in ACQ score failed to reach the MCID. At 6 months, better asthma-related quality of life, and fewer self-reported exacerbations were observed in the MASTERY group. However, changes in lung function between groups were not significant. This study also

established the role of WAAP guided self-management in optimising asthma control in pregnancy. Assessing asthma symptoms, monitoring lung function regularly and establishing individual WAAP are components of asthma self-management according to GINA and NAC.[3, 25] Since pregnancy may alter the severity of asthma unpredictably,[26] pregnant women with asthma should be encouraged to have self-management plans with close monitoring of asthma symptoms/control to prevent any exacerbations during pregnancy.

A Cochrane Review of self-management education and regular practitioner review has found that monitoring asthma severity and the use of WAAP could reduce the frequency of asthma exacerbations, optimise asthma medication use and decrease the cost of asthma management.[10] Monitoring asthma regularly using objective measures of lung function (FEV_1) and asthma symptoms could improve asthma control and reduce exacerbations during pregnancy.[27] Lim *et al*[22] showed that multidisciplinary care involving education and regular monitoring in pregnant women with asthma could improve maternal asthma outcomes. Our study adds further knowledge and highlights the potential role of telemonitoring of asthma in pregnancy. The automated feedback based on the individualized WAAP offered early identification of worsening asthma control and prompted appropriate intervention, potentially preventing further deterioration of asthma control. However, compared to the control group, the intervention group may have received the beneficial effects from the personalised WAAP that was also provided as part of the intervention.

The effect of combined mobile phone and web application/software on asthma control in adults was examined by Liu *et al*[14] and Ryan *et al*.[15] The intervention groups had interactive software applications installed on participants' mobile-phones which allowed recording of lung function (FEV_1) daily and asthma symptoms. Control groups were provided with a written asthma diary and WAAP. Liu et al[14] found that at six months, the intervention group had better lung function and quality of life, fewer exacerbations and unplanned visits than the control group. However Ryan *et al*[15] did not find any significant difference in outcomes of the intervention compared to the control group. Our trial included a much younger pregnant cohort, and excluded those who were not in possession of or have not used a "smart" mobile phone. Differences in participant characteristics (pregnant women vs ≥12 years) and the study settings (maternity hospitals vs primary care clinics), might explain the differences in outcomes between our study and Ryan *et al*[17]. Additionally, our usual care was less intensive than that of Liu *et al*[14] and Ryan *et al*[15] and it is possible that the observed benefits in our study resulted from the enhanced clinical care rather than the technological intervention.

Asthma self-management supported by personalised WAAP reduces severe exacerbations, unscheduled health visits and hospitalisations.[28] Studies to date have not provided a strong evidence base to guide clinicians or policy makers on the use of mobile phone apps for delivering asthma self-management programs.[29] The *Breathe-easy*© application encourages patients to manage asthma by monitoring their symptoms and lung function regularly

and provides them with instant feedback regarding their asthma control. As part of the Breathe-easy© algorithm, we also provided individualised WAAP for the MASTERY group. WAAP has been widely recommended as a component of asthma self-management rather than stand-alone intervention.[10, 30] This study showed the importance of having an individualised WAAP as part of a self-management program for every person with asthma; however a close collaboration between patients and their health care professionals and feedback are required for full benefits.[31, 32]

Our study had some strengths and limitations. This was the first study to investigate the role of telehealth for supporting asthma management in pregnant women. It was carried out in the antenatal clinics of two large maternity hospitals and included participants from a range of socio-demographic backgrounds and asthma severity. It was not possible to mask the intervention, which may have caused potential respondent bias, however we minimised bias by using objective assessments including spirometry (FEV_1 and FEV_6) and standardised questionnaires for the 3 and 6 months follow-ups. Exacerbations were self-reported by participants and no information on the amount of relievers used was collected. However, outcome assessments were performed by trained research assistants masked to group allocation.

The intervention was not suitable for patients with visual/hearing impairment and those unable to operate a smart mobile phone. It was unknown to what extent general practitioners were involved in monitoring their patients' asthma. We had no data regarding patient compliance to the advice provided (e.g. follow their WAAP or to see their doctor). Patient compliance to the recommendations as part of the telehealth intervention should be assessed in a future study. The place of mobile technology in clinical care might depend on whether it is cost effective for enhancing "usual care" to the standards recommended by guidelines. The study was not powered to assess the cost-effectiveness of the MASTERY intervention compared to usual care in the study clinics. Further studies are needed to evaluate the cost-effectiveness of telehealth interventions.

In summary, a telehealth intervention was shown to be feasible for monitoring asthma in pregnant women. The effects of Breathe-easy© application on asthma control, asthma-related quality of life and exacerbations should be evaluated in larger studies, other populations with asthma, and those with other chronic respiratory conditions such as COPD.

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Author contribution

JG conceived the project idea with input from MA, KS, CMcD and

SW. EZ further developed the trial with input from all the other authors (JG, MA, KS, CMcD and SW). JL and TD assisted EZ in developing the *Breathe-easy*© application with input from JG, MA, CMc and KS. EZ managed the trial overall, recruited participants, collected baseline data and managed the research assistants involved in data collection. EP assisted EZ in statistical analysis. EZ wrote the first draft of this manuscript. All the other authors have provided input and approved the final version. JG is the guarantor of the study.

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Chapter 7
Summary of the Research Findings and Conclusions

7.1 Introduction

Previous chapters (**Chapters 3 – 6**) have presented in detail the work undertaken for each research phase (systematic review, prospective cohort study and RCT). This chapter will discuss the overall findings in relation to the thesis objectives.

Section 7.2 summarises the key findings of the studies conducted, including a discussion of their implications. **Section 7.3** describes what this research adds to current knowledge. **Section 7.4** acknowledges the strengths and limitations of the studies. **Section 7.5** highlights some recommendations, with future research directions outlined in **Section 7.6**. **Section 7.7** presents the conclusions of this thesis.

7.2 Overall summary of the research findings

Objective 1: To evaluate non-pharmacological healthcare interventions for asthma management in pregnant women.

This systematic review (**Chapter 3**) confirmed there is currently limited evidence of non-pharmacological interventions for improving asthma control in pregnant women. Due to the heterogeneity of study designs, settings, types of intervention, follow up and outcome measures, it was difficult to draw firm conclusions. The systematic review included studies of pregnant women with asthma involving an education programme, PMR and asthma management guided by the fractional of exhaled nitric

oxide (FeNO).

Interventions that involved asthma education and management skills reduced nonadherence to ICS during pregnancy. Improvement of lung function was found in the trial using PMR, although more data are needed to confirm the effects of the intervention when applied at different stages of gestation. A significant reduction in asthma exacerbations and unscheduled visits was found in the trial of asthma management guided by FeNO-based algorithms. This was demonstrated by the lower daily dose of ICS in the intervention group compared to the control group. A higher median birth weight, as well as a reduction in pre-term deliveries and neonatal hospitalisations, was found in the intervention group of this trial.

The results of this systematic review highlighted the effectiveness of non-pharmacological interventions conducted for optimising asthma management in pregnant women. The interventions that included asthma education, self-management and self-monitoring using objective measures of lung function, were effective for improving maternal outcomes. These included reducing asthma exacerbations and unscheduled visits. They were also effective for positive neonatal outcomes, including the reduction of pre-term births and neonatal hospitalisations.

Objective 2: To investigate the role of objective measures of lung function for monitoring asthma during pregnancy.

The prospective cohort study (**Chapter 4**) highlighted the changes in lung function (FEV_1, FEV_6 and FVC) during pregnancy. Observing and comparing the changes in lung function throughout pregnancy, in women with and without asthma, suggested

that lung function declined over weeks 21 to 28 of gestation. The decline was more pronounced in women with asthma than in healthy women. From week 29 until delivery, compared to baseline (weeks 11 – 20), there was an improvement in lung function in both groups.

In women with asthma, the decline of lung function from weeks 21 to 28 was also marked by a reduction in asthma control (i.e. an increased ACQ score) and quality of life (i.e. a decline in the mAQLQ score). Then from weeks 29 to 40, the opposite changes were evident, suggesting improvement in lung function, better asthma control and quality of life.

Additionally, a greater decline in FEV_6 was found in the women with asthma at weeks 21 to 28. The drop in FEV_6 was also accompanied by a reduction in FVC. Strong and positive correlations were present between changes in FEV_6 and FVC, from baseline to weeks 21 to 28 ($r = 0.88$, $p < 0.01$), and from weeks 21 to 28 and weeks 29 to 40 ($r = 0.85$, $p < 0.01$).

In terms of perinatal outcomes, significant differences existed between the groups; pregnant women with asthma delivered slightly shorter babies ($p = 0.02$) with lower Appearance Pulse Grimace Activity Respiration (APGAR) scores at one minute ($p = 0.01$) compared to those without asthma. The results of this prospective cohort study highlighted that lung function changes in pregnant women with asthma were accompanied by changes in asthma control and asthma-related QoL. FEV_6 could be substituted for FVC to monitor lung function in pregnant women with asthma. Regular review of lung function offers a suitable objective method to assist healthcare professionals and patients in monitoring asthma during pregnancy.

Objective 3: To develop, implement and evaluate a telehealth programme for asthma management in pregnant women.

An RCT (**Chapter 6**) evaluated the application of a telehealth programme (*Breathe-easy*© application) and a WAAP. It compared these to usual care for managing asthma during pregnancy. The study determined this intervention was efficacious and feasible for optimising asthma management during pregnancy, by improving asthma control and asthma-related quality of life.

At the end of the study, the intervention (MASTERY) group had better improvement of asthma control ($p = 0.02$) and quality of life scores ($p = 0.002$) than the control group (usual care). Higher proportions of participants with well-controlled asthma and those with a clinical improvement in their ACQ score (> 0.5 minimum clinically important difference [MCID]) were found in the MASTERY group. Fewer self-reported exacerbations ($p < 0.01$), unscheduled healthcare visits and instances of oral corticosteroid use were found in the MASTERY group compared to the usual care group. However no significant differences existed between the groups in lung function (FEV_1, FEV_6 and FEV_1/FEV_6) changes or perinatal outcomes.

The results of this study highlighted that a telehealth intervention involving a mobile application (*Breathe-easy*©), supported by a handheld respiratory device for monitoring FEV_6 and WAAP, was feasible for monitoring asthma during pregnancy. This approach resulted in improved asthma control and quality of life and also reduced the frequency of exacerbations.

7.3 The significance of this research

A limited and incomplete body of evidence and intervention studies for optimising asthma management in pregnancy was available when this PhD project was commenced. The findings from this thesis have added to the current knowledge and evidence within published literature for supporting better asthma management in pregnant women. The systematic review evaluating the non-pharmacological healthcare interventions for optimising asthma management during pregnancy confirmed that a reduction of asthma exacerbations and unscheduled healthcare visits could be achieved if pregnant women were monitored regularly (at least monthly), based on their lung function, FeNO concentration and asthma symptoms throughout pregnancy.

Moreover, education about self-management skills – including knowledge about medication (e.g. how preventers or relievers worked, how to use inhalers correctly), how to self-monitor asthma (e.g. assessing asthma control and/or lung function) and possessing a WAAP – should be integrated when designing health interventions to improve asthma management in pregnant women. No previous review has assessed the effectiveness of non-pharmacological interventions in asthma during pregnancy.

The findings are supported by a subsequent Cochrane review, 'Interventions for managing asthma in pregnancy' [140]. This review found that, due to the limited evidence and a lack of effectively designed studies, future sufficiently powerful and properly designed intervention studies (pharmacological and non-pharmacological, including self-management interventions) were essential to detect improvements in maternal and neonatal outcomes.

The prospective cohort study findings supported the evidence that asthma changes unpredictably during pregnancy. The changes in lung function during pregnancy were accompanied by changes in asthma control and quality of life, with either a deterioration or improvement in asthma. This study has added to the knowledge that FEV_6 is well correlated with FVC, suggesting that it can be used for monitoring asthma during pregnancy. As any pregnant woman can experience shortness of breath during pregnancy, this marker appears to be suitable and is likely to be better tolerated than measurement of FVC.

The RCT was built on the evidence from a previous study by my supervisor's research group that showed that education and regular monitoring by a pharmacist-led multi-disciplinary team improved asthma control during pregnancy [134]. It has added to current knowledge by showing that daily monitoring of lung function and weekly monitoring of asthma symptoms improves asthma control during pregnancy. As asthma symptoms may manifest and change unpredictably throughout pregnancy, the use of both objective and subjective measurement is better for monitoring asthma in pregnant women rather than monitoring symptoms alone. The additional support of an individualised WAAP confirmed the importance of every person with asthma having a current WAAP. The use of WAAPs has been widely recommended by GINA and NAC guidelines [52, 191] as a component of asthma self-management rather than a stand-alone intervention [91, 92]. However a close collaboration between patients and their healthcare professionals and feedback are required for full benefits [192, 193].

Although all asthma guidelines recommend using a WAAP, in reality few people with asthma have one and even fewer follow their WAAP to make changes in therapy

according to change in symptoms or lung function. A WAAP will allow patients to self-monitor and recognise if their asthma symptoms worsen. A few previous studies have evaluated the use of mobile phone applications for supporting asthma management in adults, but none of these included a WAAP as part of the intervention [161, 180]. This study has showed that telehealth interventions supporting self-management are feasible and efficacious to improve asthma control and asthma-related quality of life during pregnancy.

The common components of the effective interventions by Murphy *et al* [194], Powell *et al* [190], Lim *et al* [134] and my study are regular monitoring (using lung function or asthma symptoms or both), the involvement of health care professionals such as GPs, nurses or pharmacists in providing asthma education (Murphy *et al* [194], Lim *et al* [134]), monitoring regularly throughout pregnancy (Powell *et al* [190], and a personalised WAAP with contained instructions on which medications to take when feeling well, how to recognise worsening asthma, what to do when symptoms are getting worse and what to do in the event of an acute attack, including a first aid plan (Lim *et al* [134]). The primary difference between my study and all the previous interventions evaluated, was the use of a mobile phone application (*Breathe-easy*©) to support asthma self-management. Therefore, when designing interventions to optimise asthma management in pregnant women the following components need to be considered for incorporation: the involvement of and close collaboration among health care professionals, regular monitoring of asthma symptoms, asthma-self management tool (*Breathe-easy*©), asthma education focusing on self-monitoring and self-management, and a personalised written asthma action plan.

7.4 Strengths and limitations

The research for this thesis developed an intervention, supported by a telehealth programme and a handheld COPD-6 device, informed by a systematic review and a prospective cohort study of changes in lung function during pregnancy. To my knowledge, this is the first study to develop and evaluate a telehealth programme (*Breath-easy*©) specifically for supporting asthma management in pregnant women. This study was also the first in Australia to design a telehealth application (*Breath-easy*©) for asthma management supported by a mobile phone (Android operating system), WAAP and COPD-6 device, and evaluate the intervention using an RCT design.

Although several limitations of previous research were overcome, some limitations still exist. The systematic review did not include unpublished studies or grey literature during the literature search period, which may have biased the results. A meta-analysis was not possible due to the heterogeneity of the interventions and study designs. The Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©) trial by Lim *et al* [134] was not included in the systematic review as the manuscript was still not finalised at the time of the review. A Cochrane review by Bain *et al* [140] has superseded my systematic review; however, their major findings and conclusions echo the findings of my systematic review.

Although 40 pregnant women (20 healthy and 20 with asthma) were recruited for the prospective cohort study, some participants withdrew during the observations, which limited conclusions from the study due to its relatively small sample size. Further, although small statistically significant differences in lung function between healthy

and women with asthma were detected, these differences may not be clinically important. Clinical correlation is paramount even when significant changes in objective measures such as lung function are observed.

The RCT was not powered to detect differences in the maternal or neonatal outcomes between the intervention and control groups. Recruitment was limited to two large metropolitan public teaching hospitals in Victoria. Although the cohort was representative of pregnant women with asthma attending those two hospitals, it may not be representative of women attending private hospitals, or those from regional/remote areas. It was not possible to detect to what extent general practitioners (GPs) were involved in monitoring their patients. Women who were unable to use a 'smart' mobile phone were excluded. A 'smart' mobile phone with the telehealth application (*Breath-easy*©) for asthma management supported by a WAAP and a hand-held COPD-6 device was given to each participant in the intervention group.

However, the usual care was less intensive than some of the previous telehealth intervention studies [161, 180] and it is possible that some of the benefits observed in my study resulted from enhanced clinical care rather than the technological intervention. This trial was not powered to measure the cost-effectiveness of telehealth intervention compared to usual care. Stakeholder satisfaction and patient willingness to pay for the service were also not assessed. However by using a decision support technology and an automated feedback to the patient based on asthma symptoms and lung function, a telehealth programme intervention can contribute to more effective asthma self-management and may reduce healthcare costs related to unscheduled doctor visits. As such, this telehealth intervention may not be suitable for those who

are unable to operate mobile phones and those with visual or hearing impairments.

7.5 Recommendations

The results of this thesis highlight some points that should be considered when designing an intervention model or making clinical practice recommendations for optimising asthma management in pregnant women.

The following general recommendations are made:

- Better collaboration and involvement of healthcare professionals, including the women's GPs, respiratory specialists, obstetricians, midwives, asthma educators and pharmacists, need to be established for managing asthma in pregnant women.
- As the course of asthma changes unpredictably during pregnancy, healthcare professionals need to monitor asthma actively throughout the pregnancy until delivery, to ensure optimal maternal and neonatal outcomes.
- Education about asthma control and self-management skills (e.g. how to use medicines, how to recognise worsening asthma symptoms, and how to seek medical help when asthma becomes worse) need to be provided, not only to patients, but also to healthcare professionals, to achieve better health outcomes for both mother and baby.
- The use of WAAPs as part of self-management needs to be promoted more widely, not only to patients, but also to healthcare professionals. Provision and uptake of WAAP as a key performance indicator may encourage health professionals to initiate and recommend WAAP to their patients.

