Smartphone apps for type 2 diabetes self-management and medication adherence : a multi-method study

Huang, Zhilian

2020

Huang, Z. (2020). Smartphone apps for type 2 diabetes self-management and medication adherence : a multi-method study. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/137883>

<https://doi.org/10.32657/10356/137883>

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

Downloaded on 26 Apr 2023 16:03:59 SGT

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**Smartphone apps for Type 2 diabetes self-
management and medication adherence: a
multi-method study**

HUANG ZHILIAN

Interdisciplinary Graduate School

2020

Smartphone apps for Type 2 diabetes self-management and medication adherence: a multi-method study

HUANG ZHILIAN

Interdisciplinary Graduate School

NTU Institute for Health Technologies

A thesis submitted to the Nanyang Technological University in
partial fulfilment of the requirement for the degree of
Doctor of Philosophy

2020

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research, is free of plagiarised materials, and has not been submitted for a higher degree to any other University or Institution.

10 August 2019

.....

Date

.....

Huang Zhilian

Supervisor Declaration Statement

I have reviewed the content and presentation style of this thesis and declare it is free of plagiarism and of sufficient grammatical clarity to be examined. To the best of my knowledge, the research and writing are those of the candidate except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

12 August 2019

Date

A handwritten signature in black ink, appearing to read 'Josip Car', written over a horizontal dotted line.

Josip Car

Authorship Attribution Statement

This thesis contains material from two paper(s) published in the following peer-reviewed journal(s) where I was the first and/or corresponding author.

Chapter 3 is published as: Huang Z, Soljak M, Boehm BO, Car J. Clinical relevance of smartphone apps for diabetes management: A global overview. Diabetes/Metabolism Research and Reviews [Internet]. 2018. Available from: <https://doi.org/10.1002/dmrr.2990>

The contributions of the co-authors are as follows:

- I (ZH) conceived the idea, conducted the analysis, wrote and revised the manuscript.
- Dr Michael Soljak (MS), Prof. Bernhard Boehm (BB) and Assoc Prof. Josip Car (JC) revised, commented on the manuscript and provided guidance to ZH.
- I would also like to acknowledge Tan Guan Zhong, Chua Kee Leng, Janis Lee, Wang Hua Xian, Laura Beatriz Martinengo, Tarig Osman, Geronimo Jimenez Larrain, Aspembitova Ayana, Monika Semwal and Shoko Dauwels-Okutsu's contribution in screening the apps titles and assessing the apps; and Dr Elaine Lum Pooi Ming in providing critical review of this manuscript.

Chapters 4 and 5 are published as: Huang Z, Lum E, Jimenez G, Semwal M, Sloot P, Car J. Medication management support in diabetes: a systematic assessment of diabetes self-management apps. BMC Medicine [Internet]. 2019 2019/07/17; 17(1):[127 p.]. Available from: <https://doi.org/10.1186/s12916-019-1362-1>

The contributions of the co-authors are as follows:

- I (ZH) conceptualised, developed and refined the medication management diagram and app assessment criteria; screened and assessed apps; cleaned, analysed and interpreted data; drafted and revised the manuscript.
- Dr Elaine Lum (EL) co-conceptualised the medication management diagram; provided critical input into the developed app assessment criteria; assessed apps; interpreted data; revised the manuscript.
- Mr Geronimo Jimenez (GJ) refined the app assessment criteria; assessed apps; obtained access to restricted apps; interpreted data; revised the manuscript.
- Dr Monika Semwal (MS) contributed to the development of app assessment criteria; assessed apps; reviewed the draft manuscript.
- Prof Peter Sloot (PS) provided critical input to the study and draft manuscript.
- Assoc Prof Josip Car (JC) conceptualized the overall study; obtained the funding; supervised the team; provided critical input into all stages of the study; critically reviewed the draft manuscript.
- I would also like to acknowledge Dr Ming Keat Sng (MKS), Dr Li Li (LL), and Ms My Linh Thai (MLT) for their input in piloting and refining the app assessment criteria; Ms Christina Tan (CT) and MLT for their assistance in app assessment.

10 August 2019

Date

Huang Zhilian

Acknowledgements

I would like to thank my main supervisor Assoc/Prof. Josip Car and co-supervisor Prof. Peter Sloom for their support and guidance throughout my PhD. The learning opportunities provided by both supervisors were immensely valuable in helping me grow in this journey. I am also grateful to my mentor Prof. Bernhard Boehm for his advice on my research. His immense knowledge of diabetes is an excellent source of inspiration for me. The guidance from my thesis advisory committee has been instrumental in shaping my perspective on solving complex problems.

Much gratitude goes to Dr. Elaine Lum for her academic guidance and emotional support throughout the PhD. She has been a great mentor in helping me to overcome the challenges of the PhD. I am also grateful to my collaborator Dr. Eberta Tan for supporting the study at Changi General Hospital and Dr. Chow Wai Leng for initiating the collaboration. This PhD would not be possible without their kindness and support.

I thank Asst/Prof. Lorainne Tudor Car for her guidance in conducting a systematic review; Mr. Geronimo Jimenez, Ms. Thai My Linh, Dr. Monika Semwal, Ms. Christina Tan, and Ms. Audrey Nah for their assistance in data collection; and Dr. Ram Bajpai for his guidance on statistical methods.

I thank my colleagues from the Centre for Population Health Sciences (CePHaS), Nanyang Technological University (NTU); administrative staff from the Complexity Institute, NTU; all staff from the Diabetes Centre, Changi General Hospital (CGH); all study participants from CGH; and fellow PhD students for their friendship and contribution during my PhD journey. The sharing of their expertise and experience has increased my knowledge and shaped my perspective on problem-solving. I would also like to acknowledge all co-authors of manuscripts that were submitted or published during my studies.

I also acknowledge the NTU Research Scholarship for supporting this work and NTU Institute for Health Technologies (HealthTech NTU) for funding and hosting my PhD

Lastly, I would like to thank my family and friends for their unwavering support and encouragement through this journey. Thank you for accommodating my ideas and always lending a listening ear when I needed it most.

Table of contents

List of Tables	vii
List of Figures	viii
List of Abbreviations.....	ix
List of Definitions.....	xi
List of Publications	xii
Abstract	xiv
Chapter 1.....	1
1.1 Diabetes Mellitus as a growing global problem.....	1
1.1.1 Aetiology of DM.....	1
1.1.2 Epidemiology of DM.....	3
1.1.3 Costs and burden of DM	3
1.2 Management of DM.....	5
1.2.1 Patient education in T2D management	5
1.2.2 Glycaemic control and self-monitoring of blood glucose	6
1.2.3 Lifestyle modifications to manage T2D	8
1.2.4 Pharmacologic approaches to glycaemic control	8
1.2.5 Social-environmental support for T2D self-management	9
1.2.6 Technology for T2D management	9
1.3. Medication adherence in T2D	11
1.3.1 Definition of medication adherence	11
1.3.2 Importance of medication adherence	18
1.3.3 Medication adherence in T2D	19
1.3.4 Factors and challenges to medication adherence	19
1.3.5 Technology to enhance medication adherence	21
1.4 mHealth in chronic disease management.....	22
1.4.1 mHealth evidence for T2D	23
1.4.2 mHealth evidence for medication adherence	25
1.4.3 Unrealised potential of mHealth in chronic disease management.....	27
1.4.4 Theories in mHealth.....	32
1.5 Summary of research gaps	34
1.6 Aim and objectives	36
1.6.1 Aim	37
1.6.2 Objectives	37
1.7 Content of the dissertation	38
Chapter 2.....	41
2.1 The PhD candidate's background	41

2.2 The study context: Singapore.....	42
2.2.1 A brief introduction of Singapore's health system.....	42
2.2.2 DM in Singapore	47
2.2.3 Singapore's emphasis on T2D prevention	48
2.2.4 Singapore's transition to a smart nation	50
2.2.5 Singapore as a suitable setting for health app implementation	50
2.3 Study rationale and research design	51
2.3.1 Rationale for systematic app assessments	52
2.3.2 Rationale for a randomised feasibility trial	53
Chapter 3.....	56
3.1 Motivation of the study	56
3.2 Objectives	57
3.3 Methods	58
3.3.1 Selection of apps	58
3.3.2 Search strategy	59
3.3.3 App screening	59
3.3.4 App assessments.....	60
3.3.5 Data analysis.....	61
3.4 Results.....	66
3.4.1 Proportion of apps by languages	66
3.4.2 Relevance of apps from DM-related search terms to DM self-management	67
3.4.3 Clinical relevance of DM apps	68
3.5 Discussion	71
3.5.1 Perception of health apps influences its adoption	71
3.5.2 Health app recommendations should be incorporated into clinical guidance	72
3.5.3 Populations most in need often do not have access to technology	73
3.5.4 Future directions	74
3.5.5 Limitations	75
3.6 Conclusion	75
Chapter 4.....	79
4.1 Motivation for the study	79
4.2 Objectives	82
4.3 Methods	83
4.3.1 Development of app assessment criteria and diagram	83
4.3.2 Apps selection and assessment	90
4.3.3 Statistical analysis.....	92
Chapter 5.....	94
5.1 Results.....	94
5.1.1 Characteristics of included apps (medication management features)	96
5.1.2 Characteristics of included apps (App-HONcode criteria)	100

5.1.3 Android apps by downloads	104
5.1.4 Additional findings	110
5.2 Discussion	111
5.2.1 Study limitations	116
5.2.2 Implications and future work	118
5.3 Conclusion	119
Chapter 6.....	122
6.1 Motivation for the study	122
6.2 Aim and Objectives	123
6.3 Methods	124
6.3.1 Study design	124
6.3.2 Study setting	125
6.3.3 Participant recruitment and eligibility criteria	125
6.3.4 Study procedures	127
6.3.5 Intervention	128
6.3.6 Study outcomes	131
6.3.7 Sample size.....	134
6.3.8 Randomisation	134
6.3.9 Blinding	135
6.3.10 Data analyses	135
6.3.11 Ethics approval	135
Chapter 7.....	136
7.1 Results.....	136
7.1.1 Recruitment.....	136
7.1.2 Randomisation	138
7.1.3 Outcomes.....	140
7.1.4 Adherence to trial participation	142
7.1.5 Acceptability of the medication management smartphone app	145
7.2 Discussion	147
7.2.1 Observations of the study	149
7.2.2 Participants' feedback	151
7.2.3 Study limitations	152
7.2.4 Implications and future work	155
7.3 Conclusion	155
Chapter 8.....	156
8.1 Discussion of key findings	156
8.1.1 Summary of key findings.....	156
8.1.2 Systematic assessment of apps	159
8.1.3 Effectiveness of apps in T2D self-management	161
8.2 Strengths and limitations	163
8.2.1 Systematic app assessments	163

8.2.2 Feasibility trial	164
8.3 Contributions of the research	167
8.4 Research implications and recommendations	169
8.4.1 Perspective of healthcare providers	169
8.4.2 Perspective of people with diabetes	170
8.4.3 Perspective of app developers.....	171
8.4.4 Perspective of policymakers	172
8.4.5 Perspective of health app researchers	173
8.5 Recommendations for future research	174
8.6 Reflections of the researcher on the research.....	176
8.7 Concluding remarks	177
References	179
Appendices	211
Appendix 1 Additional information on Singapore's health system.....	211
A1.1 Population demographics	211
A1.2 Political philosophy of Singapore's health system.....	211
A1.3 Costs and access to healthcare	212
A1.4 Development of the regional health system (RHS)	214
A1.5 Increased emphasis on primary care	215
Appendix 2 Pre-review app publication checklist.....	217
A2.1 Apple app store.....	217
A2.2 Google Play Store	219
Appendix 3 Smartphones and operating systems for app assessments.....	222
Appendix 4 Checklists for smartphone app feasibility trial	223
A4.1 Consort 2010 checklist for pilot or feasibility trial reporting	223
A4.2 Authors' checklist of mERA guidelines	225
Appendix 5 Feasibility trial recruitment pamphlet	227
Appendix 6 Feasibility trial questionnaires	228
A6.1 ASK-12 questionnaire.....	228
A6.2 Appraisal of diabetes scale.....	229
A6.3 Diabetes Self-Management Questionnaire (DSMQ)	230
A6.4 Intermediate survey (Intervention group only)	231
A6.5 Intervention group final survey	232
A6.6 Control group final survey.....	233
Appendix 7 Sample size estimation for a full trial	234
Appendix 8 Institutional Research Board approval letters	236
A8.1 SingHealth CIRB approval letter.....	236
A8.2 NTU IRB approval letter	238