- Policymakers should consider the merits of investment in models of asthma care based on telehealth care.

7.6 Future research directions

Future research work in this specific population should endeavour to carry out the following:

- Conduct larger scale, multi-centre RCTs to develop and evaluate non-pharmacological healthcare interventions for managing asthma in pregnant women.
- Design and evaluate an intervention that elaborates the main role of healthcare professionals in a multi-disciplinary approach, supported by a telehealth programme.
- Undertake a qualitative study to explore the opinions and concerns of people with asthma, particularly pregnant women, and healthcare professionals (e.g. GPs, midwives, specialists, obstetricians, pharmacists), on the potential role of mobile phone monitoring technology (e.g. transmitting lung function data and asthma symptoms with immediate feedback regarding asthma control and a reminder of appropriate action) in supporting asthma self-management.
- Assess the cost-effectiveness of telehealth in practice, to ensure the sustainability of this intervention for supporting asthma management, not only in pregnant women, but also in the general population.
- Conduct a larger scale study to evaluate the effectiveness of the telehealth programme (*Breath-easy*©), supported by newer handheld respiratory devices in pregnant women with varying asthma severity (intermittent, mild, moderate

or severe) on neonatal outcomes (e.g. birth weight, prematurity).

- Conduct a larger study with longitudinal markers of inflammatory changes in serum are necessary to confirm the relationship between the failure improvement of lung function during pregnancy and earlier deliveries in women with asthma.
- Conduct a larger study to confirm the impact of asthma or other comorbidities on neonatal outcomes.
- Evaluate the effectiveness of the telehealth programme in the general population with a variety of respiratory diseases, such as COPD and bronchiectasis.

7.7 Conclusions

Overall, this thesis has demonstrated that asthma management involving regular monitoring of lung function and asthma symptoms is feasible. This approach could potentially improve asthma control in pregnant women. In pregnant women with asthma, FEV_6 appears to be a suitable alternative to FVC. A telehealth programme (*Breathe-easy*©) in conjunction with home monitoring of lung function (FEV_1 and FEV_6), assessment of asthma symptoms, and use of a WAAP, can promote asthma self-management during pregnancy and lead to better asthma outcomes.

Appendices

Appendices for Chapter 4 – 6

Appendix 1 – Monash University Human Research Ethics Committee (MUHREC) approval letter

Appendix 2 – Mercy Health Human Research Ethics Committee approval letter

Appendix 3 – The Royal Women's Hospital Human research Ethics Committee approval letter

Appendix 4 – Letter of invitation for Mercy Hospital (Phase 2 – Chapter 4)

Appendix 5 – Letter of invitation for Mercy Hospital (Phase 3 – Chapters 5 & 6)

Appendix 6 – Participant explanatory statement for healthy group (Phase 2 – Chapter 4)

Appendix 7 – Participant explanatory statement for asthma group (Phase 2 – Chapter 4)

Appendix 8 – Consent form (Phase 2 – Chapter 4)

Appendix 9 – Participant explanatory statement & consent form – Mercy Hospital for Women (Phase 3 – Chapter 5 & 6)

Appendix 10 – Participant explanatory statement & consent form – the Royal Women's Hospital (Phase 3 – Chapter 5 & 6)

Appendix 11 – Notification of patient participation to GP (Phase 2 – Chapter 4)

Appendix 12 – Notification of patient participation to GP (Phase 3 – Chapters 5 & 6)

Appendix 13 – Data collection form (Phase 2 – Chapter 4)

Appendix 14 – Data collection form (Phase 3 – Chapters 5 & 6)

Appendix 15 – Asthma Control Questionnaire (ACQ)

Appendix 16 – Mini Asthma Quality of Life Questionnaire (mAQLQ)

Appendix 17 – NAC Australia – Asthma Action Plan

Appendix 18 – Asthma and lung function test brochure (NAC Australia)

Appendix 19 – Asthma and Pregnancy brochure (NAC Australia)

Appendix 20 – Recruitment poster for healthy group (Phase 2 – Chapter 4)

Appendix 21– Recruitment poster for asthma group (Phase 2 – Chapter 4)

Appendix 22 – Recruitment poster for MASTERY trial (Phase 3 – Chapters 5 & 6)

Appendix 23– COPD-6 device information brochure

Appendix 1 – Monash University Human Research Ethics Committee (MUHREC) approval letter

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	**21 March 2013**
Project Number:	**CF13/778 - 2013000353**
Project Title:	**Telehealth for optimising asthma management during pregnancy**
Chief Investigator:	**Dr Johnson George**
Approved:	**From: 21 March 2013 To: 21 March 2018**

Terms of approval

1. Approval is only valid whilst you hold a position at Monash University and approval at the primary HREC is current.
2. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
3. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
4. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

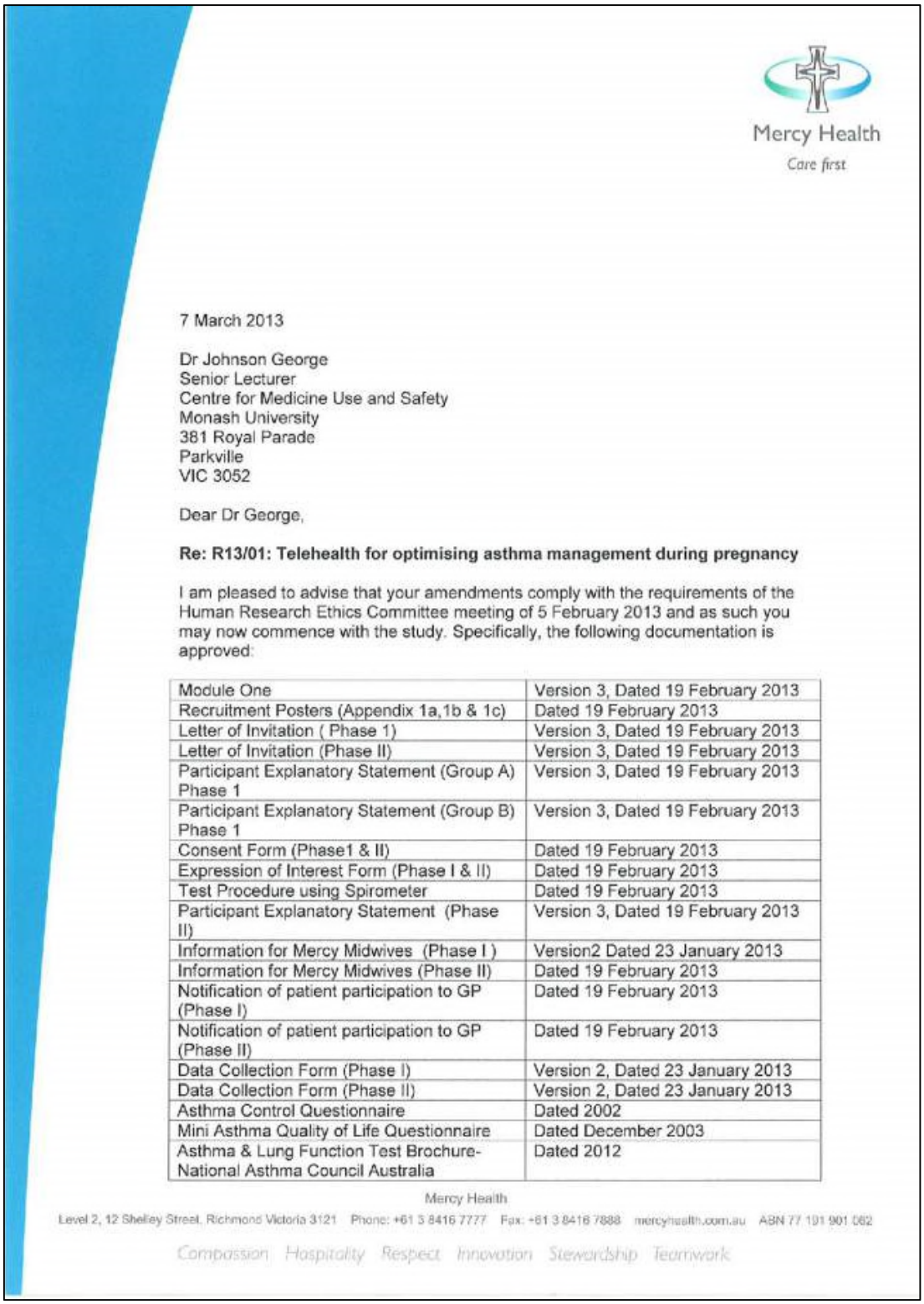
[redacted]

Professor Ben Canny
Chair, MUHREC

cc: Assoc Prof Kay Stewart, Prof Michael Abramson, Ms Elida Zairina, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford, Mr Gary Nolan

Postal – Monash University, Vic 3800, Australia
Building 3E, Room 111, Clayton Campus, Wellington Road, Clayton
Telephone +61 3 9905 5490 Facsimile +61 3 9905 3831
Email muhrec@monash.edu http://www.monash.edu.au/researchoffice/human/
ABN 12 377 614 012 CRICOS Provider #00008C

Appendix 2 – Mercy Health Human Research Ethics Committee approval letter



Mercy Health
Care first

7 March 2013

Dr Johnson George
Senior Lecturer
Centre for Medicine Use and Safety
Monash University
381 Royal Parade
Parkville
VIC 3052

Dear Dr George,

Re: R13/01: Telehealth for optimising asthma management during pregnancy

I am pleased to advise that your amendments comply with the requirements of the Human Research Ethics Committee meeting of 5 February 2013 and as such you may now commence with the study. Specifically, the following documentation is approved:

Module One	Version 3, Dated 19 February 2013
Recruitment Posters (Appendix 1a,1b & 1c)	Dated 19 February 2013
Letter of Invitation (Phase 1)	Version 3, Dated 19 February 2013
Letter of Invitation (Phase II)	Version 3, Dated 19 February 2013
Participant Explanatory Statement (Group A) Phase 1	Version 3, Dated 19 February 2013
Participant Explanatory Statement (Group B) Phase 1	Version 3, Dated 19 February 2013
Consent Form (Phase1 & II)	Dated 19 February 2013
Expression of Interest Form (Phase I & II)	Dated 19 February 2013
Test Procedure using Spirometer	Dated 19 February 2013
Participant Explanatory Statement (Phase II)	Version 3, Dated 19 February 2013
Information for Mercy Midwives (Phase I)	Version2 Dated 23 January 2013
Information for Mercy Midwives (Phase II)	Dated 19 February 2013
Notification of patient participation to GP (Phase I)	Dated 19 February 2013
Notification of patient participation to GP (Phase II)	Dated 19 February 2013
Data Collection Form (Phase I)	Version 2, Dated 23 January 2013
Data Collection Form (Phase II)	Version 2, Dated 23 January 2013
Asthma Control Questionnaire	Dated 2002
Mini Asthma Quality of Life Questionnaire	Dated December 2003
Asthma & Lung Function Test Brochure-National Asthma Council Australia	Dated 2012

Mercy Health
Level 2, 12 Shelley Street, Richmond Victoria 3121 Phone: +61 3 8416 7777 Fax: +61 3 8416 7888 mercyhealth.com.au ABN 77 191 901 092

Asthma & Pregnancy Brochure – Asthma Australia	Dated 2012

The Human Research Ethics Committee is constituted and functions in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007).

This approval by the Mercy Health Human Research Ethics Committee is valid from 7 March 2013 to 6 March 2016. That is, the project should be completed by the approval expiry date, of **6 March 2016**. Should it become apparent that an extension of the 3-year period is required, the principal researcher should apply, in writing, through the Administrative Officer of the Human Research Ethics Committee.

Please note that the research project should be commenced within 12 months from the date of this letter.

Would you kindly advise me the date that you commence your research.

In accordance with the NHMRC Guidelines, approval is subject to:

1. Immediate notification to the Administrative Officer, The Mercy Health Human Research Ethics Committee and sponsor, of any serious adverse effects on participants;
2. Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
3. Notification and reasons for ceasing the project prior to its expected date of completion;
4. The completion of a progress report at 6 months and then annually for the duration of the project; (progress report attached);
5. The Mercy Health Human Research Ethics Committee approval of any proposed modifications to the project;
6. The submission of a final report and papers published on completion of the project.

Please also note:

7. Consent Forms must be available for audit by the Mercy Health Human Research Ethics Committee and retained for the period required by law;
8. The Principal Investigator upon leaving the Institution must inform the Mercy Health Human Research Ethics Committee as to the nominated person to replace him/her.

If you have any queries, please do not hesitate to contact me on 8458 4808.

Yours sincerely

[redacted]

Carole Branch
Administrative Officer
Mercy Health Human Research Ethics Committee

Cc: Ms Elida Zairina

Appendix 3 – The Royal Women's Hospital Human research Ethics Committee approval letter

Mr Arthur Hui
Administrative Officer
Research and Ethics Secretariat
Tel: +61 3 8345 3720
Fax: +61 3 8345 3702
Email: arthur.hui@thewomens.org.au

the women's
the royal women's hospital

ABN 62 787 822 077
Locked Bag 300
Cnr Grattan St & Flemington Rd
Parkville VIC 3052 Australia
Tel +61 3 8345 2000
www.thewomens.org.au

10.9.13

Dr J George
Centre for Medicine Use and Safety
Department of Pharmacy Practice, Monash University
381 Royal Parade
Parkville Vic 3052

Dear Dr George,

Re: Project 13/26 - Telehealth for optimising asthma management during pregnancy

Thank you for submitting the clarification and amendments as requested by the RWH Human Research Ethics Committee.

I confirm the project is now approved.

Enclosed please find Project Approval and Notification of Project Commencement Forms for your record.

Prior to commencement of your project, you are reminded that you must contact the relevant RWH Divisional Directors / Department Heads to confirm your actual commencement date. Failure to inform these RWH personnel may jeopardise their approval and support for your project.

Please return the completed Notification of Project Commencement Form to me when the project begins.

Yours sincerely,

A. C. B. Hui
Administrative Officer
Research and Ethics Secretariat

Encl:

cc Ms S Wong

Appendix 4 – Letter of invitation (Phase 2 – Chapter 4)

Version 2.Date 1st July 2013

MONASH University Mercy Health Austin Health

Title of the study: ***Objective measures of lung function for monitoring asthma during pregnancy***

Dear mum-to-be,

One of our research team members will contact you prior to your **booking-in visit** at the Mercy Hospital for Women with all the information on how to participate in this study. This will be initially **by phone** and if you are interested will be followed by meeting you in person at the antenatal clinic at the hospital.

Mercy Hospital for Women, Monash University and Austin Hospital are conducting an important and exciting research about monitoring of asthma during pregnancy using breathing tests called spirometry and forced oscillation technique (FOT).

It is essential to regularly monitor asthma using breathing tests early in the pregnancy and periodically as needed. We are hoping to gain a better understanding of how lung function changes during pregnancy in women with asthma.

Aims of the study

This study will observe the changes of lung function in pregnant women using breathing tests called spirometry and forced oscillation technique (FOT). For the spirometry test, you will be asked to take the deepest breath you can and then exhale as hard as possible through a mouthpiece preferably for at least 6 seconds. For the FOT procedure you only require to breathe normally and quietly for 2 – 3 minutes through a mouthpiece. By participating, you will help provide information regarding any changes of lung function during healthy pregnancy which can help us to design an asthma self-management program for pregnant women with asthma. The results of this research will also be used by Elida Zairina to obtain her PhD, which is titled 'TELEHEALTH FOR OPTIMISING ASTHMA MANAGEMENT DURING PREGNANCY'.

Who is conducting this research?

This project is being conducted by Monash University in collaboration with Mercy Hospital for Women and Austin Hospital.

Who we are looking for?

We are inviting all pregnant women with asthma and all healthy pregnant women (i.e. with no history of

asthma/ hypertension/ other cardiovascular disease) who are in early pregnancy (up to 20 weeks gestation), aged ≥ 18 years with singleton pregnancy to participate in this study.

What your participation would involve?

- Having lung function tested 3 times during your pregnancy using spirometry and forced oscillation technique (FOT) at the Respiratory Laboratory at Austin Hospital, Heidelberg, Victoria, once every trimester (1st : early pregnancy, 2nd :21-28 weeks, and: 29-40 weeks).
- If you have asthma you will also be asked to complete a series of self-complete questionnaires about asthma control and quality of life related to asthma 3 times during your pregnancy - once every trimester (1st : early pregnancy, 2nd: 21-28 weeks, and 3rd : 29-40 weeks).

Sometimes, if for some reason we miss speaking to you at the time of your appointment and you are interested in taking part or just finding out more about the study, please do not hesitate to contact us:

Elida Zairina

[redacted]

Looking forward to your participation in our study and meeting you in person.

Best wishes,

Elida Zairina (on behalf of Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford and Mr Gary Nolan)

Monash University, Mercy Hospital for Women and Austin Hospital

Appendix 5 – Letter of invitation for Mercy Hospital (Phase 3 – Chapters 5 & 6)

MONASH University Mercy Health Core first Austin Health

Title of the study: ***Telehealth for asthma management during pregnancy***

Dear mum-to-be,

One of our research team members will contact you prior to your **booking-in visit** at the Mercy Hospital for Women with all the information on how to participate. This will be initially be **by phone** and if you are interested this will be followed by meeting you at the antenatal clinic at the hospital.

Mercy Hospital for Women, Monash University and Austin Hospital are conducting an important and exciting research about regular monitoring of asthma during pregnancy using a hand held respiratory device.

There have been many cases of poor asthma control during pregnancy. Support available to pregnant women for managing their asthma is limited. Monitoring asthma by measuring lung function regularly may detect any changes of asthma control and avoid asthma exacerbations during pregnancy. Findings of this study may result in more support services and resources for asthma management during pregnancy in the future.

Aims of this study

This study will test two ways of managing pregnant women with asthma. If one method proves to be more effective than the other, we will relay this information to health professionals and policy makers. Information generated from this trial can help prompt more support services and resources for pregnant women with asthma in the future. By participating, you will help evaluate strategies to decrease the risks of uncontrolled asthma. The results of this research will also be used by Elida Zairina to obtain her PhD, which is titled 'TELEHEALTH FOR OPTIMISING ASTHMA MANAGEMENT DURING PREGNANCY'.

Who is conducting this research?

This project is being conducted by Monash University in collaboration with Mercy Hospital for Women and Austin Hospital.

1

Who we are looking for?

We are inviting all pregnant women with asthma who are in early pregnancy (up to 16 weeks gestation), aged ≥ 18 years with singleton pregnancy and able to communicate in English to participate in this study.

What your participation would involve?

- Completing questionnaires about asthma control and quality of life related to asthma, first at the beginning of the study, then at 3 months, and 6 months later.
- If you consent to being involved in this study, you will be allocated to either the trial (intervention) group or to the conventional treatment group (usual care group). The allocation is random, like the toss of a coin; you will have a 50:50 chance of being in either group. If you have been selected for the trial group, you will receive the COPD-6 Bluetooth to measure the performance of your lungs. You will be asked to measure your lung function twice daily (morning and evening) using the device and then submit the data through an application which will be installed in your mobile phone. We will then give you feedback based on your results and notify your health professionals (GPs, obstetricians or midwives) if any changes of management decisions required. If you are in the conventional (control group) you will continue to receive usual medical care.
- We will need your permission to access your health records to collect data about you and your baby on birth.

If for some reason we miss speaking to you at the time of your appointment and you are interested in taking part or just finding out more about the study, please do not hesitate to contact us:

Elida Zairina

[redacted]

Looking forward to your participation in our study and meeting you in person.

Best wishes,

Elida Zairina (on behalf of Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford and Mr Gary Nolan)

Monash University, Mercy Hospital for Women and Austin Hospital

Appendix 6 – Participant explanatory statement for healthy group (Phase 2 – Chapter 4)

MONASH University Mercy Health Care first Austin Health

Participant Explanatory Statement

Version 5, Date 13th July 2013

Title: Objective measures of lung function for monitoring asthma during pregnancy

***Sites**: Mercy Hospital for Women and Austin Hospital*
***Principal Researcher**: Dr Johnson George*
***Associate researcher(s)**: A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford, Mr Gary Nolan,* Elida Zairina

This information sheet is for you to keep and it is four (4) pages long.

1. Introduction

You are invited to participate in a study that will observe any changes of lung function during pregnancy. You are being asked to participate in this research study because you identified yourself as having a history of asthma. Your involvement in the study will provide information about changes in lung function during pregnancy that will assist us to do a trial for improving the management of asthma in pregnant women. Feel free to ask questions about any information in the document. You may also wish to discuss the project with relatives or friends. Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not. If you decide you want to take part in this research you will be asked to sign a consent form. By signing it you are telling the researcher that you understand what you have read and that you consent to take part in the research project.

2. What is the purpose of this study?

Regular monitoring of asthma using breathing tests to measure lung function is recommended during pregnancy. The lung function test checks how your lungs are working and how asthma may affect your breathing. Some pregnant women with asthma may have few symptoms but abnormal lung function may potentially impair oxygen supply to their baby. Performing lung function tests regularly can help early detection of asthma worsening and indicate when asthma therapy needs to be adjusted. For pregnant women with asthma, conducting breathing tests called spirometry early in the pregnancy and periodically as needed is essential. This study will observe the changes of lung function in pregnant women with asthma using breathing tests called spirometry and forced oscillation technique (FOT). By participating, you will help provide information regarding any changes of lung function during pregnancy which can be used to design an asthma self-management program. The results of this research will also be used to help Elida Zairina obtain her PhD, which is titled 'TELEHEALTH FOR OPTIMISING ASTHMA MANAGEMENT DURING PREGNANCY'.

3. What does participation in this study involve?

If after reading and signing this form you agree to participate in the study, we will check to see if your

medical condition matches our study criteria. To determine whether you are eligible to participate, you will be asked questions about your age, history of asthma, and use of any medications for asthma in the last 12 months before or during your current pregnancy.

Research treatment:

If you qualify for the study, you will be asked to fill out a questionnaire giving details about you such as age, ethnicity, weight, and gestational age as well as about your asthma severity (mild, moderate or severe). Then you will be referred to the Respiratory Laboratory at Austin Hospital, Heidelberg, Victoria to measure your lung function, and the following will happen:

- You will have your lung function tested using spirometry by taking the deepest breath you can and then exhale as hard as possible for a short time (preferably at least 6 seconds) into a tube connected to a machine that measures how well your lungs are working before and after you have inhaled two puffs of a medication that can open your airways. Then For the FOT procedure you only require to breathe quietly for 2 – 3 minutes on a mouthpiece. All the procedures will be performed in the sitting position and at least three measurements will be conducted. During the test, soft nose clips may be used to prevent air escaping through the nose. The test will take approximately 30 – 60 minutes.
- You will do the measurement three times during your pregnancy, once in every trimester (First: early pregnancy, Second: 21-28 weeks, and third: 29-40 weeks).
- You will be asked to fill out the Asthma Control Questionnaires (ACQ) and Mini Asthma Quality of Life Questionnaire (Mini AQLQ) which consists of simple questions once in every trimester (1st trimester: 8-20 weeks, 2nd trimester: 21-28 weeks, and 3rd trimester: 29-40 weeks). It will need approximately 20 minutes to complete both of the questionnaires.

4. Will I or my baby benefit from this study?

All women in the study will be given information on and support for asthma management during pregnancy which may improve asthma control leading to better outcomes for you and your baby. However, we cannot promise you any benefits from participation in this study. If this study is successful, findings may result in more support for asthma management during pregnancy, such as asthma antenatal clinics and asthma monitoring programs to help other women in your situation in the future. Data gathered from this study may inform health professionals leading to better management of pregnant women with asthma.

5. Are there risks to me or my baby in taking part in this study?

There are no foreseeable risks associated with participation in this study. Pregnant women with asthma and other common lung disease can require full lung function tests. The procedures of lung function tests are simple and will be performed by trained laboratory scientists from the Respiratory Laboratory at Austin Hospital. During the test you will be supervised and asked about any discomfort

symptoms which may immediate discontinuation of the test. The medical help and usual hospital procedures will be available if needed. You may withdraw from the study at anytime without being disadvantaged. If during the study, it becomes evident that there is a concern with your asthma condition, we will notify you and/or your doctor, with your permission.

6. **Are there other treatments/procedures that may be advantageous whilst participating in this project?**

This research project will not be offering any additional treatments or procedures.

7. **How will my confidentiality be protected?**

All data collected from you, your health records, your doctor or your pharmacy will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies on password protected computers; both will **ONLY** be accessible by the investigators. Results may be presented at various conferences and in journal publications, but no participants nor health professionals will be identified. All information will be de-identified before data storage. . There is no possible way for someone outside the research team to identify you.

8. **What if new information arises during the research project?**

Should any new relevant information arise during this research, the investigator will advise you of same and discuss whether this affects your participation in this research.

9. **How will I be informed of the results of this research?**

For a summary of this study's findings, please contact one of the investigators listed at the end of this explanatory letter after the research is completed in 2015.

10. **What if I need further information or I have any problems during the study?**

If you require further information about the study or experience any problems as a result of your participation in this study, please contact one of the research investigators named at the end of this explanatory letter.

11. **What if I have a complaint?**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact Ms Carole Branch, Administrative Officer of Mercy Health Human Research Ethics Committee (HREC).

[redacted]

12. **Do I have to take part in this research project?**

Participation in any research study is voluntary. If you are interested in participating, please complete and return the consent form in the enclosed reply-paid envelope. You will only be contacted again if you fill in the consent form.

3

13. Has this research been approved?

The project has been approved by the Mercy Health Human Research Ethics Committee and the Monash University Human Research Ethics Committee. This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies. In accordance with the National Medical Health and Research Council guidelines, the Mercy Health Human Research Ethics Committee is required to conduct audits of research projects from time to time. It may therefore be possible that the Mercy Health Human Research Ethics Committee which has approved this research will seek to view a copy of your signed consent form, or to contact you, to ensure that the research is being conducted according to the ethical standards required by these guidelines.

14. Will I be reimbursed for my participation?

Parking charges or public transport costs for every visit to the hospital related to the study will be reimbursed on submission of receipts. If you are required to come to the hospital for any study related visit outside your visit to the antenatal clinic, we will reimburse your time in the form of a shopping voucher valued at $50.

Contact details for further enquiries, feedback or complaints in relation to this project are given below.

If you would like to contact the researchers about any aspect of this study, please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Mercy Health Human Research Ethics Committee:
Dr Johnson George [redacted] Ms Elida Zairina [redacted]	Executive officer Monash University Human Research Ethics Committee (MUHREC) [redacted] Mercy Health Human Research Ethics Committee [redacted]

Yours sincerely,

Elida Zairina (on behalf of Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford and Mr Gary Nolan

PLEASE FILL OUT AND RETURN THE CONSENT FORM AND THE EXPRESSION OF INTEREST FORM BELOW IF YOU ARE INTERESTED IN PARTICIPATING

4

Appendix 7 – Participant explanatory statement for asthma group (Phase 2 – Chapter 4)

MONASH University Mercy Health Care first Austin Health

Participant Explanatory Statement

Version 5, Date 13th July 2013

Title: Objective measures of lung function for monitoring asthma during pregnancy

***Sites**: Mercy Hospital for Women and Austin Hospital*
***Principal Researcher**: Dr Johnson George*
***Associate researcher(s)**: A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford, Mr Gary Nolan, Elida Zairina*

This information sheet is for you to keep and it is four (4) pages long.

1. Introduction

You are invited to participate in a study that will observe any changes of lung function during pregnancy. You are being asked to participate in this research study because you identified yourself as having a healthy pregnancy without any respiratory disease previously. Your involvement in the study will provide information about changes in lung function during pregnancy that will assist us to do a trial for improving the management of asthma in pregnant women. Feel free to ask questions about any information in the document. You may also wish to discuss the project with relatives or friends. Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not. If you decide you want to take part in this research you will be asked to sign a consent form. By signing it you are telling the researcher that you understand what you have read and that you consent to take part in the research project.

2. What is the purpose of this study?

The lung function test checks how your lungs are working during your pregnancy. This study will observe the changes of lung function in pregnant women using breathing tests called spirometry and forced oscillation technique (FOT). By participating, you will help provide information regarding any changes of lung function during healthy pregnancy which can help us to to design an asthma self-management program for pregnant women with asthma. The results of this research will also be used to help Elida Zairina obtain her PhD, which is titled 'TELEHEALTH FOR OPTIMISING ASTHMA MANAGEMENT DURING PREGNANCY'.

3. What does participation in this study involve?

If after reading and signing this form you agree to participate in the study, we will check to see if your medical condition matches our study criteria. To determine whether you are eligible to participate, you will be asked questions about your age, smoking status and weeks of gestation.

Research treatment:

If you qualify for the study, you will be asked to fill out a questionnaire including your age, ethnicity,

1

on password protected computers; both will **ONLY** be accessible by the investigators. Results may be presented at various conferences and in journal publications, but no participants nor health professionals will be identified. All information will be de-identified before data storage. There is no possible way for someone outside the research team to identify you.

8. What if new information arises during the research project?

Should any new relevant information arise during this research the investigator will advise you of same and discuss whether this affects your participation in this research.

9. How will I be informed of the results of this research?

For a summary of this study's findings, please contact one of the investigators listed at the end of this explanatory letter after the research is completed in 2015.

10. What if I need further information or I have any problems during the study?

If you require further information about the study or experience any problems as a result of your participation in this study, please contact one of the research investigators named at the end of this explanatory letter.

11. What if I have a complaint?

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact Ms Carole Branch, Administrative Officer of Mercy Health Human Research Ethics Committee (HREC).

[redacted]

12. Do I have to take part in this research project?

Participation in any research study is voluntary. If you are interested in participating, please complete and return the consent form in the enclosed reply-paid envelope. You will only be contacted again if you fill in the consent form.

13. Has this research been approved?

The project has been approved by the Mercy Health Human Research Ethics Committee and the Monash University Human Research Ethics Committee. This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies. In accordance with the National Medical Health and Research Council guidelines, the Mercy Health Human Research Ethics Committee is required to conduct audits of research projects from time to time. It may therefore be possible that the Mercy Health Human Research Ethics Committee which has approved this research will seek to view a copy of your signed consent form, or to contact you, to ensure that the research is being conducted according to the ethical standards required by these guidelines.

14. Will I be reimbursed for my participation?

Parking charges or public transport costs for every visit to the hospital related to the study will be reimbursed on submission of receipts. If you are required to come to the hospital for any study related visit outside your visit to the antenatal clinic, we will reimburse your time in the form of a shopping voucher valued at $50.

Contact details for further enquiries, feedback or complaints in relation to this project are given below.

If you would like to contact the researchers about any aspect of this study, please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Mercy Health Human Research Ethics Committee:
Dr Johnson George [redacted] Ms Elida Zairina [redacted]	Executive officer Monash University Human Research Ethics Committee (MUHREC) [redacted] Mercy Health Human Research Ethics Committee [redacted]

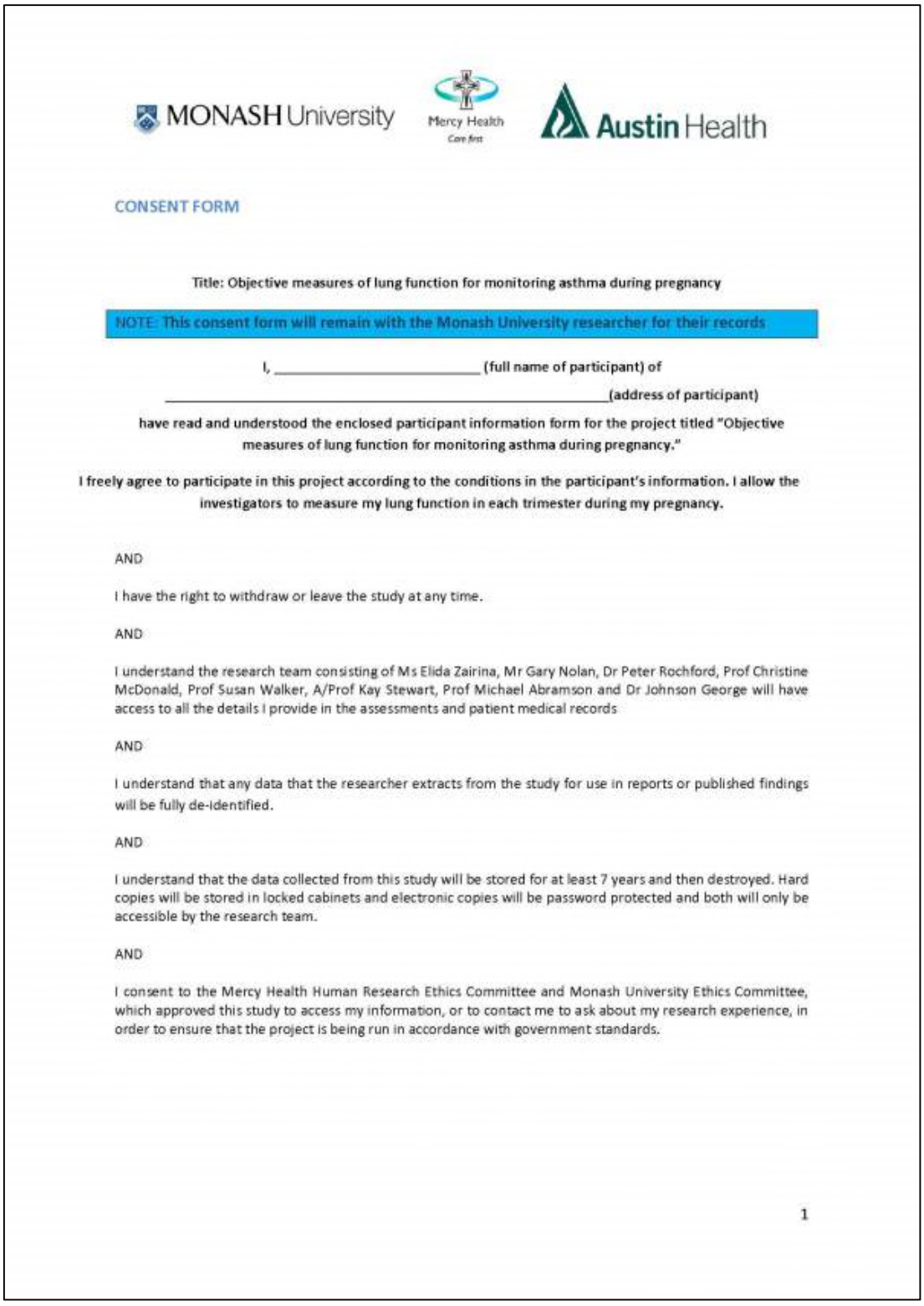
Yours sincerely,

Elida Zairina (on behalf of Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford and Mr Gary Nolan)

PLEASE FILL OUT AND RETURN THE CONSENT FORM AND THE EXPRESSION OF INTEREST FORM BELOW IF YOU ARE INTERESTED IN PARTICIPATING

4

Appendix 8 – Consent form (Phase 2 – Chapter 4)



MONASH University Mercy Health Care first Austin Health

CONSENT FORM

Title: Objective measures of lung function for monitoring asthma during pregnancy

NOTE: This consent form will remain with the Monash University researcher for their records

I, _____ (full name of participant) of

_____(address of participant)

have read and understood the enclosed participant information form for the project titled "Objective measures of lung function for monitoring asthma during pregnancy."