List of Tables

Table 1.1 Summary of instruments to measure medication adherence	13
Table 3.1 Selected ADA standards mapped with possible diabetes melitus self-management app functions.....	62
Table 4.1 App assessment criteria with the corresponding guidance/evidence extracted from international diabetes and medication management guidelines and literature. This set of assessment criteria focuses on but is not limited to Type 2 diabetes.....	86
Table 4.2 Adapted HONcode (App-HONcode) criteria for health app assessment	89
Table 5.1 Frequency of app features grouped by platform	98
Table 5.2 Profile of app attributes grouped by platform	103
Table 5.3 Profile of medication management app features grouped by downloads (Android apps only).....	105
Table 5.4 Profile of App-HONcode criteria grouped by number of downloads (Android apps only).....	109
Table 7.1 Baseline characteristics of patients included in the analyses	138
Table 7.2 Adjusted mean differences between treatment groups	141
Table 7.3 Perception, attitude and satisfaction of app use in the intervention group.....	146

List of Figures

Figure 1.1 Overview of the PhD study	40
Figure 2.1 Illustration of the private and public proportion in primary care, tertiary care, wellness care and continuing care sectors.	44
Figure 3.1 Number and proportion of diabetes apps suitable for diabetes mellitus (DM) self-management after app description screening	67
Figure 3.2 Proportion of apps relevant to diabetes mellitus (DM) self - management by language.....	68
Figure 3.3 Profile of apps assessed in ten languages against an American Diabetes Association clinical guideline derived checklist.	70
Figure 4.1 Diagram of app features mapped with factors for good medication management practice.....	84
Figure 5.1 Flowchart for app selection	95
Figure 5.2 Number and Proportion of diabetes apps meeting the App-HONcode app criteria.....	101
Figure 6.1 (b) Screenshot of a participant's medication list	130
Figure 6.1 (a) Screenshot of a participant's visual pillbox.....	130
Figure 6.1 (d) Screenshot of a participant's medication adherence	130
Figure 6.1 (c) Screenshot of a participant's medication adherence	130
Figure 6.2 Schedule of outcome measurements	133
Figure 7.1 Diagram of participant flow	137
Figure 7.2 (a) Aggregated weekly medication adherence over 12-weeks, extracted from participants' "Medisafe®" reports	143
Figure 7.2 (b) Weekly medication adherence over 12-weeks of a participant who used an app but was medication non-adherent.....	143
Figure 7.2 (c) Weekly medication adherence of a participant who had intermittent app usage over a period of 12 weeks	144
Figure 7.2 (c) Weekly medication adherence over 12-weeks of a participant who had intermittent app usage.....	144
Figure 7.2 (d) Weekly medication adherence of a participant whose app usage was responsive to the research team's prompts over a period of 12 weeks	144

List of Abbreviations

ADA	American Diabetes Association
ADS	Appraisal of Diabetes Scale
Apps	Mobile applications
ASK-12	Adherence Starts with Knowledge - 12
BCT	Behavioural Change Technique
BMI	Body Mass Index
CGH	Changi General Hospital
CGM	Continuous Glucose Monitoring
DM	Diabetes Mellitus
DSME	Diabetes Self-Management education
DSMQ	Diabetes Self-Management Questionnaire
FDA	Food and Drug Administration
FGM	Flash Glucose Monitoring
FPG	Fasting Plasma Glucose
GP	General Practitioner
GPS	Global Positioning System
HbA1c	Haemoglobin A1c
HBM	Health Belief Model
HITAM	Health Information Technology Acceptance Model
HONcode	Health On the Net code
ICL	Imperial College London
IoT	Internet of things
LEA	Lower extremities amputation
LMIC	Lower- and Middle-Income Country
MEMS	Medication Events Monitoring System
mERA	mHealth evidence reporting and assessment (mERA)
MNT	Medical Nutrition Therapy
MPA	Mobile Phone Appropriation
MRC	Medical Research Council
NHG	National Healthcare Group
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NUHS	National University Health System
OGTT	Oral Glucose Tolerance Test
OHA	Oral Hypoglycaemic Agent
PDA	Personal digital assistant
PPC	Patient-Provider Communication
QOL	Quality of Life
RCT	Randomised Controlled Trial
RHS	Regional Health System
SCT	Social Cognitive Theory
SMBG	Self-monitoring of blood glucose
SMS	Short Messaging Service
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAM	Technology Acceptance Model
TCM	Traditional Chinese Medicine

TPB	Theory of planned behaviour
UK	United Kingdom
USA	United States of America
UTAUT	Unified Theory of Acceptance and Use of Technology
VAS	Visual Analogue Scale
WHO	World Health Organization

List of Definitions

App market (or app store(s)) refers to a single or multiple digital distribution platforms for smartphone applications. This definition covers various digital distribution platforms in this thesis.

Complex intervention was defined by the UK Medical Research Council as interventions that contain several interacting components but have characteristics that evaluators should consider.

Diabetes apps refer to smartphone apps that can assist the user in performing diabetes self-care activities. Many features of diabetes apps are applicable to people with all types of diabetes. Therefore, this definition largely refers to but is not confined to apps that can assist people with the self-management of T2D in this thesis.

Internet of things is the extension of internet connectivity to physical devices and everyday objects, such as the integration of hardware, electronics, and internet connectivity. This concept was discussed in this thesis.

Mandarin is a form of the Chinese Language. It is used interchangeably with the Chinese Language in this thesis.

Medication adherence refers to the extent to which a person's medication-taking behaviour corresponds to an agreed recommendation from a healthcare provider. A broader definition of medication adherence depending on the measurement instrument was used in this thesis. An 80% cut-off value is used as an objective measure when needed.

mHealth is defined by the World Health Organization as a component of eHealth (electronic health) where medical or public health practices are supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices. Smartphone health apps are part of mHealth.

A systematic app assessment is a method developed for the studies described in this thesis. It is the adaptation of systematic review methodology for the assessment of the content and quality of smartphone health apps.

Type 2 diabetes is an adult-onset long-term metabolic disorder characterised by high blood glucose resulting from insulin resistance, a lack of insulin, or both. It constitutes 95% of diabetes cases and represents a growing prevalence worldwide. This thesis focused on Type 2 diabetes.

List of Publications

Published papers relevant to the thesis

Car J, Tan WS, **Huang Z**, Sloot P, Franklin BD. eHealth in the future of medications management: personalisation, monitoring and adherence. BMC Medicine [Internet]. 2017 2017/04/05; 15(1):[73 p.]. Available from: <https://doi.org/10.1186/s12916-017-0838-0>.

Huang Z, Soljak M, Boehm BO, Car J. Clinical relevance of smartphone apps for diabetes management: A global overview. Diabetes/Metabolism Research and Reviews [Internet]. 2018. Available from: <https://doi.org/10.1002/dmrr.2990>.

Lum E, Jimenez G, **Huang Z**, Thai L, Semwal M, Boehm BO, et al. Decision Support and Alerts of Apps for Self-management of Blood Glucose for Type 2 Diabetes. JAMA [Internet]. 2019; 321(15):[1530-2 pp.]. Available from: <https://doi.org/10.1001/jama.2019.1644>.

Huang Z, Lum E, Jimenez G, Semwal M, Sloot P, Car J. Medication management support in diabetes: a systematic assessment of diabetes self-management apps. BMC Medicine [Internet]. 2019/07/17; 17(1):[127 p.]. Available from: <https://doi.org/10.1186/s12916-019-1362-1>.

Huang Z, Tan E, Lum E, Sloot P, Boehm B, Car J. A Smartphone App to Improve Medication Adherence in Patients With Type 2 Diabetes in Asia: Feasibility Randomized Controlled Trial. JMIR Mhealth Uhealth [Internet]. 2019;7(9): e14914. Available from: <https://mhealth.jmir.org/2019/9/e14914/>

Lum E, Jimenez G, **Huang Z**, Thai L, Car J. Appropriateness of hypoglycaemia and hyperglycaemia in type 2 diabetes self-management apps. Diabetes/Metabolism Research and Reviews [Internet]. 2019. Available from: <https://doi.org/10.1002/dmrr.3235>

Jimenez G, Lum E, **Huang Z**, Theng YL, Boehm B, Car J. Reminders for medication adherence in Type 2 Diabetes management apps. J Pharm Pract Res. [Internet]. 2020;50(1):78-81. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/jppr.1595>

Huang Z, Lum E, Car J. Medication management apps for diabetes: Systematic assessment of the transparency and reliability of health information dissemination. JMIR Mhealth Uhealth. [Internet]. 2020;8(2):e15364. Available from: <https://mhealth.jmir.org/2020/2/e15364/>

Other published papers

Huang Z, Semwal M, Lee SY, Tee M, Ong W, Tan WS, et al. Digital Health Professions Education on Diabetes Management: Systematic Review by the Digital Health Education Collaboration. J Med Internet Res [Internet]. 2019; 21(2):[e12997 p.]. Available from: <http://www.jmir.org/2019/2/e12997/>.

Poster presentations

Huang Z, Soljak M, Boehm B, Car J. A global overview of smartphone apps for people with diabetes. 17th Annual Diabetes Technology Meeting, Maryland, Bethesda, United States [Poster presentation] [Dated 3rd November 2017].

Huang Z, Lum E, Car J. Systematic assessment of the quality of health information dissemination of smartphone apps targeted at people with diabetes for medicines management. 5th SingHealth Duke-NUS scientific congress, Singapore [Short-listed for poster competition] [Dated 21st October 2018].

Abstract

Type 2 diabetes (T2D) is a growing public health problem for many countries. Smartphone apps are increasingly used to assist in T2D self-management due to their convenience, ubiquity, and emerging positive evidence. Currently, the rate of diabetes apps production far outpaces their adoption. There is a lack of evidence on the quality, utility, and clinical relevance of health apps and whether these apps meet the users' needs.

This dissertation investigated the quality and clinical relevance of apps for diabetes mellitus (DM) management through three sub-studies: (1) An assessment of the clinical relevance of DM self-management apps in ten languages of countries with the highest prevalence of diabetes; (2) a systematic assessment of the medication management features of apps for people with T2D against its (i) congruence with international diabetes and medication management guidelines, and (ii) the quality of health information disseminated; and (3) a pilot assessing the feasibility and impact of a smartphone app in improving medication adherence in people with T2D in Singapore.

The global assessment of DM self-management apps showed that apps in English and Mandarin dominated the app market. Although highly downloaded apps had more clinically relevant app features, they still lacked important features for DM self-management, such as information provision, physical activity tracking, diet modification, medication management, and risk reduction strategies.

Next, the systematic assessment of the medication management features of apps for people with T2D identified essential gaps in (i) app features for enhancing medication adherence and safety, such as the ability to enter medication-taking instructions, and (ii) variable adherence to the transparency and reliability of health information disseminated via these apps. Finally, the feasibility pilot showed that a smartphone app intervention for (self-reported) medication non-adherent T2D patients was acceptable, improved awareness of medication adherence, and reduced self-reported barriers to medication adherence.

Access to high-quality diabetes apps is unequal across populations. Apart from English and Mandarin DM apps, those in other major languages lacked comprehensive features for self-management. Of concern is the paucity of medication management features in T2D apps elicited via the in-depth assessment. The assessment criteria from this research could be used as a checklist for app development and selection for usage to raise the standard of future DM apps. A good app should possess essential evidence-based features, safeguard data privacy and security, disseminate accurate and high-quality content, and be easy to use.

Chapter 1

Introduction

This chapter provides background information pertinent to the thesis and outlines the structure of the thesis. The chapter is structured using a funnel approach. The aetiology, epidemiology, and magnitude of the problem of diabetes mellitus (DM) are first introduced, followed by a description of evidence-based guidelines for Type 2 diabetes (T2D) management. Type 2 diabetes management is narrowed to focus on medication adherence because it is an important self-care behaviour. mHealth is next introduced as a potential tool for the management of T2D, followed by a discussion of the challenges and gaps of mHealth implementation in T2D management. A summary of the research gaps and the aim and objectives of the thesis are then presented. This chapter ends with an outline of the structure of the thesis.

1.1 Diabetes Mellitus as a growing global problem

The term “diabetes” has gained prominence over the last two decades in the literature and among health policy planners, researchers, and the general population. It represents a growing problem worldwide due to the large increase in the number of people with diabetes mellitus (DM)¹. This global epidemic is a significant public health problem that challenges the economy and health system of many countries²⁻⁴.

1.1.1 Aetiology of DM

Diabetes mellitus is a long-term metabolic disorder characterised by high blood glucose resulting from insulin resistance, lack of insulin or both. The disease can currently be classified into four categories: Type 1, Type 2, gestational, and other specific types of diabetes⁵. New classifications may emerge as research on DM progresses; a recent study proposed classifying DM into five subgroups according to disease progression and risk of DM-related complications⁶.