I freely agree to participate in this project according to the conditions in the participant's information. I allow the investigators to measure my lung function in each trimester during my pregnancy.

AND

I have the right to withdraw or leave the study at any time.

AND

I understand the research team consisting of Ms Elida Zairina, Mr Gary Nolan, Dr Peter Rochford, Prof Christine McDonald, Prof Susan Walker, A/Prof Kay Stewart, Prof Michael Abramson and Dr Johnson George will have access to all the details I provide in the assessments and patient medical records

AND

I understand that any data that the researcher extracts from the study for use in reports or published findings will be fully de-identified.

AND

I understand that the data collected from this study will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Mercy Health Human Research Ethics Committee and Monash University Ethics Committee, which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

1

Required participant's details

Full name:_____

Address :_____

Contact phone number :_____

Email address :_____

Please nominate the general practitioner and/ or specialist you wish us to contact regarding your asthma management

(1) Name:_____

Clinic name:_____

Clinic Address:_____

Clinic phone number: _____

(2) Name:_____

Clinic name:_____

Clinic Address:_____

Clinic phone number: _____

Participant's name (printed)_____

Participant's signature _____ Date_____

Name of witness to Participant's signature (printed)_____

Witness' signature_____Date_____

Declaration by researcher

Researcher's name (printed)_____

Researcher's signature _____Date_____

2

Appendix 9 – Participant explanatory statement & consent form – Mercy Hospital for Women (Phase 3 – Chapters 5 & 6)

MONASH University Mercy Health Austin Health

Participant Explanatory Statement

Version 3, Date 19th February 2013

Title: Telehealth for asthma management during pregnancy

***Sites**: Mercy Hospital for Women*

***Principal Researcher**: Dr Johnson George*

***Associate researcher(s)**: A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford, Mr Gary Nolan, Elida Zairina*

This information sheet is for you to keep and it is four (4) pages long.

1. Introduction

You are invited to participate in a study to trial a remote monitoring program for asthma management during pregnancy. You are being asked to participate in this research study because you identified yourself as having a history of asthma. Your involvement in the study will provide information about the effectiveness of the remote monitoring programme for management of asthma during pregnancy. Feel free to ask questions about any information in this document. You may also wish to discuss the project with relatives or friends. Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not. If you decide you want to take part in this research you will be asked to sign a consent form. By signing it you are telling the researcher that you understand what you have read and that you consent to take part in the research project.

2. What is the purpose of this study?

There have been many cases of poor asthma management during pregnancy and complaints about limited support available to pregnant women for management of asthma. Many women are unsure what to do with their asthma medications during pregnancy and are concerned about how asthma will affect their pregnancy. Monitoring asthma daily by measuring lung function regularly may detect any changes of asthma and avoid exacerbations during pregnancy. This trial will test two ways of managing pregnant women with asthma. If one method proves to be more effective than the other, we will relay this information to health professionals and policy makers. Information generated from this trial can help prompt more support services and resources for pregnant women with asthma in the future. By participating, you will help evaluate strategies to decrease the risks of uncontrolled asthma in the future. The results of this research will also be used to help Elida Zairina obtain her PhD, which is titled 'TELEHEALTH FOR OPTIMISING ASTHMA MANAGEMENT DURING PREGNANCY'.

3. What does participation in this study involve?

If after reading and signing this form you agree to participate in the study, we will check to see if your medical condition matches our study criteria. To determine whether you are eligible to participate, you will be asked questions about your age, history of asthma, and any medications for asthma used in the last 12 months before or during your current pregnancy.

1

This study will involve three assessments using standard questions, one in each trimester. The first assessment will be at the beginning of the study, the second at three months from baseline and the third six months later. These assessments will be done face to face and can be conducted at your preferred location and time. These will involve answering a few questions about how your asthma is going and your general physical well being and may take 15 – 20 minutes. Conveniently, you have the option of being assessed at your next appointment at the Mercy Hospital for Women. **If you choose this option, your parking or public transport costs will be reimbursed.** During the assessment you will be asked some questions about medication use and asthma management and will not be intrusive. You also need to give us permission to speak to your nominated doctor who usually supervises your asthma management (for example your GP and/ or asthma specialist) who we will liaise with on your asthma management.

We will also be trialling the use of a handheld respiratory device (COPD-6 Bluetooth) in pregnancy. If you consent to being involved in this study , you will be allocated to either the trial (intervention) group or to the conventional treatment group (control group). The allocation is random, like the toss of a coin; you will have a 50:50 chance of being in either group. If you have been selected for the trial group, you will receive the COPD-6 Bluetooth to measure the performance of your lungs. You will be asked to measure your lung function twice daily (morning and evening) using the device and then submit the data through an application which will be installed in your mobile phone. We will then give you feedback based on your results and notify your health professionals (GPs, obstetricians or midwives) if any changes of management decisions required. The COPD-6 Bluetooth will be yours to keep after the study. We will notify you if you are chosen to trial this device and application and organize the visits accordingly.

If you are in the conventional (control group) you will receive usual medical care regarding your asthma. You will be asked to fill out the research questionnaires first at the commencement of the study, second after three months and third after six months later. You will be given a summarised version of the "Asthma and Pregnancy" brochure from the national Asthma Council of Australia which explains about asthma in pregnancy including the asthma first aid and emergency assistance number for you to contact if you have any concerns regarding your asthma. We will need your permission to access to your health records to collect data about you and your baby on birth.

4. Will I or my baby benefit from this study?

All women in the study will be given information and support on asthma management during pregnancy which may improve asthma control leading to better outcomes for you and your baby. However, we cannot promise you any benefits from participation in this study. If this study is successful, findings may result in more support for asthma management during pregnancy, such as asthma antenatal clinics, asthma monitoring programs etc. and help contribute to helping other women in your situation in the future. Data gathered from this study may inform health professionals leading to better management of pregnant women with asthma.

5. Are there risks to me or my baby in taking part in this study?

There are no foreseeable risks associated with participation in this study. The equipment is easy to use and we will provide adequate training beforehand. The questions are simple and we will not be asking any intrusive or sensitive questions. You may withdraw from the study at anytime without being disadvantaged. If during the

study, it becomes evident that there is a concern about your asthma condition, we will notify you and/or your health professionals, with your permission. In the "Asthma & Pregnancy" brochure you can find information about asthma first aid and emergency assistance number for you to contact if you have any concerns regarding your asthma.

6. Are there other treatments/procedures that may be advantageous whilst participating in this project?

This research project will not be offering any additional treatments or procedures.

7. How will my confidentiality be protected?

All data collected from you, your health records, your doctor or your pharmacy will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies on password protected computers; both will **ONLY** be accessible by the investigators. Results may be presented at various conferences and in journal publications, but no participants, doctors nor pharmacies will be named. All information will be de-identified before data storage. There will be no possible way for someone outside the research team to identify you.

8. What if new information arises during the research project?

Should any new relevant information arise during this research the investigator will advise you of same and discuss whether this affects your participation in this research.

9. How will I be informed of the results of this research?

For a summary of this study's findings, please contact one of the investigators listed at the end of this explanatory letter after the research is completed in 2015.

10. What if I need further information or I have any problems during the study?

You are more than welcome to contact one of the research investigators or ethics committees named at the end of this explanatory letter.

11. What if I have a complaint?

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact Ms Carole Branch, Administrative Officer of Mercy Health Human Research Ethics Committee (HREC).

[redacted]

12. Do I have to take part in this research project?

Participation in any research study is voluntary. If you are interested in participating, please complete and return the consent form in the enclosed reply-paid envelope. You will only be contacted again if you fill in the consent form.

13. Has this research been approved?

The project has been approved by the Mercy Health Human Research Ethics Committee and the Monash University Human Research Ethics Committee. This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people

who agree to participate in human research studies. In accordance with the National Medical Health and Research Council guidelines, the Mercy Health Human Research Ethics Committee is required to conduct audits of research projects from time to time. It may therefore be possible that the Mercy Health Human Research Ethics Committee which has approved this research will seek to view a copy of your signed consent form, or to contact you, to ensure that the research is being conducted according to the ethical standards required by these guidelines.

14. Will I be reimbursed for my participation?

All participants will be reimbursed for any additional appointments at the hospital which arise from this research. COPD-6 Bluetooth will be supplied free of charge to chosen participants.

Contact details for further enquiries, feedback or complaints in relation to this project are given below.

If you would like to contact the researchers about any aspect of this study, please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Mercy Health Human Research Ethics Committee:
Dr Johnson George [redacted] Ms Elida Zairina [redacted]	Executive officer Monash University Human Research Ethics Committee (MUHREC) [redacted] Mercy Health Human Research Ethics Committee [redacted]

Yours sincerely,

Elida Zairina (on behalf of Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford and Mr Gary Nolan)

PLEASE FILL OUT AND RETURN THE CONSENT FORM AND THE EXPRESSION OF INTEREST FORM BELOW IF YOU ARE INTERESTED IN PARTICIPATING

Please separate the consent form from the participant explanatory statement so you may keep all the details of the participant explanatory statement

MONASH University

Austin Health

Mercy Health
Care first

the women's
the royal women's hospital

CONSENT FORM

Title: Telehealth for optimising asthma management during pregnancy

NOTE: This consent form will remain with the Monash University researcher for their records

I, _____ (full name of participant) of

_____(address of participant)

have read and understood the enclosed participant information form for the project titled "Telehealth for optimising asthma management during pregnancy." I freely agree to participate in this project according to the conditions in the participant's information. I allow the investigators to monitor my asthma using remote monitoring program supported by a handheld respiratory device during my pregnancy.

AND

I have the right to withdraw or leave the study at any time.

AND

I understand the research team consisting of Ms Elida Zairina, Mr Gary Nolan, Dr Peter Rochford, Prof Christine McDonald, Prof Susan Walker, A/Prof Kay Stewart, Prof Michael Abramson and Dr Johnson George will have access to all the details I provide in the assessments and patient medical records.

AND

I understand that any data that the researcher extracts from the study for use in reports or published findings will be fully de-identified.

AND

I understand that the data collected from this study will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Royal Women's Hospital Human Research Ethics Committee, the Mercy Hospital for Women Research Ethics Committee and Monash University Ethics Committee, which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

5

Required participant's details

Full name:_____

Address :_____

Contact phone number :_____

Email address :_____

Please nominate the general practitioner and/ or specialist you wish us to contact regarding your asthma management

(1) Name:_____

Clinic name:_____

Clinic Address:_____

Clinic phone number: _____

(2) Name:_____

Clinic name:_____

Clinic Address:_____

Clinic phone number: _____

Participant's name (printed)_____

Participant's signature _____ Date_____

Name of witness to Participant's signature (printed)_____

Witness' signature_____Date_____

Declaration by researcher

Researcher's name (printed)_____

Researcher's signature _____Date_____

6

Appendix 10 – Participant explanatory statement & consent form – the Royal Women's Hospital (Phase 3 – Chapters 5 & 6)

MONASH University

Austin Health

Mercy Health
Care first

the women's
the royal women's hospital

Participant Explanatory Statement

Version 2 Date 30 August 2013

Title: Telehealth for optimising asthma management during pregnancy

***Site**: The Royal Women's Hospital*

***Principal Researcher**: Dr Johnson George*

***Associate researcher(s)**: A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford, Mr Gary Nolan, Elida Zairina*

This information sheet is for you to keep and it is four (4) pages long.

1. Introduction

You are invited to participate in a study to trial a remote monitoring program for asthma management during pregnancy. You are being asked to participate in this research study because you identified yourself as having a history of asthma. Your involvement in the study will provide information about the effectiveness of the remote monitoring programme for management of asthma during pregnancy. Feel free to ask questions about any information in this document. You may also wish to discuss the project with relatives or friends. Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not. If you decide you want to take part in this research you will be asked to sign a consent form. By signing it you are telling the researcher that you understand what you have read and that you consent to take part in the research project.

2. What is the purpose of this study?

There have been many cases of poor asthma management during pregnancy and complaints about limited support available to pregnant women for management of asthma. Many women are unsure what to do with their asthma medications during pregnancy and are concerned about how asthma will affect their pregnancy. Monitoring asthma daily by measuring lung function regularly may detect any changes of asthma and avoid exacerbations during pregnancy. This trial will test two ways of managing pregnant women with asthma. If one method proves to be more effective than the other, we will relay this information to health professionals and policy makers. Information generated from this trial can help prompt more support services and resources for pregnant women with asthma in the future. By participating, you will help evaluate strategies to decrease the risks of uncontrolled asthma in the future. The results of this research will also be used to help Elida Zairina obtain her PhD, which is titled 'TELEHEALTH FOR OPTIMISING ASTHMA MANAGEMENT DURING PREGNANCY'.

3. What does participation in this study involve?

If after reading and signing this form you agree to participate in the study, we will check to see if your medical condition matches our study criteria. To determine whether you are eligible to participate, you will be asked questions about your age, history of asthma, and any medications for asthma used in the last 12 months

1

before or during your current pregnancy. This study will involve three assessments using standard questionnaires and as part of the questionnaires we will also perform the lung function test (Spirometry). The first assessment will be at the beginning of the study, the second at three months from baseline and the third six months later. These assessments will be done face to face and can be conducted at your preferred location and time. The questionnaires will involve answering a few questions about how your asthma is going and your general physical wellbeing and may take 15 – 20 minutes. Conveniently, you have the option of being assessed at your next appointment at the Royal Women's Hospital. **If you choose this option, your parking or public transport costs will be reimbursed.** You also need to give us permission to speak to your nominated doctor who usually supervises your asthma management (for example your GP and/ or asthma specialist) who we will liaise with on your asthma management.

We will also be trialling the use of a handheld respiratory device (COPD-6 Bluetooth) in pregnancy. If you consent to being involved in this study, you will be allocated to either the trial (intervention) group or to the conventional treatment group (control group). The allocation is random, like the toss of a coin; you will have a 50:50 chance of being in either group. If you have been selected for the trial group, you will receive the COPD-6 Bluetooth to measure the performance of your lungs. You will be asked to measure your lung function twice daily (morning and evening) using the device and then submit the data through an application which will be installed in your mobile phone. The equipment is easy to use and we will provide adequate training beforehand. We will then give you feedback based on your results and notify your health professionals (GPs, obstetricians or midwives) if any changes of management decisions required. The COPD-6 Bluetooth will be yours to keep after the study. **All costs related to the project including installation of the application and data transmission will be taken care of by the investigators of the study.** We will notify you if you are chosen to trial this device and application and organize the visits accordingly.

If you are in the conventional (control group) you will receive usual medical care regarding your asthma. You will be asked to fill out the research questionnaires first at the commencement of the study, second after three months and third after six months later. You will be given a summarised version of the "Asthma and Pregnancy" brochure from the national Asthma Council of Australia which explains about asthma in pregnancy including the asthma first aid and emergency assistance number for you to contact if you have any concerns regarding your asthma. We will need your permission to access to your health records to collect data about you and your baby on birth.

4. Will I or my baby benefit from this study?

All women in the study will be given information and support on asthma management during pregnancy which may improve asthma control leading to better outcomes for you and your baby. However, we cannot promise you any benefits from participation in this study. If this study is successful, findings may result in more support for asthma management during pregnancy, such as asthma antenatal clinics, asthma monitoring programs etc. and help contribute to helping other women in your situation in the future. Data gathered from this study may inform health professionals leading to better management of pregnant women with asthma.

5. Are there risks to me or my baby in taking part in this study?

There are no foreseeable risks associated with participation in this study. The questions are simple and we will

study, it becomes evident that there is a concern about your asthma condition, we will notify you and/or your health professionals, with your permission. In the "Asthma & Pregnancy" brochure you can find information about asthma first aid and emergency assistance number for you to contact if you have any concerns regarding your asthma.

6. Are there other treatments/procedures that may be advantageous whilst participating in this project?

This research project will not be offering any additional treatments or procedures.

7. How will my confidentiality be protected?

All data collected from you, your health records, your doctor or your pharmacy will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies on password protected computers; both will **ONLY** be accessible by the investigators. Results may be presented at various conferences and in journal publications, but no participants, doctors nor pharmacies will be named. All information will be de-identified before data storage. There will be no possible way for someone outside the research team to identify you.

8. What if new information arises during the research project?

Should any new relevant information arise during this research the investigator will advise you of same and discuss whether this affects your participation in this research.

9. How will I be informed of the results of this research?

For a summary of this study's findings, please contact one of the investigators listed at the end of this explanatory letter after the research is completed in 2015.

10. What if I need further information or I have any problems during the study?

You are more than welcome to contact one of the research investigators or ethics committees named at the end of this explanatory letter.

11. What if I have a complaint?

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact Ms Carole Branch, Administrative Officer of Mercy Health Human Research Ethics Committee (HREC).

[redacted]

12. Do I have to take part in this research project?

Participation in any research study is voluntary. If you are interested in participating, please complete and return the consent form in the enclosed reply-paid envelope. You will only be contacted again if you fill in the consent form.

13. Has this research been approved?

The project has been approved by the Mercy Health Human Research Ethics Committee and the Monash University Human Research Ethics Committee. This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people

Please separate the consent form from the participant explanatory statement so you may keep all the details of the participant explanatory statement

MONASH University

Austin Health

Mercy Health
Care first

the women's
the royal women's hospital

CONSENT FORM

Title: Telehealth for optimising asthma management during pregnancy

NOTE: This consent form will remain with the Monash University researcher for their records

I, _____ (full name of participant) of

_____(address of participant)

have read and understood the enclosed participant information form for the project titled "Telehealth for optimising asthma management during pregnancy." I freely agree to participate in this project according to the conditions in the participant's information. I allow the investigators to monitor my asthma using remote monitoring program supported by a handheld respiratory device during my pregnancy.

AND

I have the right to withdraw or leave the study at any time.

AND

I understand the research team consisting of Ms Elida Zairina, Mr Gary Nolan, Dr Peter Rochford, Prof Christine McDonald, Prof Susan Walker, A/Prof Kay Stewart, Prof Michael Abramson and Dr Johnson George will have access to all the details I provide in the assessments and patient medical records.

AND

I understand that any data that the researcher extracts from the study for use in reports or published findings will be fully de-identified.

AND

I understand that the data collected from this study will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Royal Women's Hospital Human Research Ethics Committee, the Mercy Hospital for Women Research Ethics Committee and Monash University Ethics Committee, which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

5

Required participant's details

Full name:_____

Address :_____

Contact phone number :_____

Email address :_____

Please nominate the general practitioner and/ or specialist you wish us to contact regarding your asthma management

(1) Name:_____

Clinic name:_____

Clinic Address:_____

Clinic phone number: _____

(2) Name:_____

Clinic name:_____

Clinic Address:_____

Clinic phone number: _____

Participant's name (printed)_____

Participant's signature _____ Date_____

Name of witness to Participant's signature (printed)_____

Witness' signature_____Date_____

Declaration by researcher

Researcher's name (printed)_____

Researcher's signature _____Date_____

6

Appendix 11 – Notification of patient participation to GP (Phase 2- Chapter 4)

MONASH University Mercy Health Care first Austin Health

Dear [Name of doctor]

This is a courtesy letter to inform you that your patient, [Name of participant] has expressed interest in participating in a study to investigate the role of spirometry for monitoring asthma management during pregnancy. This study will observe the changes of lung function in pregnant women with asthma and healthy pregnant women using breathing tests called spirometry and forced oscillation technique (FOT). The lung function tests will be performed once in each trimester during pregnancy at the Respiratory Laboratory at Austin Hospital, Heidelberg, Victoria.

We will also ask participants with asthma to complete the Asthma Control Questionnaire (ACQ) and the Mini Asthma Quality of Life questionnaire (Mini-AQLQ) once in each trimester during pregnancy and will provide you a copy of these results. **This study will not require you to do anything in addition to the usual care provided by you, but we wanted to let you know that your patient is enrolled in our study. However, we will inform you if your patient requires any changes in their medication or care.**

All information obtained in this study will be de-identified.

Enclosed is the participant explanatory statement we have given your patient so you are aware of the information they have received. Our contact details are also on this form. Please do not hesitate to contact us if there are any concerns.

Thank you for your participation.

Yours sincerely,

Elida Zairina (on behalf of Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford and Mr Gary Nolan)

Monash University, Mercy Hospital for Women and Austin Hospital

Appendix 12 – Notification of patient participation to GP (Phase 3 – Chapters 5 & 6)

MONASH University

Austin Health

Mercy Health
Care first

the women's
the royal women's hospital

Dear [Name of doctor]

This is a courtesy notice to inform you that your patient, [Name of participant] has expressed interest in participating in a study to evaluate the telehealth program for asthma management during pregnancy. This study will test an intervention to improve asthma outcomes in pregnant women via remote monitoring program. We will be monitoring asthma remotely using application loaded onto mobile phone; supported by a handheld respiratory device throughout pregnancy. **This study will not require you to do anything in addition to the usual care provided by you, but we wanted to let you know that your patient is considering enrolment in our study. If your patient's lung function changes such that it appears they may require early review or adjustment of their medication we will contact you.**

All information obtained in this study will be de-identified.

Enclosed is the participant explanatory statement we have given your patient so you are aware of the information they have received. Our contact details are also on this form. Please do not hesitate to contact us if you have any concerns.

Thank you for your participation.

Yours sincerely,

Elida Zairina (on behalf of Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson, Prof Susan Walker, Prof Christine McDonald, Dr Peter Rochford and Mr Gary Nolan)

Monash University, Mercy Hospital for Women, the Royal Women's Hospital and Austin Hospital

Appendix 13 – Data collection form (Phase 2 – Chapter 4)

MONASH University Mercy Health Care first Austin Health

Version 2, Date 23rd January 2013

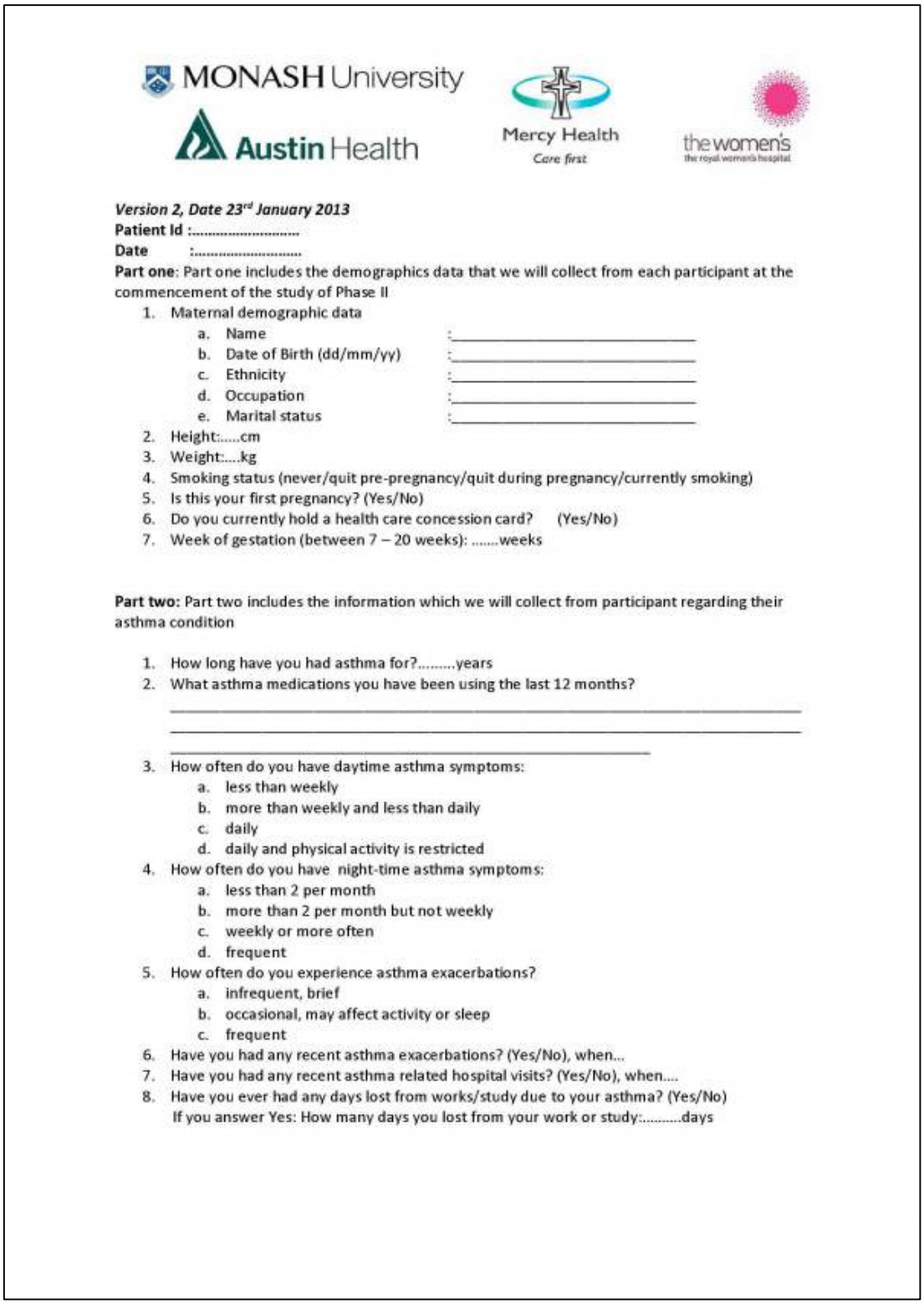
Part one: Part one includes the demographics data that we will collect from each participant at the commencement of the study of Phase I (Group A and Group B)

1. Maternal demographic data:
   a. Name:_____
   b. Date of Birth (dd/mm/yy):_____
   c. Ethnicity: _____
   d. Occupation: _____
   e. Marital status: _____
2. Height:.....cm
3. Weight:.....kg
4. Smoking status (never/quit pre-pregnancy/quit during pregnancy/currently smoking)
5. Is this your first pregnancy? (Yes/No)
6. Do you currently hold a health care concession card? (Yes/No)
7. Week of gestation (between 7 – 20 weeks): .....weeks

Part two: Part two includes the information which we will collect from participant regarding their asthma condition (Group A)

1. How long have you had asthma for?.....years
2. What asthma medications you have been used for the last 12 months?
   _____
   _____
   _____
3. How often do you have daytime asthma symptoms:
   a. less than weekly
   b. more than weekly and less than daily
   c. daily
   d. daily and physical activity is restricted
4. How often do you have night-time asthma symptoms:
   a. less than 2 per month
   b. more than 2 per month but not weekly
   c. weekly or more often
   d. frequent
5. How often do you experience asthma exacerbations?
   a. infrequent, brief
   b. occasional, may affect activity or sleep
   c. frequent
6. Have you had any recent asthma exacerbations? (Yes/No)
7. Have you had any recent asthma related hospital visits? (Yes/No)

Appendix 14 – Data collection form (Phase 3 – Chapters 5 & 6)



MONASH University

Austin Health

Mercy Health
Care first

the women's
the royal women's hospital

Version 2, Date 23rd January 2013

Patient Id :.....

Date :.....

Part one: Part one includes the demographics data that we will collect from each participant at the commencement of the study of Phase II

1. Maternal demographic data
   a. Name :_____
   b. Date of Birth (dd/mm/yy) :_____
   c. Ethnicity :_____
   d. Occupation :_____
   e. Marital status :_____
2. Height:.....cm
3. Weight:....kg
4. Smoking status (never/quit pre-pregnancy/quit during pregnancy/currently smoking)
5. Is this your first pregnancy? (Yes/No)
6. Do you currently hold a health care concession card? (Yes/No)
7. Week of gestation (between 7 – 20 weeks): .....weeks

Part two: Part two includes the information which we will collect from participant regarding their asthma condition

1. How long have you had asthma for?.....years
2. What asthma medications you have been using the last 12 months?
   _____
   _____
   _____
3. How often do you have daytime asthma symptoms:
   a. less than weekly
   b. more than weekly and less than daily
   c. daily
   d. daily and physical activity is restricted
4. How often do you have night-time asthma symptoms:
   a. less than 2 per month
   b. more than 2 per month but not weekly
   c. weekly or more often
   d. frequent
5. How often do you experience asthma exacerbations?
   a. infrequent, brief
   b. occasional, may affect activity or sleep
   c. frequent
6. Have you had any recent asthma exacerbations? (Yes/No), when...
7. Have you had any recent asthma related hospital visits? (Yes/No), when....
8. Have you ever had any days lost from works/study due to your asthma? (Yes/No)
   If you answer Yes: How many days you lost from your work or study:.....days

Appendix 15 – Asthma Control Questionnaire (ACQ)

ASTHMA CONTROL QUESTIONNAIRE

ENGLISH FOR AUSTRALIA

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
[redacted]
Web: http://www.qoltech.co.uk

This translation has been made possible through a grant from GLAXOSMITHKLINE
Translated by MAPI RESEARCH INSTITUTE
Senior Translator: Libby Jurd

APRIL 2002

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ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR AUSTRALIA)

PATIENT ID:_____

DATE:_____

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been in the last week.

1. On average, in the last week, how often were you **woken by your asthma** during the night?
   - 0 Not at all
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, in the last week, how **were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, in the last week, how **limited were you in your day-to-day activities** because of your asthma?
   - 0 Not at all limited
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, in the last week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 Very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 An extreme amount

P:\INSTITUTCULTADAPPROJECTS\pid1169QuestionFINAL VERSION\Asthma

ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR AUSTRALIA)

PATIENT ID:_____

DATE:_____

5.	In general, in the last week, how often did you wheeze?	0 None of the time 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6.	On average, in the last week, how many **puffs of relief medication** (short-acting bronchodilator such as Ventolin, Bricanyl, etc) have you used each day? *(If you are not sure how to answer this question, please ask for help.)*	0 None 1 1 - 2 puffs per day 2 3 - 4 puffs per day 3 5 - 8 puffs per day 4 9 - 12 puffs per day 5 13 - 16 puffs per day 6 More than 16 puffs per day

To be completed by a member of the clinic staff

7.	FEV_1pre-bronchodilator: ..... FEV_1predicted:..... FEV_1%predicted:..... *(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column.)*	0 > 95% predicted 1 95 - 90% 2 89 - 80% 3 79 - 70% 4 69 - 60% 5 59 - 50% 6 < 50% predicted

Appendix 16– Mini Asthma Quality of Life Questionnaire (mAQLQ)

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (MiniAQLQ)

SELF-ADMINISTERED AUSTRALIAN ENGLISH VERSION

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
[redacted]
Web: http://www.qoltech.co.uk

Developement and validation supported by GLAXO WELLCOME, INC.

DECEMBER 2003

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(AUSTRALIAN ENGLISH VERSION)
SELF-ADMINISTERED

PATIENT ID_____

DATE_____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2. Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4. Feel bothered by COUGHING?	1	2	3	4	5	6	7
5. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6. Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7. Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8. Have DIFFICULTY GETTING A GOOD NIGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(AUSTRALIAN ENGLISH VERSION)
SELF-ADMINISTERED

PATIENT ID_____

DATE_____

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN DURING **THE LAST 2 WEEKS** DOING THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

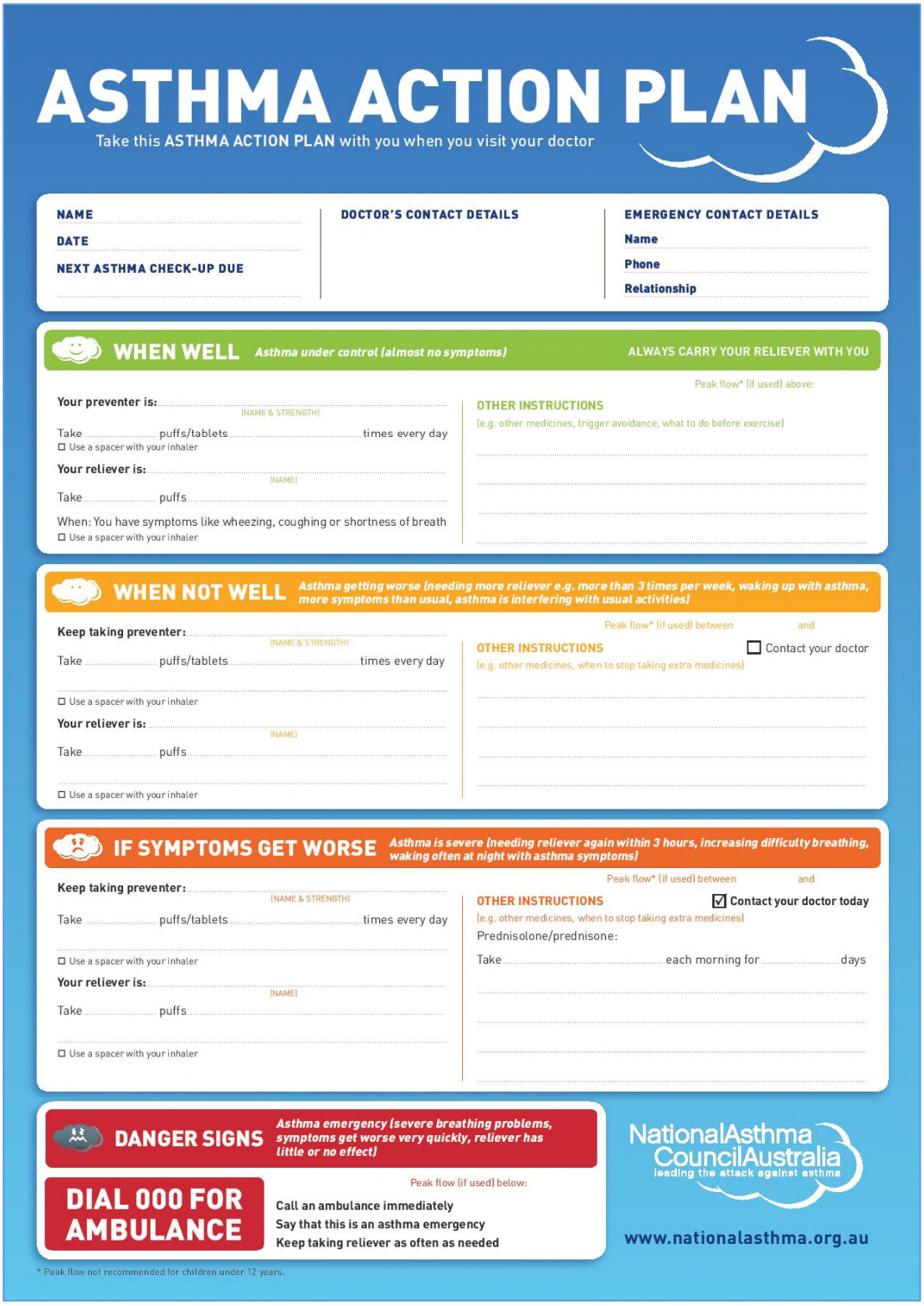
	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, playing sports)	1	2	3	4	5	6	7
13. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15. WORK-RELATED ACTIVITIES (tasks you have to do at work*)	1	2	3	4	5	6	7

** If you are not employed or self-employed, these should be tasks you have to do most days.*

DOMAIN CODE:

Symptoms: 1, 4, 6, 8, 10
Activity Limitation: 12, 13, 14, 15
Emotional Function: 3, 5, 9
Environmental Stimuli: 2, 7, 11

Appendix 17 – NAC Australia – Asthma Action Plan



ASTHMA ACTION PLAN

Take this **ASTHMA ACTION PLAN** with you when you visit your doctor

NAME

DATE

NEXT ASTHMA CHECK-UP DUE

DOCTOR'S CONTACT DETAILS

EMERGENCY CONTACT DETAILS

Name

Phone

Relationship

WHEN WELL *Asthma under control (almost no symptoms)* ALWAYS CARRY YOUR RELIEVER WITH YOU

Peak flow* (if used) above:

Your preventer is: [NAME & STRENGTH]

Take ..... puffs/tablets ..... times every day

☐ Use a spacer with your inhaler

Your reliever is: [NAME]

Take ..... puffs

When: You have symptoms like wheezing, coughing or shortness of breath

☐ Use a spacer with your inhaler

OTHER INSTRUCTIONS

(e.g. other medicines, trigger avoidance, what to do before exercise)

WHEN NOT WELL *Asthma getting worse (needing more reliever e.g. more than 3 times per week, waking up with asthma, more symptoms than usual, asthma is interfering with usual activities)*

Peak flow* (if used) between ..... and .....