Type 2 diabetes (T2D), also known as adult-onset diabetes, represents 90–95% of the population with DM⁵. The focus of this thesis will be on T2D due to its large proportion amongst people with DM. Unlike gestational or Type 1 diabetes (T1D), T2D can be managed with behavioural and lifestyle modifications to achieve good glycaemic (or blood glucose) control^{7, 8}. Good glycaemic control reduces the risk of microvascular complications such as retinopathy (leading to blindness), renal failure (kidney failure) and neuropathy (leading to nerve damage and amputation), and macrovascular complications such as cardiovascular diseases (leading to stroke and heart attack)^{9, 10}.

Approximately a third of T2D cases are undiagnosed as their early stages are asymptomatic¹¹. Common symptoms include increased hunger and thirst, dry mouth, frequent urination and infections, fatigue, blurred vision, headaches, tingling, pain or numbness in the hands and feet, and slow healing wounds and cuts^{2, 12}. Suspected T2D cases should be tested in a healthcare setting.

Three types of tests can be used to test for the onset of T2D⁸. The glycated haemoglobin (HbA1c) is an indirect indicator that measures the 3-month non-fasting average blood glucose of the patient. A HbA1c value above or equal to 6.5% indicates the presence of DM. The Fasting Plasma Glucose (FPG) test checks the 8-hour fasting blood glucose levels of the patient. Type 2 diabetes is diagnosed with a reading higher than or equal to 7 mmol/L or 126 mg/dl. The Oral Glucose Tolerance Test (OGTT) checks the patient's blood glucose levels before and 2 hours after ingesting a solution containing 75 grams of glucose. This test determines the way the body processes sugar and T2D is diagnosed with a reading higher than or equal to 11mmol/L or 200mg/dl. Two of the above three tests are usually conducted to diagnose a patient with T2D⁸.

A patient diagnosed with T2D will need to make substantial lifestyle changes to maintain blood glucose levels within a healthy range^{13, 14}. Unfortunately, T2D cannot be cured but can be managed with medications and healthy lifestyle habits. Good T2D care which delays the onset of complications, can increase patients' life expectancy¹⁵.

1.1.2 Epidemiology of DM

The current prevalence of DM is approximately 9% worldwide^{2, 16}. According to the 2017 estimates from the International Diabetes Federation, 425 million adults aged 20 – 75 have DM, and three out of four of these adults are people of working age². This number was a 42% increase from 10 years ago and is expected to increase by 50% in the next 25 years if the trend continues². The prevalence of DM is higher in males (9.1%) than in females (8.4%), and highest within the 65 – 79 age group^{2, 16}.

The prevalence of DM is unevenly distributed across geographical regions. Approximately 79% of people with DM live in lower-and middle-income countries (LMICs)². Countries with large populations also have more people with DM. China has the highest number of people with DM, followed by India and the United States of America (USA)². The global estimates did not break down the number of people with different types of DM and its associated costs but mentioned that T2D accounted for approximately 90% of DM cases.

The most significant contributors to the increase in the number of people with T2D worldwide² are population growth and an ageing population. However, the increase in T2D prevalence outstrips the rate of ageing, which means that people are getting diagnosed with T2D at a younger age and living with T2D with extended periods of time¹⁷⁻¹⁹. This phenomenon is partly attributed to urbanisation induced sedentary lifestyles and nutrition-poor diets, which led to an increase in the prevalence of obesity, a significant cause of T2D^{18, 20, 21}.

1.1.3 Costs and burden of DM

Diabetes mellitus is a costly disease. It is costly not only to individuals but also to their families, the health system and the economy. A large collaborative study estimated the 2014 global direct cost of DM to be at Intl\$825 billion^a, with China, USA and India as the most significant contributors to this cost¹⁶. Direct cost refers to

^a Costs were converted to international dollars (Intl) and adjusted to 2011 values.

the expenses incurred from inpatient and outpatient treatment of the disease, while indirect cost refers to reduced productivity attributed to ill-health and disability. For example, the American Diabetes Association (ADA) estimated the cost of diagnosed DM in the USA to be \$327 billion in 2017. Of this amount, \$237 billion was attributed to direct medical costs and \$90 billion was associated with indirect costs in the form of reduced productivity²². In the United Kingdom (UK), T2D care accounted for at least 5% of healthcare expenditure and up to 10% of the National Health Service (NHS) expenditure in 2013²³.

Healthcare resources are finite. The increased use of inpatient and outpatient services strains the health system². When more healthcare resources are spent on T2D treatment, less will be available for other medical conditions²⁵. Many countries dealing with an ageing population are also grappling with the problem of T2D²⁴⁻²⁶. Life expectancy increased by 30 years in the 20th century in Western Europe, North America, Australia, New Zealand and Japan. Longer life expectancy in these high-income countries increases the prevalence of chronic diseases such as T2D and hypertension, which in turn places greater pressure on healthcare expenditure²⁵. An estimate in 2013 measuring the prevalence of T2D in 216 countries showed that 74% and 41% of people with T2D residing in high- and low-income countries are over the age of 50²⁶. Although low-income countries (mainly in the African region) have a younger profile of people with T2D, these countries face the double burden of infectious disease and growing prevalence of T2D and may be unprepared to manage a large number of people with T2D in the next two decades²⁷. The case of Singapore—a country grappling with an ageing population and increasing prevalence of T2D—will be elaborated on in Section 2.2.

Living with T2D causes tremendous stress to patients and their family members. Long term lifestyle changes, such as remembering to take medication or adjusting personal diets, need to be made to cope with T2D. Complications that arise from poorly managed T2D lead to a decrease in quality of life (QOL) and loss in work productivity^{28, 29}. The decline in or inability to work, coupled with high medical cost increases the emotional and financial burden to the individual and family. These

problems are more prominent in LMICs than high income countries, where high out-of-pocket healthcare costs can result in financial hardship for the family¹⁶.

The economic cost of DM is expected to increase with the increasing prevalence of T2D worldwide^{2, 30, 31}. It is, therefore, necessary to manage the cost of DM by preventing or slowing the progression of T2D.

1.2 Management of DM

Diabetes mellitus is a chronic disease that requires long term management. Evidence-based guidelines are essential in providing clinicians with best practice recommendations³². This section describes selected recommended practices of T2D management with reference to guidelines from the ADA and UK National Institute for Health and Care Excellence (NICE), as well as the outcomes of large DM studies^{33, 34}. The management of complications, pregnant or older adults, obesity, and psychosocial issues will not be discussed in this thesis.

1.2.1 Patient education in T2D management

Patient education is an integral part of DM management, as it helps in improving understanding, achieving shared decision-making, enhancing treatment adherence and encouraging self-management³⁵. Diabetes Self-Management Education (DSME) and support should be ongoing to help people with DM maintain effective self-management throughout their lifetime, as they face challenges and undergo new treatments that emerge along the way³⁶. DSME has been associated with improved knowledge on DM³⁵, better glycaemic control³⁷, lower self-reported weight³⁸ and improved QOL^{39, 40}. A Hong Kong study comparing the presence and absence of DSME among people with T2D showed that the DSME group had significantly higher HbA1c reduction (-0.2%) and body weight loss (-1.19kg) within three months⁴¹. Another retrospective analysis of T2D patients attending an accredited ADA center in the US found that DSME patients had a 1.5 fold improvement in their

T2D bundle (retinal eye exam, nephropathy screening, blood pressure <140/90 mmHg, LDL <100 mg/dL, and HbA1c <8.0%) and 2.8 fold decline in HbA1c compared with those without DSME³⁹. A meta-analysis also showed a positive effect size of 0.28 in the QOL of people with T2D who received DSME compared with people without DSME⁴⁰.

NICE recommends a structured education for T2D patients and their family members or carers during annual reviews⁴². The ADA also stresses the importance of ongoing patient self-management education to prevent acute complications and reduce long-term complications⁴³. Lifelong self-management education is necessary to help patients to follow-up with advances in treatment and cope with new challenges.

A core component of DSME is patient-centredness. Education should focus on the preferences, needs, and values of each patient^{36, 42}. It should also integrate with the rest of the care pathway to ensure consistency. The education content should be evidence-based, theory-driven and tailored to patients' needs⁴². Resources should also be dedicated to supporting and training educators to ensure the quality and relevance of their skills^{36, 42}.

1.2.2 Glycaemic control and self-monitoring of blood glucose

Good glycaemic control is vital in delaying T2D related macro- and microvascular complications.

Glycaemic targets

Large trials have shown that achieving HbA1c targets of <7.0% (<8.6mmol/L) reduces microvascular complications of T2D, especially for patients improving from very poor to fair/good HbA1c control. A reduction of HbA1c to 6.0% (7.0mmol/L) further reduces microvascular complications despite smaller effects^{33, 44}. Glycaemic targets are individualised to different population groups. The ADA recommends more stringent HbA1c control for patients who are newly diagnosed, younger,

without comorbidities or vascular complications, highly motivated to be adherent to self-care, and have adequate resources and support to manage hyperglycaemia⁴⁵.

NICE recommends supporting adults with T2D through the management of a combination of lifestyle, diet, and/or a single type of medication without associations with hypoglycaemia, to aim for a HbA1c level of 6.5% (7.8mmol/L). Adults on drugs associated with hypoglycaemia risk should aim for a HbA1c level of 7.0% (8.6mmol/L). The target for HbA1c can be 7.5% (9.4mmol/L) or higher for HbA1c levels that cannot be adequately controlled by a single medication, or adjusted on a case-by-case basis for people who are older, frail or unlikely to achieve longer-term risk-reduction benefits. Patients should be involved in decisions and encouraged to maintain their individual HbA1c target if efforts to achieve their target do not cause adverse effects (e.g. hypoglycaemia) or greatly impair their QOL²³.

Recommended frequency of HbA1c testing

Both ADA and NICE recommend HbA1c testing every quarter (or intervals of 3-6 months, tailored to individual needs) for patients who are changing to or starting a new T2D therapy. Adults with T2D who have stable glycaemic control are recommended to have their HbA1c levels tested at least twice annually (6-monthly)^{23, 45}.

Self-monitoring of blood glucose (SMBG)

Self-monitoring of blood glucose (SMBG) is an integral part of T2D management as it allows patients to evaluate their own body's response to the therapy relative to set goals/targets. SMBG is essential for patients on insulin²³. The importance of SMBG for patients who are not on insulin is questioned, although evidence has shown that SMBG can reduce the HbA1c level of these patients by 0.25–0.3% in the short-term (6 months)³⁴.

1.2.3 Lifestyle modifications to manage T2D

Lifestyle modification is essential for the majority of people with newly diagnosed T2D to achieve optimal glycaemic targets. Lifestyle management includes nutritional therapy, physical activity, smoking cessation counselling and psychosocial care³⁶. Overweight T2D adults should aim for an initial body weight loss of 5 –10%, although a lower degree of weight loss may still be beneficial²³. These topics are usually covered during DSME sessions and reviewed annually according to individual needs. Lifestyle modification interventions were found to significantly reduce mean values of fasting blood glucose by -11.5 mg/dl (95% CI -22.4 to -0.6), waist circumference by -2.7 cm (95% CI -4.6 to -0.9), Systolic Blood Pressure by -6.4 mmHg (95% CI -9.7 to -3.2), Diastolic Blood Pressure by -3.3 mmHg (95% CI -5.2 to -1.4), and triglycerides by -12.0 mg/dl (95% CI -22.2 to -1.7)⁴⁶.

1.2.4 Pharmacologic approaches to glycaemic control

Newly diagnosed T2D patients usually require medication to lower their glycaemic levels while adjusting to lifestyle changes. Metformin is recommended by both the ADA and NICE as a first-line pharmacologic treatment of T2D^{23, 47}. Advice about diet, lifestyle and adherence to medications should be reinforced to the patient to aim for a HbA1c level of 7.0% (8.6mmol/L). Pharmacotherapy should be intensified if the HbA1c levels are inadequately controlled (HbA1c rises to 7.5% (9.4mmol/L)) by a single type of medication. A combination of two non-insulin blood glucose-lowering therapies should be offered as the first treatment intensification strategy. Further treatment intensification strategies will include a combination of three non-insulin blood glucose-lowering therapies or any treatment combination containing insulin^{23, 47}.

Pharmacotherapy should be tailored to the individual's needs and clinical circumstances. The presence of comorbidities, risks from polypharmacy, long-term benefits of pharmacotherapy on the individual, and the cost of the medication are considerations for formulating a medication treatment plan. Prescribers should follow

relevant professional guidance and take full responsibility for treatment decisions made while patients should provide informed consent which should be documented²³.

1.2.5 Social-environmental support for T2D self-management

Interventions and guidelines on T2D self-management have tended to focus on individual-centric approaches for self-care. Although individual responsibility is essential in T2D self-management, there is a need to examine the broader social context that shapes behaviours, practices and the roles members fulfil in a collective network⁴⁸. The social cognitive theory (SCT) supports the consideration of the social context, where personal factors (personal beliefs and cognition) and environmental factors (physical and social) interact to influence behaviour, which in turn influences the thoughts and actions of the individual^{49, 50}.

As illustrated by the SCT, the efficacy in self-management occurs in a context that includes the formal healthcare providers, informal social network and physical environment of the individual⁴⁹. For example, a supportive spouse may foster healthier living by encouraging a healthier diet and regular exercise. Friends may also encourage an individual to partake in social events that improve the mental well-being of the individual. Reviews have shown that greater social support was associated with better T2D self-management in the USA, Europe, South America and Asia⁵¹⁻⁵⁴. The level of help and support received from the social network can improve an individual's psychological well-being, which in turn, motivates efficacy in T2D self-management.

1.2.6 Technology for T2D management

Technology has become a useful tool for patients and their healthcare providers in T2D management. Patients can keep in closer contact with their healthcare providers without additional clinic visits, and healthcare providers can obtain granular, real-

time patient information instead of relying on patients' recount every three to six months^{55, 56}.

Several types of digital tools have been used for T2D management. Telecommunication technologies were used to educate, monitor and support healthcare delivery remotely⁵⁷. Also known as telehealth, these technologies range from telephone calls, video consultations, and interactive online quizzes to health measurement devices that can transmit health data automatically⁵⁸⁻⁶⁰. A systematic review found that T2D patients receiving home telehealth had better glycaemic control and a reduced number of hospitalisations and bed days of care compared with patients receiving usual care⁵⁹.

Smartphone apps have changed conventional healthcare delivery by enabling the integration of day-to-day living with T2D management. Apps designed for T2D management have many features such as goal setting, organisation, reminders, and monitoring to ease patients' burden in making lifestyle adjustments for T2D management⁶¹. The evidence on the effectiveness of smartphone apps for T2D management is increasing in recent years as more studies (e.g. feasibility studies; randomised controlled trials) emerge in the literature^{62, 63} (Refer to section 1.4.1 for a more thorough discussion on the evidence of mHealth for T2D).

Digital glucose monitoring devices have enabled granular data to be collected for better monitoring and decision support. For example, devices that support continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) reduce the inconvenience for patients by eliminating the need for repeated testing of their blood glucose levels⁶⁴⁻⁶⁶. These devices and insulin pens can also be linked to smartphone apps for better data management^{67, 68}. A meta-analysis showed that the use of CGM, compared with a control group, resulted in a significant 0.20% (95% confidence interval [CI] -0.31 to -0.09) reduction in HbA1c. No significant results were observed from the use of FGM, therefore, the effectiveness of FGM cannot be established due to a lack of studies⁶⁹.

The evidence for the use of technology in T2D management will be discussed further in section 1.4.1.

1.3. Medication adherence in T2D

Medication adherence is an important self-care behaviour for patients with T2D. This section introduces the concepts of medication adherence, its challenges, and recent technological advancements to tackle this problem.

1.3.1 Definition of medication adherence

Medication adherence is broadly defined as the extent to which patients take their medication as prescribed⁷⁰. The World Health Organization (WHO) defined adherence to long term therapies as “the extent to which a person’s behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider”⁷¹. Therefore, medication adherence can be interpreted as “the extent to which a person’s medication-taking behaviour corresponds to the agreed recommendation from a healthcare provider” when taking both statements into account.

The terms “adherence” and “compliance” should not be confused with each other, although they are sometimes used interchangeably in medication adherence studies⁷¹. “Adherence” requires agreement on the part of the patient while “compliant” implies that the patient follows the healthcare provider’s recommendations regardless of whether they agree⁷¹⁻⁷³. Another term less commonly seen is “persistence”, defined as either the mean number of days treatment was discontinued or the proportion of patients who remained on the treatment for a period of time⁷².

Medication adherence can be measured through self-reported questionnaires, biomarkers, medication gaps, pill counts, pharmacy refill records, and medication events monitoring system (MEMS). MEMS can monitor patients electronically in

real-time via a chip on the cap of the medication bottle and is currently defined by the WHO as the gold standard for measuring medication adherence^{70, 74, 75}. Liquid chromatography using routine urine samples was recently found to be a more objective measure of medication adherence in T2D patients, but the efficacy of this diagnostic tool remains unknown in larger populations⁷⁶. Each method of measurement comes with its advantages and disadvantages and leads to different medication adherence estimations⁷⁵. A summary of the instruments for measuring medication adherence, their advantages, disadvantages and suitability for different types of research is shown in Table 1.1 below.

An 80% cut-off value is generally used with an objective measure to determine medication non-adherence^{70, 77-79}. Medication non-adherence includes failing to fill or refill a prescription, premature discontinuation of therapy, taking less than required and taking the dose at the wrong time⁸⁰. Non-adherence can also include overdosing as it increases the risk of adverse events and mortality⁷⁸. It is therefore acceptable to define medication adherence as having taken between 80 – 120% of the recommended dose^{79, 81}.

Medication “adherence” instead of “compliance” is used in this thesis, as the pharmacological treatment for T2D is often an agreement between the patient and the doctor. I adopted a broader definition of medication adherence depending on the measurement instrument and used an 80% cut-off when an objective measure was required for a feasibility trial study (elaborated on in Chapters 6 and 7).

Table 1.1 Summary of instruments to measure medication adherence

Instrument	Description	Advantages	Disadvantages	Type of research
Biological measures	Measurement of drug or its metabolic concentration from body fluids such as blood, urine or a biomarker.	<ul style="list-style-type: none"> Provides physical evidence Considered “Accurate” 	<ul style="list-style-type: none"> Whitecoat adherence Unsuitable for multi-drug regimes Intrusive, pressure and anxiety for patients Problems with drug metabolism and quantification Does not reveal the cause of non-adherence Expensive and manpower-intensive Interactions with food/other drugs 	<ul style="list-style-type: none"> Single-dose treatment Intermittent administration Laboratory research on drugs
Direct observation	Directly observing patients' medication-taking behaviour			<ul style="list-style-type: none"> Hospitalised patients
Secondary database	<p>Patterns derived from electronic prescription services or pharmacy insurance claims. Analyses include:</p> <ol style="list-style-type: none"> 1. Medication possession ratio 2. Dichotomous variable 3. Continuous, multiple/single interval measures of medication acquisition 4. Continuous, multiple/single interval measures of medication gaps 	<ul style="list-style-type: none"> Allows analysis of a large population Data can be verified by insurance or prescription managers 	<ul style="list-style-type: none"> Assumes medication was taken as prescribed Arbitrary measure (Not as “Accurate”) Requires consistency across providers Able to assess multi-drug adherence 	<ul style="list-style-type: none"> Health services research Analysis of a large population

Medication events monitoring system (MEMS)	A “chip” or microprocessor on the container measures the time and date when the container is opened, assuming that the patient takes the medication	<ul style="list-style-type: none"> • Considered as a “gold standard” by WHO • Helps to identify medicines-taking behaviour • Less tendency to “cheat” as pillbox needs to be opened • Can be used to validate other medication adherence methods 	<ul style="list-style-type: none"> • Very expensive • No assurance that medication is taken • Bulkiness of container • Anxiety that the patient is under surveillance • Need to ensure correct usage of the MEMS • Danger of equipment loss • Patients can transfer medication 	<ul style="list-style-type: none"> • Health services research • Medication adherence in outpatient settings • Small studies • Clinical trials
Pill count	Count remaining pills brought by patients or to turn up at patients’ house unexpectedly to count pills	<ul style="list-style-type: none"> • Low-cost • Simple • Can be used for multiple variables • More accurate than subjective methods 	<ul style="list-style-type: none"> • Underestimation due to surplus medication • Discrepancy when comparing with other methods of adherence (equation) • Does not guarantee correct dosing regime • Unable to inform adherence patterns and identify causes • Intrusive for unexpected pill count method 	<ul style="list-style-type: none"> • Health services research • Medication adherence in outpatient settings • For PRN medications
Self-reported questionnaires	Patients are asked to answer (semi-)structured questions regarding their recent/past medication-taking behaviour	<ul style="list-style-type: none"> • Able to conduct online • Simple and low-cost • Availability of validated tools 	<ul style="list-style-type: none"> • Poor sensitivity and specificity (false data input) • Patients’ psychological state affects accuracy • Recall bias 	<ul style="list-style-type: none"> • Health services research • Medication adherence in outpatient settings • For a wide range of medication

	<p>Morisky Medication adherence scale (MMAS-8) - This was developed to incorporate an assessment of medication-taking behaviours. The first seven items are Yes/No responses while the last item is a 5-point Likert response.</p>	<ul style="list-style-type: none"> • High sensitivity (93%) and moderate specificity (53%) • Reliable and validated in a broad range of chronic diseases • Validated in Singapore population (Warfarin) 	<ul style="list-style-type: none"> • Patients' psychological state affects accuracy • Recall bias • Expensive due to copyright issues 	<ul style="list-style-type: none"> • Research • Screening tool for validated conditions in a clinical setting
	<p>Brief medication questionnaire – consists of a 5-item Regime screen, a 2-item Belief screen, and a 2-item Recall screen.</p>	<ul style="list-style-type: none"> • Able to evaluate multi-drug regimen • Able to assess behaviour and beliefs 	<ul style="list-style-type: none"> • May be time-consuming as patients' prescribed regime should be assessed first • More complicated to assess compared to other instruments 	<ul style="list-style-type: none"> • Suggested for diabetes and depression management
	<p>Hill-Bone Compliance scale - 3 subscales, medication-taking behaviour, ability to keep an appointment, and sodium intake, rated on a four-point Likert-type scale</p>	<ul style="list-style-type: none"> • Culturally sensitive and high internal consistency 	<ul style="list-style-type: none"> • Limited generalizability 	<ul style="list-style-type: none"> • Specific to black populations with anti-hypertensive drugs
	<p>Medication Adherence Questionnaire (MAQ) – also known as the 4-item Morisky Medication Adherence Scale</p>	<ul style="list-style-type: none"> • Quick to administer and score • Able to identify barriers to adherence • Validated in a broad range of diseases • High sensitivity (81%) 	<ul style="list-style-type: none"> • Poorer psychometric properties compared to MMAS-8 	<ul style="list-style-type: none"> • Widely used in research

	<p>Medication adherence Report scale (MARS) – It is a combination of the Drug Attitude Inventory survey and MAQ. 10 questions with a simple scoring to evaluate patient's adherence behaviour, attitude towards medication, and general disease control during the past week</p>	<ul style="list-style-type: none"> Assesses both beliefs and barriers to medication adherence Higher validity and reliability (than DAI or MAQ) 	<ul style="list-style-type: none"> Unclear internal validity 	<ul style="list-style-type: none"> For psychoactive medicines. First designed for schizophrenic patients
Clinician assessment	<p>Metrics used by the clinicians to assess patients' medication adherence. They include:</p> <ol style="list-style-type: none"> Clinician Rating Scale (CRS) - An ordinal scale of 1–7 to quantify the clinician's assessment of the level of adherence shown by the patient Brief adherence rating scale (BARS) – three questions about the patient's knowledge of their own medication regimen and episodes of missed medication. A visual analogue scale rating by the clinician is the key measure of adherence provided by the BARS 	<ul style="list-style-type: none"> Easy and low-cost to administer Time-saving BARS have good sensitivity (73%) and specificity (74%) 	<ul style="list-style-type: none"> Subjected to only the clinician's impression CRS may not be sensitive to actual compliance BARS has not been examined in a non-psychotic psychiatric condition 	<ul style="list-style-type: none"> CRS measures outcomes of patients receiving compliance therapy BARS – currently only valid for psychiatric conditions

	3. Medicines assessment compliance tool – Yes/No questions to judge how well a patient is able to follow their medication regimen correctly			
Patient kept diaries	Patient records their day-to-day medication-taking regime	<ul style="list-style-type: none"> • First-hand account • Low-cost and simple 	<ul style="list-style-type: none"> • Common to over-report • False entries/Patient does not return the diary • Can be unreliable 	<ul style="list-style-type: none"> • Routine clinical practice • Cognitively sound patients • Encourage consistent behaviour with incentives
Patient interviews	<p>Patients are asked to estimate their medication-taking behaviour or probed on their knowledge on their prescribed medication regimen before health care professionals make an estimate.</p> <p>Alternatively, a motivational interview can be combined with other measures</p>	<ul style="list-style-type: none"> • Convenient to conduct • Able to discover reasons for medication non-adherence 	<ul style="list-style-type: none"> • Patients' psychological state affects accuracy • Recall bias • Social desirability problem • Tedious, can only interview small numbers 	<ul style="list-style-type: none"> • Routine clinical practice • Behavioural change can be used for research • Interviewer needs to be trained
Triangulation	Using multiple methods to increase the validity of the measure			<ul style="list-style-type: none"> • For research on medication adherence

Table 1.1 shows a summary of available instruments for measuring medication adherence. The advantages, disadvantages and suitability of the instrument for different types of research are also listed in the table⁸²⁻⁸⁵.