Keep taking preventer: [NAME & STRENGTH]

Take ..... puffs/tablets ..... times every day

☐ Use a spacer with your inhaler

Your reliever is: [NAME]

Take ..... puffs

☐ Use a spacer with your inhaler

OTHER INSTRUCTIONS ☐ Contact your doctor

(e.g. other medicines, when to stop taking extra medicines)

IF SYMPTOMS GET WORSE *Asthma is severe (needing reliever again within 3 hours, increasing difficulty breathing, waking often at night with asthma symptoms)*

Peak flow* (if used) between ..... and .....

Keep taking preventer: [NAME & STRENGTH]

Take ..... puffs/tablets ..... times every day

☐ Use a spacer with your inhaler

Your reliever is: [NAME]

Take ..... puffs

☐ Use a spacer with your inhaler

OTHER INSTRUCTIONS ☑ Contact your doctor today

(e.g. other medicines, when to stop taking extra medicines)

Prednisolone/prednisone:

Take ..... each morning for ..... days

DANGER SIGNS *Asthma emergency (severe breathing problems, symptoms get worse very quickly, reliever has little or no effect)*

DIAL 000 FOR AMBULANCE

Peak flow (if used) below:

Call an ambulance immediately

Say that this is an asthma emergency

Keep taking reliever as often as needed

National Asthma Council Australia

leading the attack against asthma

www.nationalasthma.org.au

* Peak flow not recommended for children under 12 years.

ASTHMA ACTION PLAN
what to look out for

WHEN WELL

THIS MEANS:
- you have no night-time wheezing, coughing or chest tightness
- you only occasionally have wheezing, coughing or chest tightness during the day
- you need reliever medication only occasionally or before exercise
- you can do your usual activities without getting asthma symptoms

WHEN NOT WELL

THIS MEANS ANY ONE OF THESE:
- you have night-time wheezing, coughing or chest tightness
- you have morning asthma symptoms when you wake up
- you need to take your reliever more than usual eg. more than 3 times per week
- your asthma is interfering with your usual activities

IF SYMPTOMS GET WORSE

THIS MEANS:
- you have increasing wheezing, cough, chest tightness or shortness of breath
- you are waking often at night with asthma symptoms
- you need to use your reliever again within 3 hours

THIS IS AN ASTHMA ATTACK

DANGER SIGNS

THIS MEANS:
- your symptoms get worse very quickly
- you have severe shortness of breath, can't speak comfortably or lips look blue
- you get little or no relief from your reliever inhaler

CALL AN AMBULANCE IMMEDIATELY: DIAL 000 SAY THIS IS AN ASTHMA EMERGENCY.

DIAL 000 FOR AMBULANCE

ASTHMA MEDICINES

PREVENTERS

Your preventer medicine reduces inflammation, swelling and mucus in the airways of your lungs. Preventers need to be taken **every day**, even when you are well.

Some preventer inhalers contain 2 medicines to help control your asthma (combination inhalers).

RELIEVERS

Your reliever medicine works quickly to make breathing easier by making the airways wider.

Always carry your reliever with you – it is essential for first aid. Do not use your preventer inhaler for quick relief of asthma symptoms unless your doctor has told you to do this.

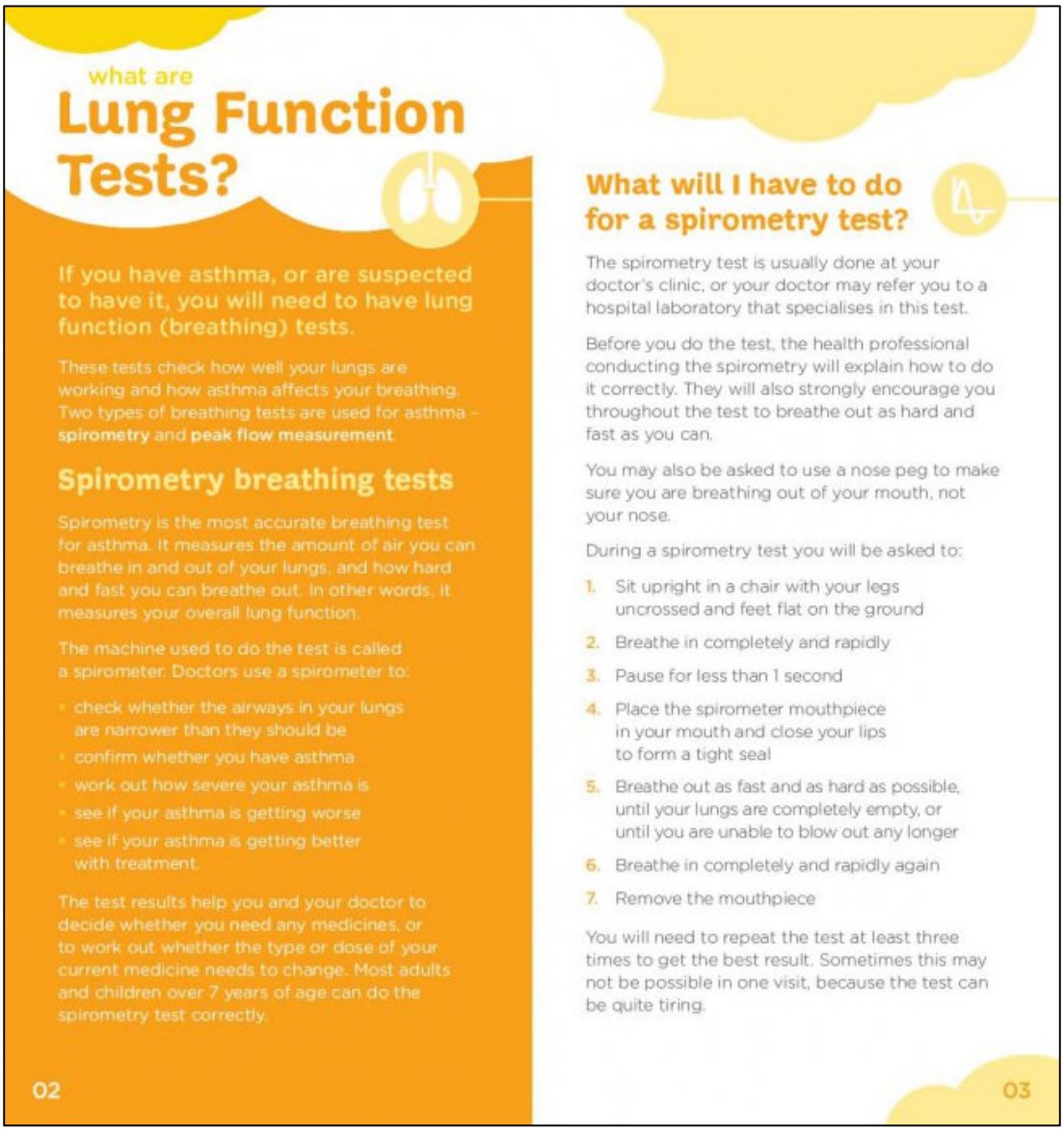
To order more Asthma Action Plans visit the National Asthma Council website. A range of action plans are available on the website – please use the one that best suits your patient.

www.nationalasthma.org.au

National Asthma Council Australia
leading the attack against asthma

Developed by the National Asthma Council Australia and supported by GlaxoSmithKline Australia.
National Asthma Council Australia retained editorial control.

Appendix 18 – Asthma and lung function test brochure (NAC Australia)



what are

Lung Function Tests?

If you have asthma, or are suspected to have it, you will need to have lung function (breathing) tests.

These tests check how well your lungs are working and how asthma affects your breathing. Two types of breathing tests are used for asthma – **spirometry** and **peak flow measurement**.

Spirometry breathing tests

Spirometry is the most accurate breathing test for asthma. It measures the amount of air you can breathe in and out of your lungs, and how hard and fast you can breathe out. In other words, it measures your overall lung function.

The machine used to do the test is called a spirometer. Doctors use a spirometer to:

- check whether the airways in your lungs are narrower than they should be
- confirm whether you have asthma
- work out how severe your asthma is
- see if your asthma is getting worse
- see if your asthma is getting better with treatment.

The test results help you and your doctor to decide whether you need any medicines, or to work out whether the type or dose of your current medicine needs to change. Most adults and children over 7 years of age can do the spirometry test correctly.

02

What will I have to do for a spirometry test?

The spirometry test is usually done at your doctor's clinic, or your doctor may refer you to a hospital laboratory that specialises in this test.

Before you do the test, the health professional conducting the spirometry will explain how to do it correctly. They will also strongly encourage you throughout the test to breathe out as hard and fast as you can.

You may also be asked to use a nose peg to make sure you are breathing out of your mouth, not your nose.

During a spirometry test you will be asked to:

1. Sit upright in a chair with your legs uncrossed and feet flat on the ground
2. Breathe in completely and rapidly
3. Pause for less than 1 second
4. Place the spirometer mouthpiece in your mouth and close your lips to form a tight seal
5. Breathe out as fast and as hard as possible, until your lungs are completely empty, or until you are unable to blow out any longer
6. Breathe in completely and rapidly again
7. Remove the mouthpiece

You will need to repeat the test at least three times to get the best result. Sometimes this may not be possible in one visit, because the test can be quite tiring.

03

The test is not painful – it just needs you to put in your best effort to breathe out as hard as you can!

Sometimes you may be asked to do the spirometry test again after having some puffs of a 'reliever' medicine (usually a blue- or grey-coloured puffer). The test will be done about 10 minutes after you've taken the reliever to check if the medicine helps your lungs to work better.

Your doctor should always explain your spirometry tests results to you.

For more information on what a spirometry test involves, go to our website to watch a video:

nationalasthma.org.au

Peak flow breathing tests

A peak flow test is done with a peak flow meter. It measures the maximum (or peak) speed at which you can blow air out. This gives an idea of how narrow your airways are. It also shows how much your airways are changing. However, a peak flow test cannot be used to confirm whether you have asthma — this is what a spirometer is used for *(see Spirometry breathing tests)*.

Your doctor may ask you to use a peak flow meter to check your asthma at home. Most children over the age of 7 years are able to use a peak flow meter correctly.

Peak flow tests are sometimes used as part of a Written Asthma Action Plan, which is developed with your doctor. A Written Asthma Action Plan will help you recognise whether your asthma is getting worse, and tell you what to do if it does.

If you are using a peak flow meter, you will need to find your 'best' test score. To do this, record your scores everyday for 1–2 weeks when your asthma is under control. Your 'best' score will then be used as a guide for you and your doctor to make changes to your asthma management.

For example, you will know if your asthma becomes worse because your score will be less than your recorded 'best' score. You can then make changes to your medicines as instructed in your Written Asthma Action Plan or by your doctor.

A peak flow meter is only one way for you to check your asthma. If you are feeling unwell despite good peak flow test results, follow the instructions on your Asthma Action Plan or see your doctor.

How to use a peak flow meter

Your doctor (or another health professional, such as a nurse, pharmacist or asthma educator) will show you how to use your peak flow meter correctly.

The main steps to using a peak flow meter are:

1. Stand up
2. Hold the peak flow meter level, so that the indicator faces upwards. Make sure the indicator is on zero or 'start'
3. Take in as deep a breath as possible
4. Place your lips tightly around the mouthpiece and blow as hard and fast as you can (for about 2 seconds)
5. Check your score on the meter
6. Repeat steps 1–5 two more times
7. Record the highest score out of the three scores.

If your airways are narrower than usual, the peak flow meter will have a lower score than your 'best'. When your airways are wide open, the score will be the same as or close to your 'best'. (A person's 'best' score depends on their height, age and gender – so 'best' scores will be different for each person.)

Always use the **same** peak flow meter for each measurement, because the scores can vary between different meters. For this reason, it is a good idea to take your own peak flow meter with you when you visit your doctor.

06

Other times you may need to use a peak flow meter

A peak flow meter may be useful to monitor your asthma when you:

- leave hospital
- need to take your blue reliever puffer more often
- are getting a cold
- are not feeling as well as you usually do
- have been exposed to a known trigger (for example, pollen)
- have had any changes made to your medicines, including different doses or new medicines
- are waking up at night with asthma symptoms (a sign of poorly controlled asthma).

07

Further Information

- Talk to your doctor or pharmacist
- Visit the National Asthma Council Australia website at: nationalasthma.org.au
- Contact your local Asthma Foundation 1800 645 130 asthmaaustralia.org.au

Information in this brochure does not replace professional medical advice. If you have any questions about your asthma, speak to your doctor.

Acknowledgements

Developed by the National Asthma Council Australia in consultation with an expert panel of respiratory scientists and clinicians.

Supported through funding from the Australian Government Department of Health and Ageing

To access more brochures in this series, visit the National Asthma Council Australia: **nationalasthma.org.au**

Note for health professionals:
Visit the National Asthma Council Australia website to:

- Order printed copies of this brochure
- Access the related information paper for health professionals

National Asthma Council Australia
leading the attack against asthma

Appendix 19– Asthma and Pregnancy brochure (NAC Australia)

Asthma Australia

This brochure, developed by Asthma Australia, provides basic information about managing asthma while you are pregnant.

To find out more about asthma contact your local Asthma Foundation
1800 645 130
asthmaaustralia.org.au

Translating and Interpreting Service
131 450

Asthma First Aid

1 **Sit the person upright**
— Be calm and reassuring
— Do not leave them alone

2 **Give 4 puffs of blue reliever puffer medication**
— Use a spacer if there is one
— **Shake** puffer
— Put **1 puff** into spacer
— Take **4 breaths** from spacer
Repeat until **4 puffs** have been taken
Remember: Shake, 1 puff, 4 breaths

3 **Wait 4 minutes**
— If there is no improvement, give **4 more puffs** as above

4 **If there is still no improvement call emergency assistance (DIAL 000)***
— Say 'ambulance' and that someone is having an asthma attack
— Keep giving **4 puffs** every **4 minutes** until emergency assistance arrives
* If calling Triple Zero (000) does not work on your mobile phone, try 112

Call emergency assistance immediately (DIAL 000)
— If the person is not breathing
— If the person's asthma suddenly becomes worse, or is not improving
— If the person is having an asthma attack and a puffer is not available
— If you are not sure if it's asthma
Blue reliever medication is unlikely to harm, even if the person does not have asthma

Asthma Australia
To find out more contact your local Asthma Foundation
1800 645 130
asthmaaustralia.org.au

Asthma & Pregnancy

Breathing for two: what you should do

Asthma Australia

Pregnant or planning a pregnancy?

Looking after your asthma is more important than ever. You will be breathing for yourself and your baby.

Living well with your asthma means you can provide the best protection for your baby.

However, it is possible that your asthma could become worse with pregnancy. Make sure you are well prepared.

DO:

— Keep taking your asthma medication, including your daily preventer.

— Be sure your obstetrician, doctor or midwife knows you have asthma and alert them to any change in your symptoms.

— Develop an asthma plan with your obstetrician or doctor. This will describe which medications you need, when to take them and what to do if your asthma becomes worse.

Will my asthma become worse?

There is a significant chance it could, so prevention is vital. Around half of the women in Australia with asthma will find it becomes temporarily worse during pregnancy.

The risk of a serious asthma attack is higher if you stop taking your asthma medications. Follow your asthma plan and have regular health checks throughout your pregnancy.

Will asthma medications harm my baby?

Most asthma medications, both preventers and relievers, are safe and should be continued during pregnancy. If you stop taking your medications there is a far greater risk of harm to your baby as it increases your chance of a serious asthma attack.

Remember: if you can't breathe, neither can your baby!

Can I just put up with asthma symptoms while I'm pregnant?

No — this is unsafe and not recommended. Asthma can increase the risk of pregnancy complications such as low birth weight, pre-term birth or lack of oxygen.

What happens if I have an asthma attack while I'm pregnant?