1.3.2 Importance of medication adherence

Proper medication management (including medication safety) includes taking the correct dose of medication(s) within an appropriate interval, or as directed by a healthcare professional⁸⁶. Knowledge of patients' medication adherence is also necessary for clinicians, as unsatisfactory treatment outcomes caused by medication non-adherence may mislead clinicians to increase the medication dosage, which is undesirable for the patient⁷³. Studies have shown the importance of adhering to one's medication for the treatment of a temporary condition and long-term well-being⁸⁷⁻⁸⁹.

Poor medication adherence can lead to inadequate blood glucose control in people with T2D, which leads to higher medical costs, higher use of healthcare resources and increased mortality⁹⁰⁻⁹². For example, T2D patients with poor medication adherence have a higher risk of developing both acute and chronic-related complications (due to inferior glycaemic control)⁹³ compared with fully adherent patients in the long term⁸². Complications resulting from T2D not only decreases the QOL of the patient in terms of decreased work productivity but also leads to a higher cost to society and the health system with increased hospitalisation and emergency department visits⁸². The 2012 US National Health and Wellness Survey found a significant 0.21% increase in HbA1c for every one-point decrease in medication adherence to basal insulin in the Morisky Medication adherence scale. Each point of non-adherence also led to a 4.6%, 20.4%, and 20.9% increase in the number of physician visits, emergency room visits, and hospitalisations⁹⁰.

Non-adherence to anti-diabetic agents was associated with markedly higher mortality in people with T2D. A large retrospective UK study (n = 15,984) on people with T2D found that medication non-adherence and missed clinical appointments were each independently associated with a significant ($P < 0.001$) 1.6 fold increase in all-cause mortality⁹¹. Another US retrospective cohort study (n = 11532) on people with DM similarly found a significant ($P < 0.001$) increase in the odds of all-cause hospitalisation (odds ratio: 1.6) and all-cause mortality (odds ratio: 1.8) among medication non-adherent patients⁹².

Improving medication adherence can provide overall cost savings if the cost of intervention does not exceed the cost of medication non-adherence^{94, 95}. It is therefore essential to understand the factors for non-adherence and continuously explore innovative solutions to improve medication adherence, especially for long-term conditions⁷⁸.

1.3.3 Medication adherence in T2D

A third to half of the medications prescribed for chronic diseases were not taken as required⁷¹. Medication adherence rates are usually higher for short-term (acute) treatments compared with long-term (chronic) treatments⁹⁶. Patients with asymptomatic chronic conditions are also less likely to adhere to their medications if the gravity of the condition is not recognised.

Many people with T2D are not fully adherent to their medications. A systematic review found the overall adherence rate among T2D patients to be 36–93% (retrospective studies) and 67–85% (prospective studies) for oral hypoglycaemic agents (OHA), and 63–80% for insulin use⁷³. The variation in medication adherence rates can be attributed to differences in study design and methods for measuring medication adherence. Although the systematic review was conducted more than a decade ago, medication adherence rates among T2D patients did not improve over the years⁷⁹.

1.3.4 Factors and challenges to medication adherence

Poor adherence to medication is a multi-dimensional problem, including factors ranging from demographic, socioeconomic, therapy, condition, healthcare provider to health system-related factors⁷¹. Medication non-adherence is complex and dynamic as adherence status may change according to patients' circumstances over time. For example, reviews have found that older patients have better adherence to medication^{81, 97}, but a systematic review on oral anti-cancer medications found much

older (≥ 85 years) and younger patients (≤ 45 years) to be less adherent to their medication regimen⁹⁸. Long treatment duration decreases adherence, but patients who have chronic illnesses for a long time have better adherence when they come to accept their illness⁸¹.

Medication non-adherence can also be classified as intentional or unintentional. Unintentional non-adherence is a “passive process whereby patients fail to adhere to prescribed instructions through forgetfulness, carelessness, or circumstances out of their control”⁹⁹. In these instances, patients may not be able to obtain a pharmacy refill due to disability or a lack of time, confused about their medication regimen, or are cognitively impaired^{81, 100}. At some point in time, most patients would have unintentionally forgotten to take their medications or misunderstood medication-taking instructions. These factors could be addressed with simpler care regimens and more effective patient-provider communication. Studies have shown better medication adherence in T2D patients who have less frequent dosing requirements, simpler care regimens and better provider-patient communication^{89, 101, 102}. A systematic review found that reducing the frequency of oral medication from multiple-dosing to once-daily dosing led to a threefold increase in increase in medication adherence¹⁰³.

Intentional non-adherence is a complex problem as it is an “active decision on the part of patients to forego the prescribed therapy”⁹⁹. Studies have shown that factors governing the decision are usually behavioural, such as having a negative attitude to medicine taking, fearing side effects, dissatisfaction with their healthcare provider, high out-of-pocket payment, lack of motivation, and negative beliefs on the efficacy of the treatment^{89, 104, 105}. These factors suggest that intentional behavioural change is required to tackle medication non-adherence. Patient engagement in self-care and patient-centred care are also important considerations in reducing medication error and fostering better medication adherence^{106, 107}. Aikens et al. found that DM-specific patient-provider communication (PPC) significantly (all $P < 0.05$) improved all measured self-care behaviours (i.e. eating, exercise, medication-taking, glucose testing) while general communication only improved eating behaviour in people with

T2D. The study conducted a phone interview with an ethnically diverse sample of 752 people with T2D about their self-care activities and T2D-specific PPC¹⁰⁸.

As discussed in section 1.2.5, the social environment exerts a considerable amount of influence on T2D self-management behaviour. The influence of the social environment also applies to medication adherence^{49, 52, 109, 110}. For example, a supportive spouse can provide verbal encouragement and help to facilitate medication adherence. Similarly, unsupportive family members and friends may discourage medication adherence by discarding the patient's medications or by offering conflicting advice due to misconceptions.

Studies have shown that greater social support can improve medication adherence in people with T2D. A Chinese study on adults with T2D found that social support (measured by a validated, 14-item scale) was significantly ($p=0.003$) higher in the high medication adherence group compared with the low adherence group⁵². Another Mexican study also found that social support was associated with adherence to diet ($p=0.007$) and medication ($p=0.002$) in people with non-insulin dependent DM¹⁰⁹. These and studies on other chronic illnesses^{49, 111} suggest that the wider context of self-management such as the social environment should be considered in the promotion of medication adherence.

1.3.5 Technology to enhance medication adherence

A Cochrane review by Haynes et al. (2008) concluded that long term complex interventions are not very effective and suggested innovative solutions to aid patients in medication adherence⁷⁸. In an update of the review, the authors suggested opportunities for mobile text messaging to improve medication adherence⁷⁷. Unintentional non-adherence such as forgetfulness can be tackled by reminding patients to take their medication, while intentional non-adherence requiring behavioural change can be tackled with knowledge transfer and effective communication.

The advent of smartphone disruption has changed the way people manage their medications. Smartphone apps are increasingly seen as a novel and convenient method to improve medication adherence. For example, users can schedule multiple medications within the app, be reminded to take their medications, track medication intake and assess medication adherence^{61, 112}.

Despite the potential for technology to enhance medication adherence, technology adoption for tracking medication management is slower compared with other health-related metrics. According to the national digital health consumer surveys conducted by Rock Health, a company that supports digital health start-ups, only 11% of the respondents tracking health goals tracked their medications¹¹³. Medication adherence is also least likely to be tracked in an app (10%) amongst other trackable health-related metrics¹¹⁴. The evidence for the effectiveness of technology in the enhancement of medication adherence is continuously evolving and will be further discussed in section 1.4.2.

1.4 mHealth in chronic disease management

Technology has transformed the way people communicate and manage health. The term “mHealth”, as defined by the WHO Global Observatory for eHealth, is a component of eHealth (electronic health) where medical or public health practices are supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices¹¹⁵. Components of mHealth are linked to mobile phone utilities, such as voice or short messaging services (SMS), Bluetooth technology, Global Positioning System (GPS) and mobile applications (apps). A search conducted on PubMed using the keyword “mHealth” in May 2019 returned over 32,000 results, a threefold increase compared to a decade ago. The growing literature on mHealth signifies interest and development in this area. Governments worldwide are also increasingly undertaking mHealth initiatives as a complementary strategy to strengthen health systems¹¹⁵.

mHealth technologies emerged in the mid-1990s when mobile technologies became more prevalent. Initial mHealth technologies were developed to reduce administrative work and improve communication between patients and their healthcare providers. For example, SMS reminders are now widely incorporated in the appointment reminder systems of many healthcare institutions worldwide¹¹⁶.

Smartphone apps first appeared in the Apple store in 2008. Since then, the number of apps has proliferated, and the use of apps has infiltrated the daily living of people. The global number of health apps has almost doubled from 165,000 in 2015 to 318,000 in 2017, according to estimates from the IQVIA Institute for Human Data Science (formerly Quintiles IMS Holdings)^{62, 117}. Medical or health apps are designed for a multitude of purposes such as data collection, health and disease education, disease and lifestyle management, surveillance, monitoring, and health promotion to support and manage one's health. This section explores the current mHealth evidence for T2D and medication adherence and identifies the unrealised potential of mHealth in T2D management.

1.4.1 mHealth evidence for T2D

Diabetes apps^b are highly downloaded with the high global prevalence of DM and the large number of DM apps in the market¹¹⁸. mHealth initiatives that focus on improving DM care and outcomes have also increased in recent years. Studies have demonstrated the clinical effectiveness of smartphone apps in HbA1c reductions through patient education, telemonitoring and interventions eliciting behavioural change^{63, 119-121}. Hou et al.'s (2016) meta-analysis found that the use of an app for T2D self-management resulted in a statistically significant ($p < 0.01$) mean HbA1c reduction of 0.5%. The review found that younger patients and feedback from healthcare professionals contributed to the most significant improvement in HbA1c reduction⁶³. Another meta-analysis by Bonoto et al. (2017) also found that apps can

^bMany features of diabetes apps are applicable to people with all types of diabetes. Therefore, when referring to apps, the use of the term "DM apps" broadly refers to but is not confined to apps that can assist people with the self-management of T2D.

significantly ($p < 0.05$) reduce mean HbA1c by 0.44% and strengthen the perception of self-care in people with T2D by enhancing health knowledge¹²². According to a report by the IQVIA, strong clinical evidence of app efficacy exists for DM care which may be considered for incorporation into standard care recommendations in the future⁶².

Despite positive evidence on the clinical effectiveness of smartphone apps for DM, these apps are still not as widely used by people with DM¹²³ compared with apps for commercial purposes (e.g. apps for banking)¹²⁴. Apps for chronic diseases have not reached the tipping point to disrupt the way healthcare is managed¹¹⁸. According to an industry report published in 2017, less than 10% of health apps in the market have more than 50,000 users that use the app more than once a month¹¹⁸. In addition, a study assessing the use of a diet and activity tracker app in T2D participants found highly inconsistent or intermittent app usage (78.6%) over an 8-week trial. Consistent users have higher baseline motivation scores and may be more motivated to manage their condition¹²⁵.

Smartphone app developers are increasingly incorporating behavioural change techniques (BCTs) such as self-monitoring, goal-setting, action and feedback, and social support to encourage sustained improvements in chronic disease management^{126, 127}. Gamification, which refers to the use of game playing element to encourage the use of certain services, has also gained attention in recent years as a mHealth strategy to effect behavioural change^{128, 129}. Studies have suggested better engagement and app user retention with the incorporation of gamification components^{128, 130}. A pilot study reported an increased frequency of blood glucose measurement with the use of gamification incentives by encouraging adolescents with T1D to use an app linked to a blood glucose monitoring device¹³¹.

There is stronger evidence for SMS-based compared with app-based T2D interventions in LMICs due to the relatively higher cost of smartphones¹³²⁻¹³⁴. Examples of SMS-based interventions include T2D self-management education, encouragement, and raising awareness of T2D through the provision of bite-sized information on top of usual care. A systematic review by Dobson et al. (2012)

concluded that SMS-based interventions have led to short-term HbA1c reductions, although the long-term effect remains unclear¹³⁵. SMS-based interventions for people with T2D were associated with lower mean HbA1c values in the intervention group compared with the control group in studies conducted in Senegal (Mean difference: 0.6%, $p=0.0038$)¹³² and Bangladesh (Mean difference: 0.66%, $P<0.001$)¹³³. However, another randomised trial assessing the effects of SMS text messages (DSME vs DSME+SMS) for DM self-management in three LMICs (Democratic Republic of Congo, Cambodia, Philippines) found that receiving text messages on top of routine care did not significantly improve the proportion of people achieving good glycaemic control ($\text{HbA1c} < 7\%$)¹³⁴. The mixed results imply that the success of SMS-based interventions depends on the quality of the routine programme, the coverage, and the stage of the disease.