It should be treated the same as an attack that occurs at any other time. Commence Asthma First Aid. Remember to tell ambulance and emergency staff that you are pregnant.

Hayfever and allergy control?

If hayfever or other allergies trigger your asthma symptoms, you may be able to treat this with medications. Speak to your doctor or midwife before buying or taking allergy medications.

Need help to quit smoking?

Smoking is harmful to your unborn baby, and increases the chance that your baby will develop asthma or have other health problems. It can also make your own asthma worse. There has never been a more important time to quit. For help, speak to your doctor or call the **Quitline** on **13 78 48**.

Look after your asthma during pregnancy.

Is your asthma well-managed?

Do you?

- ☐ Ever wake up at night coughing, wheezing or breathless?
- ☐ Become short of breath with normal activity?
- ☐ Use your blue reliever puffer 3 or more times a week?

If you answered YES to any of these questions, see your obstetrician, doctor or midwife.

What should I do now?

- ☐ Tell your obstetrician, doctor or midwife that you have asthma and if your asthma gets worse
- ☐ Get an asthma plan from your obstetrician or doctor
- ☐ Keep taking your preventer medication
- ☐ Always carry your reliever medication with you
- ☐ Have regular asthma check-ups during your pregnancy

Appendix 20 – Recruitment poster for healthy group (Phase 2 – Chapter 4)

MONASH University

Mercy Health
Care first

Austin Health

The Centre of Medicine Use and Safety of Monash University, Mercy Hospital for Women and Austin Hospital would like to invite all pregnant women to join a study to improve support services to pregnant women with asthma

Are you pregnant ??

And in your first trimester??

Would you like to participate in a study to measure LUNG FUNCTION in each trimester during pregnancy?

By participating in this study you will help us to design a program to support asthma monitoring in pregnant women with asthma

If you are interested, please take some information and leave your contact details in the box provided

Appendix 21 – Recruitment poster for asthma group (Phase 2 – Chapter 4)

MONASH University Mercy Health Care first Austin Health

The Centre of Medicine Use and Safety of Monash University, Mercy Hospital for Women and Austin Hospital would like to invite all pregnant women with Asthma to join a study to improve support services to pregnant women with asthma

Are you, Pregnant and Asthmatic??

And in your first trimester??

Would you like to participate in a study to measure LUNG FUNCTION in each trimester during pregnancy?

If you are interested, please take some information and leave your contact details in the box provided

Appendix 22 – Recruitment poster for MASTERY trial (Phase 3 – Chapters 5 & 6)

MONASH University Mercy Health Care first Austin Health

The Centre of Medicine Use and Safety of Monash University, Mercy Hospital for Women and Austin Hospital would like to invite all pregnant women with Asthma to join a study to improve support services to pregnant women with asthma

Are you, Pregnant and Asthmatic??

And in your first trimester??

Would you like to participate in a study offering FREE asthma monitoring support during your pregnancy?

If you are interested, please take some information and leave your contact details in the box provided

Appendix 23 – COPD-6 device information brochure

Vitalograph
Your respiratory partner

Vitalograph copd-6 range

COPD screening monitors

Vitalograph copd-6

Case selection for spirometry and monitoring diagnosed COPD sufferers

- For the early detection of COPD - quickly, simply & accurately
- Identifies those at risk of COPD at the pre-symptomatic stage to allow early medical intervention and facilitate better clinical outcomes
- Screens out those whose FEV_1 is normal, and who therefore do not have COPD, without the risk of false COPD negatives
- Facilitates 'case selection' so that spirometry resources can be focused on those most likely to be diagnosed with COPD
- Monitors COPD patients using their 'number', the obstructive index – FEV_1 as a percent of predicted
- Displays FEV_1, FEV_6, ratio and % predicted, obstructive index, COPD classification and lung age
- Built-in quality of blow indicator on a large, easy to read display
- Easy to clean flowhead
- Can be used with hygienic SafeTway® mouthpieces or a BVF™
- Displays the GOLD COPD classification (stage I – IV) to help recognise the need for a change in the patient's management plan
- Requires only minimal instruction for use by non-respiratory specialists

Vitalograph is a world leading provider of outstanding quality cardio-respiratory diagnostic devices, clinical trial services and medical equipment servicing. With a pioneering heritage of excellence spanning half a century Vitalograph continues to make valuable contributions to effective medical care and enhanced quality of life.

The copd-6™ comes complete with:

- 3 SafeTway mouthpieces
- Carry pouch
- Guide for the healthcare professional
- 2 AAA Batteries

The copd-6 is very easy to use, simply:

- Enter age, height and gender
- Blow for 6 seconds (device beeps after 6 seconds)
- Blow 3 times
- Press 'Enter' to view results
- Transmit report to PDF from USB variant

Vitalograph copd-6 usb

Compatible with Vitalograph Reports Software

- Single page record for screening or monitoring
- Various report options
- Optional subject ID and name fields (weight field optional)
- Ability to add comments to the report
- Age, height, gender, device ID, time/date fields automatically populated
- Predicted values, 3 test results, best test, % predicted and lung age automatically tabulated
- Obstructive index, COPD (GOLD) Classification indicator
- BMI calculated
- Blow quality indicator
- Interpretation of results
- Can automatically name the PDF file
- Ability to customise report headers
- Ability to add comments to the report

The copd-6 usb comes complete with:

- Reports software & API documents CD
- USB cable
- 4 SafeTway mouthpieces and disposable noseclips
- Carry pouch
- Guide for the healthcare professional
- 2 AAA batteries

4000 Respiratory Monitors

Variant	PEF	FEV_1	FEV_6	FEV_1 Ratio	FEF 25-75%	FEV 0.5/0.75	Lung Age	Memory	Personal	GOLD Best	PDF Reports	SPV Reports
asma-1™ standard	●	●	o	o	o	o	o	600	●	o	o	o
asma-1 child version	●	●	o	o	o	●	o	600	●	o	o	o
asma-1 usb/s/bt	●	●	o	o	o	o	o	600	●	o	●	●
copd-6™ standard	o	●	●	●	o	o	●	o	o	●	o	o
copd-6 usb/s/bt	o	●	●	●	o	o	●	o	o	●	●	o
lung monitor standard	o	●	●	●	o	o	o	200	●	o	o	o
lung monitor usb/s/bt	o	●	●	●	●	o	o	200	●	o	●	o
lung age standard	o	●	o	o	o	o	●	o	o	o	o	o

● Available o Not available

usb - USB bt - Bluetooth® s - Serial

Technical Specification:

Product: Respiratory Monitor

Model Number: 4000

Parameters Displayed: FEV_1/ FEV_6/ ratio and % predicted

Quality of Blow Indicator: Yes

Obstructive Index: Mild, Moderate, Severe (FEV_1% predicted)

COPD Classification: Normal (not COPD); Stage I, II, III & IV (FEV_1% predicted)

Lung Age Indicator: Yes

Accuracy: Better than +/-3%

Range: 0 - 9.99 L BTPS

Sensor: Stator rotor

Flow Impedance: Better than 0.15 kPa/L/s at 14 L/s

Power Supply: AAA batteries

Display: Custom liquid crystal display

Size: 113 x 63 x 48mm

Weight: 55g

Performance Standards: ISO 26782:2009; ISO 23747:2007; ATS//ERS 2005

Operating Temperature: 17 - 37°C

Safety Standards: IEC 60601-1:2005

Medical Safety Standard: Medical Devices 93/42/EEC (as amended)

Designed & Manufactured Under: ISO 13485:2003, FDA 21CFR820

Ordering Info:

40200 4000 Respiratory Monitor copd-6
40450 4000 Respiratory Monitor copd-6 usb
40850 4000 Respiratory Monitor copd-6 s
40350 4000 Respiratory Monitor copd-6 bt
20242 2024 SafeTway mouthpieces (200)
20980 2024 SafeTway mini mouthpieces (50)
28350 2820 BVF Bacterial Viral Filters (50)
20303 2030 Noseclips disposable (200)
36020 2040 Precision Syringe 3 Litre

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Appendices for Poster Presentations

Appendix 24– A Systematic review of healthcare interventions for asthma management during pregnancy

Appendix 25– Changes in lung function during gestation in healthy and asthmatic women: a prospective cohort study

Appendix 26– Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy (MASTERY©)

Appendix 24 – A Systematic review of healthcare interventions for asthma management during pregnancy

A Systematic Review of Healthcare Interventions for Asthma Management During Pregnancy

Elida Zairina[1]; Kay Stewart[1]; Michael J Abramson[2,3]; Johnson George[1]
1. Centre for Medicine Use and Safety, Monash University, Parkville, VICTORIA; 2. Department of Epidemiology and Preventive Medicine, Monash University;
3. The Alfred Hospital, Melbourne, VICTORIA

INTRODUCTION

- Asthma is the most common chronic disease affecting pregnant women, complicating more than 12% of pregnancies in Australia. (Sawicki et al, 2011)
- More than half of pregnant women do not take their asthma preventer medications on a regular basis before and during pregnancy, which might lead to asthma exacerbations. (Kwon et al, 2006)
- Poorly controlled asthma during pregnancy increases the risk of poor outcomes in the mother (e.g. pre-eclampsia, perinatal mortality, and need for cesarean delivery) and the baby (e.g. low birth weight and prematurity). (Dombrowski & Schatz, 2010)
- Pregnant women with asthma is a high-risk group for whom additional care including education, self-monitoring and optimising asthma management may be required. (Wen, 2001)
- Asthma management during pregnancy requires close collaboration between obstetricians, primary care physicians, paediatricians and asthma-care specialists. (Guy, 2004)
- Little is known of the effectiveness of non-pharmacological interventions for optimising asthma management in pregnant women.

OBJECTIVE

To identify healthcare interventions for optimising asthma management during pregnancy and to examine their effects on maternal and neonatal outcomes.

METHODS

Eligibility criteria

Type of studies
Randomised controlled trials (RCTs) or quasi-RCTs, controlled clinical trials (CCTs), controlled before and after studies (CBAs) and interrupted time series (ITS).

Type of participants
Pregnant women with asthma.

Type of intervention
non-pharmacological interventions (e.g. behavioural or educational interventions) targeting patients and/or health care professionals, patient self-management programs, patient monitoring and follow-up of asthma management in pregnant women.

Type of outcome measures
- Primary outcomes
  - Asthma symptom scores
  - Asthma-related quality of life scores
  - Frequency of scheduled and unscheduled health care visits due to asthma exacerbations or complications
- Secondary outcomes
  - Lung function measurements
  - Days home sick (e.g. lost from work, school, university)
  - Self-reported asthma medication adherence
  - Neonatal outcomes (i.e. birth weight, APGAR scores)

Search methods for identification of studies
- A systematic literature search was completed using the following electronic bibliographic databases: MEDLINE, EMBASE, PsycINFO, CINAHL Plus, International Pharmaceutical Abstracts (IPA) and The Cochrane Central Register of Controlled Trials (CENTRAL).
- The comprehensive electronic database search was carried out on 31 July 2012. A limited update-search was performed until 30 September 2012.
- Published English-language reports of human studies were considered for inclusion. The broad terms asthma* AND pregnan* all as (text word) was used. A MeSH search was also performed in Medline and PubMed using asthma and pregnancy as keywords.

Data extraction
- All studies identified were imported into an Endnote® library; duplicates and irrelevant titles were removed.
- Two reviewers independently assessed full-text versions of all potentially eligible studies.
- Disagreement was resolved by discussion in the presence of an adjudicator.

Data analysis and reporting
- The data are presented in tabular form to explain variation in the results of the included studies.
- The effects of the intervention are described by comparing the changes in outcome measures from baseline to end of study between the groups.

RESULTS

Figure 1. Flow chart of selection process for including studies in the systematic review

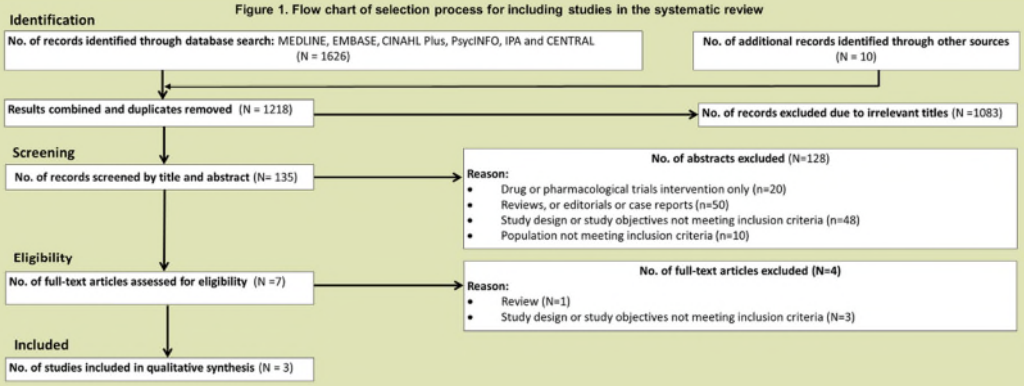

Table 1. Key features of studies included in systematic review

First author, year, study	Aim	Study design	Interventions	Follow-up	Outcome	Main findings
"Education Programme" Murphy et al (2005) *Eur Respir J* 26:435-41	To determine the level of asthma self-management skills and knowledge and to implement asthma education programme	Before-and-after analysis	I: Received education about asthma control and self-management skills in two visits (each session 30-60 minutes) (N=211) C: no control group	20 – 33 weeks gestation	Self-reported nonadherence to ICS, lung function, symptoms and reliever medication use	Nonadherence to ICS decreased [p=0.006]; no significant difference in reported lung function symptoms and reliever medication use between the two visits
"Progressive muscle relaxation (PMR)" Nickel et al (2006) *Psychother Psychosom* 75:237-43	To examine the efficacy of Progressive Muscle Relaxation (PMR) in pregnant women	RCT	I: 30 minutes PMR session, 3 times a week (N=32) C: placebo (30 minutes sham training), 3 times a week (N=32)	8 weeks	Lung function (PEF, FEV_1), quality of life (SF-36)	FEV_1 (l): Diff (95%CI) = 0.5 (0.2 to 0.6), p=0.005 PEF (l/min): Diff (95%CI) = 54.8 (47.7 to 61.9), p<0.001 SF-36 (mental component): Diff (95%CI) = 5.8 (1.4 to 10.2), p=0.01
"FeNO based Algorithm" Powell et al (2011) *Lancet* 378:983-90	To test the hypothesis that a management algorithm for asthma in pregnancy based on FeNO and symptoms would reduce asthma exacerbations	Double-blind RCT	I: FeNO algorithm to adjust therapy: (1) FeNO concentration used to adjust dose of ICS (2) ACQ score used to adjust dose of long-acting β_2-agonist (N=100) C: clinical guideline algorithm based on ACQ (N=103)	From 22 weeks gestation until delivery	Exacerbation types (unscheduled doctor visits, OCS use, hospital admission, ER/labour ward visits), quality of life (SF-12 and AQLQ-M), lung function (FEV, and FEV_1%), current treatment and perinatal outcomes	Significant reduction in unscheduled doctor visits for asthma and OCS use (p=0.002;p =0.042); quality of life (SF-12 mental component) higher in FeNO group (p=0.006) - remained significantly different after adjustment for baseline values (p=0.037, effect size 0.3). AQLQ-M scores low at the completion of the study and not different between the groups (p=0.54). No significant difference in FEV, and FEV_1%

I = Intervention, C = Control, FeNO = Fraction exhaled nitric oxide, PEF = Peak expiratory flow, FEV, = Forced expiratory volume in one second, ACQ = Asthma Control Questionnaire, ICS = Inhaled corticosteroid, OCS = Oral corticosteroid, AQLQ-M = Asthma Quality of Life Questionnaire-Marks, SF-12 = short form 12, SF-36 = Short form 36, Diff = Difference in change between the groups

CONCLUSIONS

- A clinical algorithm for asthma management based on objective measures and asthma symptoms could potentially reduce asthma exacerbations during pregnancy.
- The effects of educational interventions and PMR in pregnant women with asthma at different stages of gestation are unknown.
- Further evidence from well-designed studies for optimising asthma management during pregnancy is required.

REFERENCES:

Dombrowski & Schatz (2010) *Clin Obstet Gynecol* 53:301-10
Guy et al (2004) *Cnt Care Clin* 20: 731-45
Kwon et al (2006) *Immunol Allergy Clin N Am* 26:29-62
Sawicki et al (2011) *Aust N Z J Obstet Gynaecol* 51:333-8
Wen et al (2001) *Ann Epidemiol* 11:7-12

MONASH University Institute of Pharmaceutical Sciences

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- Directorate General of Higher Education of Indonesia Scholarship
- Airlangga University, Surabaya, East Java, INDONESIA

TheAlfred

Appendix 25 – Changes in lung function during gestation in healthy and asthmatic women: a prospective cohort study

Changes in lung function during gestation in healthy and asthmatic women: a prospective cohort study

Elida Zairina[1], Kay Stewart[1], Michael J Abramson[2,3], Christine F McDonald[4], Peter Rochford[4], Gary Nolan[5], Johnson George[1]

[1]Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, AUSTRALIA; [2]Dept of Epidemiology and Preventive Medicine, Monash University, [3]Allergy, Immunology & Respiratory Medicine, The Alfred Hospital, Melbourne, Victoria, AUSTRALIA, [4]Dept of Respiratory and Sleep Medicine, The Austin Health, Heidelberg, Victoria, AUSTRALIA, [5] Respiratory and Sleep Medicine, The Townsville Hospital, Douglas, Queensland, AUSTRALIA

BACKGROUND

- Poor asthma control during pregnancy is hazardous for both mother and fetus. Pregnant women with asthma may have minimal symptoms but abnormal lung function could potentially impair fetal oxygenation.
- Regular monitoring of asthma using pulmonary function tests (PFTs) and health-related quality of life (QoL) measures might help early detection of worsening asthma, allowing changes in management.

OBJECTIVES

- To compare changes in lung function during pregnancy in healthy and asthmatic pregnant women .
- To determine the relationship between lung function and asthma-related QoL in pregnancy.

METHODS

- Pregnant women were recruited when attending scheduled antenatal visits at a tertiary care maternity hospital in Melbourne, Australia.
- PFTs were measured three times during pregnancy (weeks 8 – 20, 21 – 28, and 29 – 40) using a spirometer (Jaeger Master Screen Carefusion, Hoechberg, Germany). ATS/ERS 2005 guidelines were followed. The best values achieved at each visit were chosen for analysis. [1]
- The percentage predicted for FEV_1 and FVC were calculated for each subject using ATS/ERS 2005 equations and corrected for ethnicity as required.
- The asthmatic group also completed the 7-item Asthma Control Questionnaire (ACQ)[2] and the mini Asthma Quality of Life Questionnaire (mAQLQ)[3] before the PFTs.
- A linear mixed effects model with repeated measures was used to describe the changes in lung function occurring during pregnancy. Time (i.e. visit) and group were treated as fixed effects. Pairwise comparisons between the estimated means were made using the Bonferroni correction, when relevant.

RESULTS

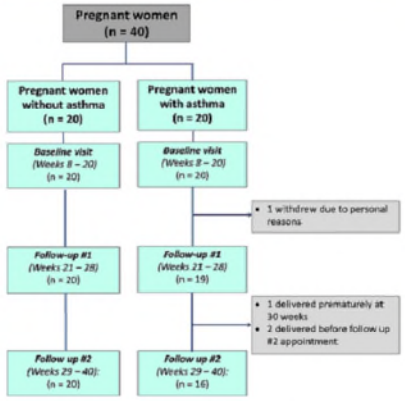


Figure 1. Flow of subjects through the study

Table 1. Demographic and Clinical characteristics of the study sample

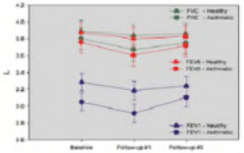
	Healthy women (n=20)	Women with asthma (n=20)	*P* value
Demographic Characteristics[1]			
Ethnicity			
• Caucasian	16 (80)	19 (95)	NS
• Other	4 (20)	1 (5)	NS
Employed	16 (80)	16 (80)	-
Smoking Status			
• Never	12 (60)	14 (70)	NS
• Past smoker	8 (40)	6 (30)	NS
Maternal Characteristics[2]			
Age (year)	33.2 ± 5.0	32.3 ± 3.1	NS
Height (cm)	165.8 ± 6.7	162.1 ± 6.6	NS
BMI (kg/m2) at baseline	25.6 ± 4.9	28.2 ± 7.1	NS
Weight (kg)			
• Baseline	70.7 ± 15.8	74.2 ± 20.0	NS
• Follow-up #1	72.9 ± 14.7	78.3 ± 19.5	NS
• Follow-up #2	79.5 ± 15.0	80.9 ± 19.1	NS
Gestational age (weeks)			
• Baseline	16.3 ± 1.2	15.5 ± 2.8	NS
• Follow-up #1	24.3 ± 2.4	25.4 ± 1.6	NS
• Follow-up #2	35.1 ± 1.7	35.4 ± 1.5	NS
Pregnancy Outcomes			
Gestational age at delivery (weeks)[2]	39.9 (38.6 – 40.5)	39.4 (39 – 40.7)	NS
Vaginal delivery [1]	16 (80)	11 (55)	NS
Cesarean section (elective)[1]	2 (10)	2 (10)	-
Cesarean section (Emergency)[1]	2 (10)	5 (25)	-
Forceps / Vacuum[1]	-	2 (10)	-
Birth weight (gm) [3]	3600 (3339 – 3745)	3400 (3118- 3523)	NS
Length (cm) [3]	51.5 (51 – 52.0)	50.3 (47.4 – 51.0)	0.02
Head circumference (cm) [3]	34.5 (34.4 – 36.0)	34.3 (33.6 – 35.0)	NS
APGAR score at 1 minute[3]	9 (9 – 9)	9 (6.75 – 9)	0.01
APGAR score at 5 minutes[3]	9 (9 – 9.25)	9 (9 – 9)	NS

APGAR, Appearance Pulse Grimace Activity Respiratory; BMI, Body Mass Index; NS (p > 0.05). Data are presented as: [1]Number (%), [2]mean ± SD, [3]median (interquartile range).

Table 2. Parameters during pregnancy in healthy and asthmatic women

Test	Baseline	Follow-up #1	Follow-up #2
Healthy women	**n = 20**	**n = 20**	**n = 20**
FEV_1 (L)	3.29 ± 0.11	3.18 ± 0.11*	3.24 ± 0.11**
FEV_6 (L)	3.92 ± 0.13	3.85 ± 0.13*	3.88 ± 0.13**
FVC (L)	3.94 ± 0.13	3.88 ± 0.13*	3.91 ± 0.13
FEV_1 %	103.05 ± 2.22	99.60 ± 2.22*	101.75 ± 2.22**
FVC %	103.35 ± 2.17	101.40 ± 2.17*	102.50 ± 2.17
Women with asthma	**n = 20**	**n = 19**	**n = 16**
FEV_1 (L)	3.05 ± 0.11	2.92 ± 0.11*	3.11 ± 0.11**
FEV_6 (L)	3.81 ± 0.13	3.65 ± 0.13*	3.77 ± 0.13**
FVC (L)	3.85 ± 0.13	3.72 ± 0.13*	3.80 ± 0.13
FEV_1 %	96.90 ± 2.22	92.68 ± 2.23*	98.86 ± 2.28**
FVC %	102.90 ± 2.74	99.18 ± 2.18*	101.55 ± 2.22
ACQ score	0.5 (0.3 – 1.2)	1.43 (1 -1.6)	0.7 (0.4 – 1.4)
mAQLQ score	6.1 (5.6 – 6.5)	5.3 (4.9 – 6.2)	6.2 (5.3 – 6.6)

ACQ, Asthma Control Questionnaire; mAQLQ, mini Asthma Quality of life Questionnaire; FEV_1, Forced expiratory volume in 1 second; FEV_6, Forced expiratory volume in 6 seconds; FVC, Forced vital capacity; FEV_1%, FEV_1 percentage predicted; FVC%, FVC percentage predicted. Pulmonary function data presented as mean ± SE; ACQ and mAQLQ scores as median (interquartile range).
** $P \leq 0.05$ for comparison with baseline; ** $P \leq 0.05$ for comparison with follow-up #1.*



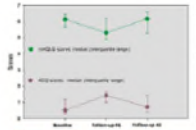
- Lung function values changed significantly during pregnancy within both healthy and asthmatic groups.
- The differences in change of FEV_1, FEV_6, FVC, FEV_1/FEV_6 and FEV_1% between healthy and asthmatic women were statistically significant ($p \leq 0.05$).

Figure 2. FEV_1, FEV6 and FVC during pregnancy in healthy and asthmatic women. Data are expressed as mean ± SE.

Table 3. Changes in baseline lung function values in healthy and asthmatic women

Test	Mean Difference (95% CI)			
	Healthy women		Women with asthma	
	Follow-up #1	Follow-up #2	Follow-up #1	Follow-up #2
FEV_1 (ml)	-103 (-142, -63)	-45 (-84, -6)*	-137 (-177, -97)	60 (16,104)*
FEV_6 (ml)	-72 (-113, -30)*	-48 (-88, -7)	-158 (-201, -115)*	-19 (-65, 26)
FVC (ml)	-54 (-105, -2)*	-36 (-78, 6)	-133 (-186, -80)*	-31 (-78, 15)
FEV_1/FEV_6	-1.11 (-1.89, -0.32)	-0.11 (-0.98, 0.76)*	-0.46 (-1.28, 0.34)	1.93 (0.96, 2.90)*
FEV_1 %	-3.45 (-4.68, -2.22)	-1.30 (-2.53, -0.1)*	-4.26 (-5.53, -3.00)	2.19 (0.82, 3.56)*
FVC %	-1.95 (-3.32, -0.59)	-0.85 (1.95, 0.25)	-3.79 (-5.19, -2.39)	-0.81 (-2.04, 0.41)

Values represent mean difference (CI) compared with baseline.
All analysis done by multiple comparisons: Bonferroni method to test the effect of group study.
** the mean difference is significant ($p \leq 0.05$)*



- A significant association was found between ACQ and mAQLQ scores in asthmatic women during pregnancy ($p < 0.01$).
- ACQ score increased at follow-up #1 suggesting a deterioration of asthma control in gestation weeks 21-28. mAQLQ scores decreased during this period suggesting decline in asthma-related QoL.
- No significant association between lung function and asthma-related QoL ($p > 0.05$).

Figure 3. ACQ and mAQLQ scores during pregnancy in women with asthma

CONCLUSIONS

- Lung function declined during gestational weeks 21 – 28, then improved in the final weeks of gestation (29 – 40) in both groups, but larger reductions were found in the asthmatic group.
- Regular monitoring of FEV_1 and FEV_6 may assist pregnant women and their health professionals in optimizing asthma management.
- ACQ and mAQLQ are useful tools for monitoring deterioration of asthma during pregnancy.

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Appendix 26– Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy (MASTERY©)

Management of Asthma with Supportive Telehealth of Respiratory function in Pregnancy (MASTERY©)

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INTRODUCTION

- Poorly controlled asthma during pregnancy is hazardous for both mother and fetus
- Self-management, including monitoring of asthma symptoms/lung function, following a written asthma action plan, and maintaining regular contact with health professionals can lead to better asthma control[1]
- Telehealth interventions have potential benefits in adults with asthma[2,3,4]
- Feasibility and efficacy of telehealth for supporting asthma management in pregnant women has not been investigated to date

AIM AND HYPOTHESIS

- **Aim:** To evaluate the efficacy of a telehealth intervention, supported by a handheld respiratory device in improving asthma control during pregnancy
- **Hypothesis:** The intervention group (MASTERY) will have better asthma control, as measured by the Asthma Control Questionnaire (ACQ) score changes, compared to the control group at 3 and 6 months from baseline

METHODS

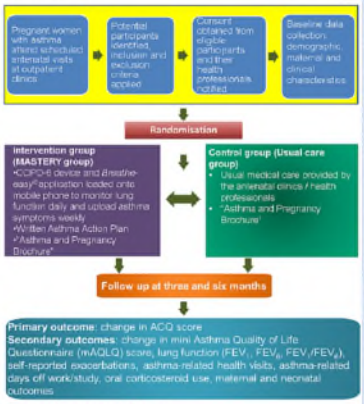


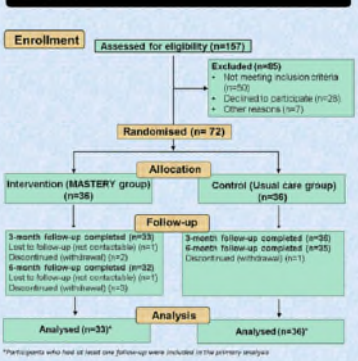
Figure 1. Flow chart of the study

Figure 2. The MASTERY© intervention schema
Participants record lung function (FEV1 and FEV6) using a *Bluetooth*-enabled COPD-6® device. Asthma symptoms and medication are entered on the *Breathe-easy*© application running on an enabled handset. Data get automatically transmitted to the secure MASTERY© website every time participants use the application.

- Longitudinal analysis was performed using the PROC MIXED procedure in SAS with subjects treated as random effects to compare change in ACQ scores at 3/6 months

Trial registration: ACTRN 12613000800729

RESULTS



*Participants who had at least one follow-up were included in the primary analysis

Figure 3. CONSORT diagram of participant flow

Table 1. Baseline demographic, maternal and clinical characteristics

	MASTERY group (n=36)	Usual care group (n=36)	p value
Demographic characteristics			
Race			1.00
Caucasian	30 (84)	30 (84)	
Other	6 (16)	6 (16)	
Australian/New Zealander citizenship	30 (83)	30 (83)	1.00
Health care/concession card holder	5 (14)	4 (11)	0.72
Level of education			0.88
Postgraduate or advanced degree	15 (42)	13 (36)	
other	21 (58)	23 (46)	
Smoking status			0.83
Never	25 (69)	23 (64)	
Quit pre-pregnancy	8 (22)	11(30)	
Quit during pregnancy	1 (3)	1(3)	
Currently smoking	2 (5)	1 (3)	
Maternal characteristics			
Age (years)[1]	31.08± 4.72	31.75 ± 4.25	0.53
Height (cm)[1]	164.03 ± 5.35	161.72 ± 7.09	0.12
Weight (kg)[1]	78.92 ± 21.57	70.75 ± 11.09	0.25
BMI (kg/m²)[1]	29.25 ± 7.41	27.06 ± 3.85	0.44
Gestational age (weeks)[1]	16.50 ± 2.94	16.17 ± 2.89	0.64
Primigravid	16 (44)	15 (42)	0.81
Other medical conditions			
Anxiety/depression	10 (28)	10 (28)	1.00
Thyroid disorder	4 (11)	2 (6)	0.39
Clinical characteristics			
Duration of asthma (years)[2]	26.50 (20.50 – 30)	25.50 (20 -30)	0.65
Asthma severity			1.00
Intermittent to Mild	15 (42)	15 (42)	
Moderate to Severe	21 (58)	21 (58)	
Asthma medications			0.89
SABA only	15 (42)	15 (42)	
ICS + SABA	3 (8)	2 (6)	
ICS/LABA + SABA	18 (50)	19 (52)	
FEV_1 (litres)[1]	2.74 ± 0.08	2.90 ± 0.08	0.18
FEV_1% predicted[1]	89.11 ± 2.29	91.58 ± 0.11	0.44
FEV_1/FEV_6 (%)[1]	80.05 ± 1.11	81.48 ± 1.04	0.49
ACQ score[1]	1.14 ± 0.10	1.19 ± 0.14	0.77
mAQLQ score[1]	5.45 ± 0.18	5.45 ± 0.19	0.99

ACQ, Asthma Control Questionnaire; BMI, Body Mass Index; mAQLQ, mini Asthma Quality of Life Questionnaire; FEV_1, Forced expiratory volume in 1 second; FEV_1%, FEV_1 expressed as a percentage of the predicted value; FEV_6, Forced expiratory volume in 6 seconds; ICS, inhaled corticosteroid; LABA, long-acting beta agonist, SABA, short-acting beta agonist. Values are presented as numbers (percentages) unless specified. [1]mean ± SD, [2]median (interquartile range), [3]mean ± SE.

Table 2. Asthma-related outcomes

Outcome	MASTERY group (n=33)	Usual care group (n=36)	p value
Self-reported exacerbations	1 (3)	18 (51)	**<0.01**
Days off work/study related to asthma	1 (3)	1 (3)	0.95
Unscheduled asthma-related health visits	0 (0)	1 (3)	0.34
Oral corticosteroid use	1 (3)	2 (6)	0.61

Values presented as number of subjects (percent)

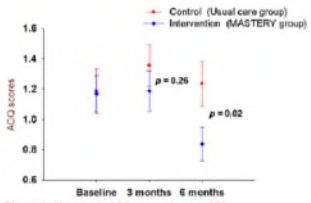


Figure 4. Changes in ACQ scores (mean ±SE)

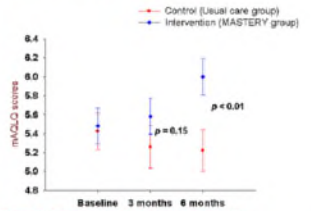


Figure 5. Changes in mAQLQ scores (mean ±SE)

Table 3. Perinatal outcome data and comparison between groups

	MASTERY group (n=33)	Usual care group (n=36)	p value
Neonatal Data			
Male sex	18 (50)	21 (58)	0.48
Birth weight (g)[1]	3411.75 ± 538.33	3446.96 ± 547.33	0.79
Length (cm)[1]	49.88 ± 2.64	50.25 ± 2.32	0.39
Head circumference (cm)[1]	34.31 ± 1.64	34.75 ± 2.75	0.99
APGAR score[2]			
At 1 minute	9 (8-9)	9 (7.25 – 9)	0.81
At 5 minutes	9 (9-9)	9 (9-9)	0.60
Gestational age (weeks)[1]	39.32 ± 1.15	39.09 ± 1.37	0.46
Admission to NICU or SCN	1 (3)	2 (6)	0.56
Premature (< 37 weeks)	1 (3)	2 (6)	0.56
Low birth weight (<10th centile for gestational age)	5 (14)	7 (19)	0.53
Delivery Data			
Mode of Delivery			0.75
Vaginal delivery	19 (58)	17 (47)	
Assisted birth delivery	4 (12)	7 (19)	
Elective caesarean	6 (18)	6 (17)	
Emergency caesarean	4 (12)	6 (17)	
Complications			
Gestational diabetes	3 (8)	6 (17)	0.29
Hypertensive disorders of pregnancy	2 (6)	2 (6)	1.00
Postpartum haemorrhage	1 (3)	2 (6)	0.56
Macrosomia	2 (6)	5 (14)	0.23

APGAR, Activity Pulse Grimace Respiration Appearance. NICU, Neonatal Intensive Care Unit; SCN, special care nursery. Values are presented as numbers (percentages) unless specified. [1]mean ± SD, [2]median (interquartile range)

CONCLUSIONS

- MASTERY improved asthma control and asthma-related quality of life in pregnant women
- No significant differences in maternal and perinatal outcomes, or lung function
- Telehealth interventions are feasible and efficacious in pregnant women with asthma

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