While the evidence on apps for T2D management is inadequate (especially in LMICs), the magnitude and capabilities of such apps are expected to increase to address unmet needs in the future. I foresee the incorporation of context-specific guidance for digital interventions into DM clinical guidelines when the evidence matures. Since 2019, the ADA has dedicated a section on “diabetes technology” in its “Standards of Medical Care in Diabetes” guidelines given increasing evidence on technologies for DM management. Although the guidelines focused mainly on insulin delivery and glucose monitoring, there are plans to expand the guidance on medical software, privacy, costs and any other use of technology on modern DM care¹³⁶.

1.4.2 mHealth evidence for medication adherence

The majority of published mHealth studies on medication adherence focused on medication reminders. SMS reminder studies have been available since the early 2000s¹³⁷, while publications on smartphone apps were only available after 2010^{63, 138}. Therefore, stronger evidence exists for SMS reminders compared with app reminders, as evidence generation requires substantial lead time.

SMS reminder studies have shown better medication adherence in chronic medication conditions such as DM, asthma and HIV patients^{139, 140}. A meta-analysis showed that mobile text messaging reminders increased the odds of medication adherence in chronic diseases by approximately two times¹⁴¹. Interventions with higher success rates were simpler, less intrusive and tailored to users' needs. For example, HIV patients that received weekly messages had higher medication adherence rates compared with patients that received daily messages¹⁴². A study which linked SMS reminders to MEMS attached on a pillbox cap also showed improved medication adherence (Intervention: 81% vs Control: 70%, $p=0.007$) in T2D patients within a 4-hour window. The SMS reminders were only sent to the patients if they forgot to take their medication within a predefined period, thus making the reminders less intrusive¹⁴³. SMS medication reminders were also well received by participants, as participant satisfaction levels were above 80% in the studies measuring satisfaction¹³⁹.

The outcomes from the SMS reminder studies showed the importance of tailored interventions, two-way communication (patient receiving the reminder and replying to confirm whether the he/she has taken medication), appropriate reminder intervals and innovative solutions to assist patients in managing their medications^{78, 144, 145}. A meta-analysis found that two-way text messaging was significantly better (1.23 vs 1.04 relative risk estimate, $p=0.007$) at improving medication adherence compared with one-way text messaging¹⁴⁶. A large four-arm trial (mailed pill strips with toggles, digital timer cap, a standard pillbox, and no intervention) found that low-cost reminder devices did not improve medication adherence in patients with chronic diseases¹⁴⁷. The findings above suggests the need for innovation and a combination of measures that go beyond mere reminders.

Compared with SMS reminders, apps have more sophisticated medication management features such as the ability to schedule medication, track medicines intake, provide information on medicines, and assess for medication adherence. There were approximately 800 apps for medication self-management in the app market in 2015, half of which were accessible and free to download¹⁴⁸. Despite a

large number of apps available, the majority of these apps lacked desirable features determined to be useful for medication adherence and were deemed to be of low quality¹⁴⁹. For example, a review on medication adherence smartphone apps by Santo et al. found the median number of apps to have three out of 17 features that were deemed to be desirable for a medication adherence app. These desirable features include flexible scheduling, medication tracking history, snooze option, visual aids, and many others¹⁴⁹.

Medication adherence apps were also lacking in BCTs^{150, 151}. A study found that a total of only 12 out of 96 BCTs were present across 166 medication adherence apps, and the apps contained a mere average of 2.77 BCTs¹⁵¹.

There is limited but increasing evidence on the efficacy of medication adherence smartphone apps for long-term conditions¹⁵². A Spanish study tested a pillbox app with elderly patients taking multiple medications and found reduced medication errors, fewer missed doses and high user satisfaction¹⁵³. Another two-arm randomised trial which assessed the effect of a medication reminder app on hypertensive patients found a small improvement in self-reported medication adherence but no improvement in systolic blood pressure¹⁵⁴. To successfully assess the effects of electronic interventions on medication adherence, the selection of an appropriate study population is essential. Studies should focus on participants who are non-adherent and willing to improve their level of medication adherence. For example, measuring patients who are already adherent to their medications at baseline is unlikely to lead to observation with significant outcomes due to ceiling effects¹⁵⁵. Patients who are non-adherent due to medication cost issues should also be assisted in another way rather than through an app intervention.

1.4.3 Unrealised potential of mHealth in chronic disease management

The banking, e-commerce and education industries have long adopted smartphone technology to manage services in many parts of the world. There is currently a large number of health apps that support chronic disease management, such as DM, mental

health and problems of the circulatory system⁶². However, app use for T2D self-management is still not part of any routine clinical care process nor widely used to manage chronic diseases. Despite estimations that 7.8% (24 million) of people with DM who own a smartphone will use an app to manage their condition by 2018¹⁵⁶, this target has yet to be achieved in 2019.

Several factors influence the adoption of health apps. One factor is the healthcare providers' advocacy in the adoption of mHealth for chronic disease management. In a survey (n = 494) on patients' expectations regarding information seeking on the internet, 62% of respondents would like their physicians to recommend specific web sites to learn more about their health care¹⁵⁷. Another survey assessing the readiness of people with T2D to use the internet and mobile services found that half of the respondents had asked a physician to recommend a specific health-related website¹⁵⁸. Although these examples are on health information websites, the findings suggest that physicians' recommendations are likely to be well received by patients. In terms of a health app, healthcare providers can encourage their patients to input daily health metrics into the app for review and/or address patients' queries via an in-app communication feature. Stronger evidence on the effectiveness of health apps for chronic disease management will also increase providers' confidence in recommending apps to complement health care, which will in turn increase patients' exposure to this alternative for health management¹⁵⁹.

Another factor that influences the adoption of health apps is the management of patients' expectations. Patients' perceptions on app use are essential in driving and sustaining health app usage, as tailored interventions have been shown to elicit more effective health behaviour changes^{127, 160}. Popular apps may have features that are aligned to users' needs but may not reflect users' preferences¹⁶¹. Studies have also emphasised the need to improve the user experience of apps for better user satisfaction^{162, 163}. App use should be incorporated into patients' care routine to encourage sustained usage. Patients' requirements and behaviours towards app usage should also be understood at a deeper level before app development to reap the full potential of health apps.

Apps are currently underutilised in chronic disease management due to existing gaps in mHealth evidence and practice. First, existing studies on medical app usage were mostly of low quality with small samples, and are relatively recent to make evidence-based recommendations¹⁶⁴. For example, an article recommended apps for DM management without a systematic search and evaluation process to support the recommendations⁶¹. Studies were also too heterogeneous in study design and outcome measurements for any pooled estimates to inform the overall effectiveness of apps in chronic disease management^{140, 165}. In addition, the lack of long-term studies throws the sustainability of outcomes beyond the intervention period into question^{121, 137, 139}.

Second, patients and health care professionals are often not involved in the design of digital health solutions. Many app developers, including top app players, initially developed an app based on personal, relatives or friends' needs in disease management¹⁶⁶. Therefore, apps are often not tailored to the general public's needs. In an interview conducted by Lithgow et al. on 12 participants with T1D, 10 participants indicated that they have never encountered an app which had all the features they had used for T1D management¹⁶¹. The involvement of health care providers in app development is also generally low. A study found that only 13.6% of apps for medication adherence involved a health care provider in app development, and only 1% of the apps were evidence-based¹⁴⁸.

There are currently over 1000 DM-related apps (either targeting people with DM or healthcare professionals who treat DM) available for download in the app market¹⁶⁷. As discussed by Velsen et al., the exponential increase in the number of apps led to the problem of app overload, where physicians and patients both had difficulty finding the right apps for themselves. The fragmentation of information scattered over too many apps also leads to app fatigue. If the added value of a single app is too low, people may choose not to download the app¹⁶⁸.

Third, many apps lack features that are important for T2D management. A 2018 study reported improvements in popular and free DM apps, but these apps were still lacking in triglycerides, lipids, moods, goal setting and Body Mass Index (BMI) features¹⁶⁹.

Another 2017 study which reviewed iOS DM management apps found that only 50% of the highest-rated apps had medication adherence features¹⁷⁰. In addition, no medication reminder studies provided long-term data (over several years) which is critical for incorporating these strategies into routine health care delivery¹¹⁹. Therefore, more work is required to assess the clinical significance of apps¹⁷¹ in order for apps to better fit their purpose.

Fourth, concerns over privacy and security of data management and sharing resulted in underutilisation of mHealth. These concerns were not unfounded due to reported lapses in data protection. A cyber-attack on the electronic health system of Singapore's largest healthcare group in 2018 compromised the personal data of 1.5 million people and revealed weaknesses that safeguarded patients' confidential information¹⁷². Data protection in apps is also immature, as an investigation of the data security of the NHS Health Apps Library revealed the non-compliance of clinically-accredited apps with principles of data protection¹⁷³. Although important, concerns over data confidentiality, safety, app features and the degree of lifestyle modifications to incorporate app use in disease management were rarely discussed in studies¹⁷⁴.

Fifth, quality assurance mechanisms in mHealth are at present underdeveloped. Many apps are not regulated nor accredited by regulators. The lack of regulation not only poses potential health risks to users but also deters providers from recommending the use of health apps to their patients¹⁷⁵⁻¹⁷⁹. Apps with accreditation from health associations such as ADA were more likely to be downloaded¹¹⁸, but the U.S. Food and Drug Administration (FDA) regulates only a small subset of apps that pose a higher risk to consumers and meet the regulatory definition of "device"^{175, 180, 181}. Even so, disease management apps that are not available in the U.S. app market fall out of the FDA's purview. Very often, app developers providing health information through apps do not disclose their qualifications or disclaim that the information provided does not replace the advice of health providers. The lack of transparency in an app's source of content may cast doubt on the reliability of the information it

disseminates^{180, 182, 183}, and can potentially mislead or bring harm to patients with lower health literacy¹⁸⁴.

Sixth, features that promote data sharing and interaction with healthcare providers are often not available in disease self-management apps. Many disease management apps act as standalone apps (i.e. not linked with the electronic health system) due to the complexities involved in protecting the privacy and security of health data. For example, a study reviewing the medication management aspect of DM iOS apps found no apps that could sync with prescribers' directly¹⁷⁰. Healthcare providers are more likely to utilise in-app consultations if they are reimbursed for their time. It would be ideal for healthcare organisations to develop their app to ensure data security. However, an average app costs US\$425,000 to develop¹⁵⁶, and this amount can only be justified if there is a sufficient user base which eventually leads to positive health outcomes. In addition to the cost of developing an app, health systems will also have to finance the cost of promoting and maintaining the app or cost associated with turning it into a viable business model.

Seventh, the shortage in mHealth evaluations and guidance may be attributed to the gap between the pace of evidence and knowledge generation, and translation into actual practice. As the field of mHealth develops rapidly, the evidence base established may be outdated by the time it is incorporated into practice. Therefore, alternative evaluation methods other than randomised controlled trials (RCTs) should be explored to address the gaps in mHealth translation to practice¹⁸⁵.

Lastly, careful planning and piloting are required before any large-scale adoption of health apps. Hasty implementations without a strong foundation will subject the intervention to failure. For example, the NHS National Programme for IT—an initiative to fully digitise the NHS, failed due to the haste of implementation, lack of planning and lack of buy-in from healthcare providers¹⁸⁶. Another company—Haptique—attempted to provide an app certification programme to fill the gap left by the FDA. The Haptique Health App Certification Program was launched in 2013 to rigorously assess apps based on their interoperability, privacy, security, and content standards. By charging mHealth developers a fee, the company hoped to build

a library of certified apps which they could sell to healthcare institutions to prescribe to patients. However, the take-up rate was lower than expected, and consumer data were exposed after a few of its certified apps got hacked within two weeks of the mHealth library launch¹⁸⁷. The library had to be closed soon after. These examples showed the importance of careful assessments before large-scale project implementations to prevent costly failures and loss of consumer confidence in health apps.

1.4.4 Theories in mHealth

Theoretical frameworks are essential in guiding the development and evaluation of health interventions. A theoretical framework links theories and concepts to the broader areas of knowledge that is being considered¹⁸⁸. Theories are important in influencing the way evidence is collected, analysed, understood and used¹⁸⁹. Many scholarly works have combined behavioural change theories and technology acceptance models in an attempt to understand and explain mHealth adoption for chronic disease management¹⁹⁰⁻¹⁹³.

The Health Belief Model (HBM), Theory of Planned Behaviour (TPB)¹⁹⁴ and Social Cognitive Theory (SCT)⁵⁰ are commonly used theories to predict and explain behavioural change in health interventions.

Health Belief Model (HBM)

The HBM predicts and explains a person's willingness to take action based on perceived vulnerability and severity to his/her illness, and the benefits and barriers to taking action¹⁹⁵. This model has been widely used to predict and explain treatment compliance to T2D regime in relation to patients' beliefs (severity, treatment benefits etc.) regarding their disease¹⁹⁶⁻¹⁹⁹. Predicting non-compliance in disease management allows for the design and enhancement of interventions which could help patients to comply better to their treatment regime.

Theory of Planned Behaviour (TPB)

The TPB states that the attitude (favourable or unfavourable outcomes of performing the behaviour), subjective norm (whether people approve or disapprove of the behaviour), and perceived behavioural control (ease or difficulty in completing the task) collectively shape the behavioural intention of an individual, which influences his/her actual behaviour¹⁹⁴. This theory has been used to predict and explain behavioural intentions on diet and physical activity modifications in people with and at risk of T2D²⁰⁰⁻²⁰².

Social Cognitive Theory (SCT)

The SCT posits that learning occurs in a social context through the dynamic interaction between the person, environment and behaviour⁵⁰. A major component of the SCT is observational learning. An individual acquires desirable and undesirable behaviour by observing others, then reproduce the learnt behaviour based on the anticipated consequences. The belief in self-efficacy (confidence), together with environmental factors (barriers and facilitators) influence the capability of the individual in performing the behaviour. This theory has been used to explain the influence of the social environment on the adherence to T2D self-care activities^{49, 53} (Refer to Section 1.2.5).

In recent years, studies have integrated behavioural change theories and the technology acceptance model (TAM) to predict and explain mHealth adoption. The TAM has been widely used to explain the intention and actual use of information systems (mHealth adoption)²⁰³⁻²⁰⁵. This model has been expanded over the years to include external social influence and cognitive processes. One successor of the TAM is the Unified Theory of Acceptance and Use of Technology (UTAUT), which aims to explain user intentions to use an information system and subsequent usage behaviour¹⁹². Another model derived from the TAM is the Health Information Technology Acceptance Model (HITAM)¹⁹⁰. The HITAM was developed with a combination of the HBM, TAM, and TPB to explain the interactions of health information technology and the behavioural intention of health consumers¹⁹⁰.

Although technology acceptance models have been useful in predicting and explaining mHealth adoption, these models were mainly focused on single adoption of technology. With the integration of smart devices into daily living, the interaction between people and technology in everyday life has to be considered for mHealth adoption. Instead of focusing on “who uses the technology”, a broader perspective needs to be considered to assess the way people use technology. Wirth et al. developed the Mobile Phone Appropriation (MPA) model to provide a theoretical framework to analyse the actual use and implementation of mobile communication technology into users’ everyday lives¹⁹¹. For example, a qualitative study which used the MPA model to examine the usage of mHealth technology for DM self-management found that people with DM would often make use of the broader mobile-media ecosystem rather than a standalone app to manage their disease²⁰⁶. Concepts from various technology adoption models such as diffusion of innovations¹⁹³, TPB¹⁹⁴ and UTAUT¹⁹² were integrated to explain the dynamic process of appropriation. The term “appropriation” was used to emphasise on users’ active renegotiation of mHealth usage within an environment of constantly evolving mobile communication technologies.

In view of dynamic and complex interactions of technologies with users, theoretical and empirical frameworks should both be considered when designing and evaluating complex mHealth interventions^{188, 207}. A theoretical approach provides a useful conceptual framework for change while empirical research provides support for implementation. Frameworks that guide mHealth adoption should be adapted to fit the context of the research interest as technology continues to evolve.

1.5 Summary of research gaps

In the previous sections, I described T2D as a growing problem worldwide with its increasing prevalence, economic and personal costs, and burden to health systems. Innovative solutions utilising digital interventions can complement multifaceted T2D

care. For example, smartphone apps are increasingly used for T2D management as they offer an innovative, convenient and easily accessible means to learn about and manage T2D. Despite positive evidence of the effectiveness and acceptability of smartphone apps for T2D management, gaps exist in the evidence for implementation.

First, less evidence of the effectiveness of health apps is available compared with the older internet-based digital tools for T2D self-management. While health app development is advancing rapidly, the number of apps intended for T2D self-management is unknown. The myriad and varied quality of DM apps make the recommendation and selection of a T2D management app challenging. Studies of health apps are also generally limited to English language apps. Disparities in health app access and usage exist within and between health systems^{208, 209}. With the high number of non-English speaking people with DM worldwide, it is imperative to understand the global DM apps landscape and appreciate the applicability of high-quality mobile health apps for different populations and contexts.

Second, few studies have systematically examined the quality of apps for T2D self-management. Despite the importance of medication adherence in T2D management, it is unclear whether these apps are supporting T2D patients in adhering to their medications or incorporating medication management features adequately. Gaps in knowledge also exist in the alignment of health apps with validated treatment guidelines, which should be addressed to ensure better safety and utility for the user.

Third, the transparency and reliability of information sources for DM apps are unclear. Concerns over the privacy and security of apps, due to the lack of app accreditation and data protection, impede app adoption.

Lastly, the adoption and sustained use of health apps are critical towards the evaluation of the effectiveness of health app interventions. While the clinical effectiveness of smartphone apps for T2D has emerged in recent years^{62, 63}, the efficacy and implementation of smartphone apps in supporting medicines taking are not well studied^{119, 141}. App fatigue occurs when users download too many apps that

they do not use regularly. The intermittent use of a health app diminishes its utility for long-term chronic disease management. In addition, population-based interventions involving smartphone apps are often complex and multifaceted. The “gold standard” Randomised Controlled Trial (RCT) is often not possible due to challenges in controlling the study environment. For example, an app study on medication reminders in the primary care setting will likely be confounded by other forms of digital reminders available in the smartphone. Therefore, alternative evaluation methods other than RCTs should be explored to address the gaps in translating mHealth into practice.

1.6 Aim and objectives

Smartphone apps are widely available for people with T2D to manage their medication, but barriers to app adoption undermine their potential to transform care. One barrier for app adoption is the shortage of high-quality mHealth evaluations and guidance for healthcare professionals to make recommendations. Other barriers include the lack of app features that are important for T2D management and hasty implementations of mHealth interventions that often led to failure. To address these gaps, I conducted several systematic assessments of DM apps to identify an app with comprehensive medication management features. The identified app was then used for a pilot study to assess the feasibility of a medication management intervention for people with T2D in Singapore. A pilot study was conducted as careful planning and piloting prior to the large-scale adoption of a mHealth intervention is essential to maximise the success rate for future large-scale adoption. The aim and objectives described below seek to address some of the research gaps described in Section 1.5.

1.6.1 Aim

My research aimed to assess the clinical relevance, quality, and impact of smartphone apps on the medication management support of people with T2D.

1.6.2 Objectives

The specific objectives of my research were to:

- 1) Systematically assess the number, proportion and clinical relevance of DM self-management smartphone apps in languages spoken by countries with the highest numbers of people with DM;
- 2) Systematically assess and characterise the medication management features in apps for T2D self-management and their congruence with international medication adherence guidelines;
- 3) Systematically assess the transparency and reliability of health information disseminated through smartphone apps with incorporated medicines management features for people with T2D; and
- 4) Assess the feasibility of using a smartphone app to support medication adherence in T2D patients attending a public healthcare institution in Singapore through a pilot study.

1.7 Content of the dissertation

Chapters 1 and 2 describe the background, context, study design and study rationale. As this is a thesis by publication, Chapters 3 to 7 describe studies that were published/accepted to peer-reviewed journals to address the research aim and objectives. Figure 1 shows a schematic summary of the PhD.

Chapter 3 addresses Objective 1 by providing a global overview of the clinical relevance of smartphone apps for DM self-management. Popular apps in languages spoken by the top ten countries with the highest numbers of people with DM were downloaded and screened for app features that were clinically relevant to T2D self-management. After gaining an overview of the T2D app landscape, the topic was narrowed down to focus on medication adherence for subsequent studies as it is an essential self-care behaviour in T2D management.

Chapters 4 and 5 address Objectives 2 and 3. Chapter 4 details the methodology of a study which systematically assessed and characterised the medication management features of T2D self-management apps with the best practice evidence-based criteria. The transparency and reliability of information disseminated via these apps were also examined with criteria adapted from the Health on the Net code of conduct (HONcode) principles. Chapter 5 describes and discusses the results of this study.

After gaining an overview of the medication management features of T2D self-management apps, the Medisafe® app was selected for a feasibility study which focused on the process and patient outcomes of actual app use. Chapters 6 and 7 address Objectives 4 and 5 by describing a study that investigated the short-term impact of an app on medication adherence and medication-taking behaviour in T2D patients attending a public healthcare institution in Singapore. In view of the challenges encountered with evaluating complex interventions, the UK Medical Research Council (MRC) recommends a feasibility and piloting phase for such interventions to optimise design and evaluation. Therefore, a feasibility study was conducted to evaluate if recruitment for an app study and sustained app use is feasible in Singapore before considering the execution of a larger study in future.

Finally, the key findings of this thesis are summarised and discussed in Chapter 8. The strengths and limitations of the methodological approaches, research implications, and recommendations for future research are also discussed in this chapter.

Figure 1.1 Overview of the PhD study

Chapter 2

Context and research design

This chapter describes the context of the research. I begin with my (the PhD candidate) background and the context (Singapore) which the research took place in Sections 2.1 and 2.2, followed by the rationale and research design of each study in Section 2.3. The study context is especially pertinent to the feasibility trial study (described in Chapters 6 and 7) set in a Singapore public outpatient clinic.

2.1 The PhD candidate's background

The researcher's position influences the research process and analytic stance²¹⁰. Therefore, an understanding of the background and experiences of the researcher is useful for the interpretation of the relationship between the researcher and the work of research. I (the PhD candidate) was born and raised in Singapore, a multi-ethnic country with a mixture of spoken languages and dialects. The official working language—the English language—is often spoken with a colloquial twist among Singaporeans (Singlish). The shared cultural background helped me to build rapport with my study participants for the feasibility trial (Chapters 6 and 7).

My educational background is in engineering, economics, and public health. Prior to the PhD study, I was employed in various roles in both the primary and tertiary healthcare sectors in Singapore. My first experience in a job with patient interaction was as a clinic assistant in two private general practices, which helped me to better understand the job scope of general practitioners (GPs) and improve my patient interaction skills.

I also worked as a management associate in a public specialist outpatient centre in Singapore. The departmental rotations helped me gain insight into the Singapore health system and physician training, which proved valuable for subsequent research

and work in Singapore. The experience gained in the clinical operations department further strengthened my patient interaction skills.

I completed a Master of Public Health (MPH) at Imperial College London (ICL) before working as a health services researcher in the public healthcare sector. As ICL is a WHO collaborating centre, I had the opportunity to visit the WHO headquarters in Geneva. These overseas experiences heightened my interest in global health issues and inspired me to explore the availability of DM apps in various languages (Chapter 3). Work experience as a researcher helped to hone my research skills, expanded my local network and influenced my decision to embark on a PhD in Population Sciences. Part of the reason for choosing Changi General Hospital as the setting for the feasibility trial was my familiarity with the healthcare setting and the established network with my previous work organisation.

2.2 The study context: Singapore

An understanding of the study context provides perspectives on the rationale and decisions made for the research. In this section, I briefly introduce Singapore's health system, the problem of T2D and Singapore's stance on T2D. I also present Singapore as a suitable setting for conducting health apps studies.

2.2.1 A brief introduction of Singapore's health system

Singapore, an urbanised and densely populated island in Southeast Asia, has one of the best healthcare systems in the world in terms of health outcomes and health efficiency. Good overall health outcomes were achieved despite a relatively low national health expenditure (4.3% of GDP) compared with other high-income countries (8% – 12% of GDP)²¹¹. The WHO ranked Singapore's health system in the 6th place (behind France, Italy, San Marino, Andorra and Malta) among 191 countries in its year 2000 World Health Report²¹². The rankings were based on index of five factors: 1) overall or average health based on disability-adjusted life years (15%); 2)

distribution or equality in health (35%); 3) overall or average responsiveness to people's expectations regarding non-health measures (12.5%); 4) distribution or equality in responsiveness regarding non-health measures (12.5%); and 5) fair financial contribution (25%). The Bloomberg Global Health Index also ranked Singapore as the fourth healthiest country in the world among 163 countries in 2017²¹³. The index was computed by summing health score metrics (mortality by communicable and non-communicable diseases, life expectancy, access to clean air, water and sanitation services etc.) and subtracting health risk penalties (e.g. high incidences of population with elevated level of blood pressure and cholesterol, tobacco and alcohol use, physical inactivity, child mortality etc.).

Population demographics

The total Singapore population of 5.64 million in 2018 comprises 3.84 million residents (i.e. citizens and permanent residents) and 1.6 million non-residents²¹⁴. Ethnic Chinese (76.2%), Malays (15.0%) and Indians (7.4%) make up the majority of the resident population. Life expectancy is high, and currently (2018) stands at 80.7 years for males and 85.2 years for females²¹⁵ (refer to [Appendix A1.1](#) for more information)

Health system, policy and financing

The achievements of the health system today are a result of good governance and sound fiscal policies. Healthcare is currently delivered through a mixed model. The public sector delivers 80% of acute hospital care, while the private sector delivers 80% of primary care. Primary care is managed by subsidised polyclinics or private GPs²¹⁶.²¹⁷ (refer to Figure 2.1 for an illustration of the various health sectors of the Singapore health system). All Singaporeans currently have access to subsidised basic medical services at government polyclinics and hospitals²¹⁶. Employers may partially cover the healthcare costs of working adults. Other than public health services and those facing financial hardship, all healthcare services are fee-paying as the government is a strong advocate of self-reliance, family responsibility and community self-help for individual welfare²¹⁶ (refer to Appendix [A1.2](#) and [A1.3](#) for more information on the political philosophy and financing of Singapore's health system).

The health system has undergone multiple restructures since the year 2000 to increase the efficiency and competitiveness of public healthcare institutions. Regional health systems (RHS) were formed to provide vertically integrated care between the primary and tertiary care sectors. There are currently three RHS clusters in Singapore²¹⁸. Each cluster is linked with a medical school to facilitate teaching and research. The speciality centres are shared by the clusters as Singapore is not large enough to warrant multiple centres for the same clinical condition. The current three RHS clusters are SingHealth, National Healthcare Group (NHG) and National University Health System (NUHS) (refer to [Appendix A1.4](#) for more information on the restructuring of Singapore's healthcare system).

Figure 2.1 Illustration of the private and public proportion in primary care, tertiary care, wellness care and continuing care sectors.

Challenges of the health system

There are currently a few challenges plaguing the Singapore health system. First, the health system (supply) has to rapidly catch up with the demand for health services to meet the needs of an ageing population. Public hospitals in Singapore experienced severe bed crunch in 2014 due to increased number of older adults with multiple readmissions and longer length of stays²¹⁹. According to forecasts, one in four Singaporeans will be above the age of 65 by 2030²⁰⁸. In a nationally representative survey of community-dwelling older Singaporeans (citizens and permanent residents) aged 60 years and above, 38% of respondents were found to have three or more chronic diseases²²⁰. The management of long-term chronic diseases is resource-intensive and costly to the health system. In the 2017 financial year, healthcare received the third largest—S\$10.7 billion—spending by the government. This amount is expected to increase by another S\$3 billion by 2020 as the population ages²²¹. Efforts to promote healthy ageing and living are underway, but that will not remove the susceptibility of an aged person to chronic illnesses.

Second, primary care resources are unequally distributed across the public and private sectors. The highly subsidised polyclinics, which accounts for 20% of primary care (refer to Figure 2.1 for an illustration of the distribution of health services in the private and public health sectors), handle half of the primary care cases²¹⁶. Many people with chronic illnesses (e.g. DM) choose subsidised care as long-term chronic disease management becomes expensive cumulatively. For example, people with T2D will be on long-term medication and will need to have three-monthly follow-ups for the doctor to monitor their condition. The government has since expanded GP services and introduced subsidies for GP visits to relieve the load of polyclinics. (Refer to [Appendix 1.5](#) for more information on the government's initiatives to shift chronic disease care to primary care.

Third, the health system is fragmented and short of trained healthcare professionals suitable for chronic disease management. Specialisations and sub-specialisations have caused a lack of diversity in tertiary care and a lack of depth in chronic disease management in primary care²¹⁶. Patients may lament seeing many specialists for a

condition without any doctor coordinating care. The primary, intermediate and long-term care needs to be integrated to deliver seamless care to a patient²²². (Refer to [Appendix 1.4](#) for information on the integration of health services)

Fourth, inappropriate utilisation should be managed. Monitoring and regulations must be in place to prevent abuse of the system. Insurers should not make healthcare free-of-charge as that will increase the expectations and demand of healthcare, which may drive costs up²²³. Too many specialists without regard to cost-effectiveness may also drive up the cost of healthcare. Costs and outcomes of medical services should also transparent to prevent doctors from being profit-oriented entrepreneurs whom may create their own demand²²⁴.

Fifth, with a shrinking work force and increased demand for health services, healthcare productivity has to be enhanced to maintain current standards without relying too much on the foreign talent pool²¹⁶. There is also a need to manage specialised services (with overseas patients seeking healthcare in Singapore) without compromising the basic care needed by the local population. The National Population and Talent Division projected that the Singapore will require 28,000 foreign healthcare workers (an increase from 13,000 in 2011) by 2030 to manage the rising demand for healthcare services and home-based care. The government has taken steps to decrease the reliance on the foreign talent pool. One solution is to encourage trained healthcare professionals who are retiring to continue working. Another solution is to improve productivity by raising the employability of healthcare staff, which in turn attracts more Singaporeans into the sector²²⁵.

Lastly, threats of infectious diseases are prevalent with increased interconnectivity with the world. The severe acute respiratory syndrome (SARS) outbreak in 2003 started from a woman who contracted the disease in Hong Kong. The disease not only infected 238 and killed 33 people in Singapore, but led to public panic, school and business closures, and a decreased number of tourist arrivals which negatively impacted the economy^{226, 227}. With approximately 100 million passengers entering Singapore annually²²⁸, threats of infectious diseases being brought in from overseas (e.g. Ebola, H1N1, Nipah) are prevalent and should not be overlooked.

2.2.2 DM in Singapore

Type 2 diabetes management

In Singapore, newly diagnosed T2D patients are usually managed in the primary care sector—either by family physicians in subsidised polyclinics or by private GPs (refer to [Appendix A1.5](#) for more details on Singapore’s increased emphasis on primary care). Severe cases such as poorly controlled HbA1c with the presence of comorbidities are referred to specialists.

Patients are generally reviewed every three to six months by the doctor for T2D management, and yearly for foot and eye examinations. Outside the clinical setting, patients are required to self-monitor their blood glucose via a glucometer and modify their lifestyle. Information on medication adherence and lifestyle behaviours are often obtained through patients’ recollection of self-care between follow-up clinic visits. Since care is primarily outside the clinical setting, individualised care tailored to the needs and circumstances of adults with T2D is essential for the patient to benefit from long-term interventions²³.

Type 2 diabetes prevalence

The prevalence of T2D among adults aged 18–69 years, diagnosed using the OGTT, was 11.3% and disproportionate among the major ethnic groups according to the 2010 National Health Survey²²⁹. Indians have the highest T2D prevalence of 17.2%, followed by Malays at 16.6% and Chinese at 9.7%²²⁹. Thirty-two per cent of the surveyed patients with T2D reported poor glycaemic control²³⁰, which is comparatively higher than the 12.9% (of American adults) reported by the U.S. Centre for Disease Control and Prevention²³¹.

Subsequent national health surveys reported T2D prevalence based on the less sensitive Fasting Plasma Glucose (FPG) test²³², picking up lower rates of T2D. Nevertheless, a clear increasing trend in the prevalence of T2D can be observed over the years with the FPG test, which showed an increase in the prevalence of T2D in Singapore from 7.3% in 1992 to 8.3% in 2010 and 8.6% in 2017²³².

Singapore has one of the highest numbers of DM-related lower extremity amputations (LEAs) among OECD countries according to a locally published study²³³. The major LEA rate has increased from 11.0 per 100,000 population in 2008 to 13.3 per 100,000 population in 2013, which puts Singapore in the top five positions among OECD countries^{233, 234}. The rate of T2D related LEA is on the rise as the prevalence of T2D rises. An average of four people loses a limb each day due to diabetic foot problems and one in five amputees dies within a year after LEA from other multiple complications²³⁵.

A public health study presented a grim forecast of the future burden of T2D if the situation remains status quo. The prevalence of T2D is forecast to increase to 15% by the year 2050, where 1 in 6 (up from 1 in 13) working adults will have T2D¹⁷. With increasingly younger patient profiles of people with T2D, the study also estimated that working people with T2D would incur more than S\$1billion per year in T2D related health costs¹⁷.

Medication adherence in T2D patients

Approximately one-third of newly diagnosed T2D patients are non-adherent to their medications in Singapore, according to a retrospective cohort study using the proportion of days covered⁸². These medication non-adherent patients had 2.6 times more hospitalisations and made 2.4 times more emergency department visits compared with fully adherent patients over five years. Another Singapore study which used a 5-item self-reported medication adherence tool found that 57% of patients had low medication adherence to at least one of their OHA²³⁶. Medication adherence rates vary between sex, ethnicity and the presence of other chronic conditions⁸².

2.2.3 Singapore's emphasis on T2D prevention

The gravity of the impact of T2D in Singapore was not apparent until the release of estimates from the 2010 National Health Survey and other public health studies around the same period. The Singapore government has since declared its stance to

tackle T2D on several occasions. In 2016, the Health Minister declared a “war on diabetes” to engage Singaporeans to “battle” against T2D by leading healthier lifestyles²³⁷. In the 2017 National Day Rally, the Prime Minister spoke about T2D as one of the three key long-term issues for Singapore²³⁸.

The Ministry of Health has devised a solution—the “3 beyonds”—to keep the healthcare in Singapore sustainable and high quality for the future. They are 1) Beyond healthcare to health (ensuring a healthier population), 2) Beyond hospital to the community (ensuring that care for patients go beyond the hospital into the community), and 3) Beyond quality to value (ensuring value for money quality care). This strategy formed the basis of subsequent initiatives to fight against T2D. Workgroups were created to tackle various aspects of the problem. One initiative is a citizen’s jury to generate recommendations that are of significance and mobilise citizens to raise awareness of T2D in the community²³⁹. Another initiative is to allow people with T2D to use their Medisave^c to pay for lancets and test strips and enable people with pre-diabetes to pay for their medical consultations²⁴⁰. The Health Promotion Board also rolled out a slew of health promotion initiatives to encourage behavioural changes towards healthier lifestyles. For example, the National Health Challenge is an app-based intervention that allowed participants to earn rewards from adopting healthier lifestyle behaviours.

In addition, a S\$15 million grant was pledged to the Health Promotion Board’s Healthier Ingredients Development Scheme to develop low-sugar foods and drinks²⁴⁰. While progress is being made in the “war against diabetes”, it was also acknowledged that the effects of this “war” would take a long time to be seen.

^c Medisave constitutes a component of the compulsory savings scheme for all working Singapore citizens and permanent residents. The savings from Medisave can be used to offset hospitalisation and selected outpatient treatment bills to reduce out-of-pocket payments for the patient and their family.

2.2.4 Singapore's transition to a smart nation

With growing digital transformation worldwide, Singapore also capitalised on its knowledge-based economy to solve complex urban problems and explore economic opportunities. The Smart Nation initiative was launched with the aim to “support better living, stronger communities, and create more opportunities, for all”²⁴¹. This was not a new concept, but a culmination of earlier efforts to digitise public service delivery. A set of enablers were relied upon to help achieve this initiative: facilitating smart solutions through test-bedding and research collaborations, nurturing a culture of experimentation, sustaining innovation, and building computational capabilities²⁴²,²⁴³. These enablers encouraged the use of big data, Information and Communications Technology and the Internet of Things (IoT) such as sensors and smart devices to enhance the daily living of Singaporeans²⁴³. The Smart Nation initiative also presents ample opportunities for businesses and research institutions to create and test-bed innovations.

The efforts to digitise Singapore is timely with an ageing population and increased demand for healthcare services. Digitisation can streamline processes for more efficient and personalised patient care. For example, telemonitoring or teleconsultation has been used in dermatology, stroke rehabilitation, T2D and heart failure for patients requiring long-term primary or community care in Singapore⁵⁸,²⁴⁴⁻²⁴⁶. On the national level, the “Health Hub” web portal and the app were launched as a one-stop portal for Singaporeans to access health information and their medical records online²⁴⁷. The Health Promotion Board also launched the “Healthy 365” mobile app to promote healthy living in Singapore²⁴⁸. Ongoing incentives were introduced to encourage long-term behavioural change.

2.2.5 Singapore as a suitable setting for health app implementation

Smartphone penetration

Singapore has one of the highest smartphone penetration rates in the world, with 85% of the population owning a smartphone²⁴⁹. There are currently 8.61 million mobile

connections in Singapore, comprising 150% of the population (an average of two or more mobile subscriptions per person)²⁵⁰; computed by the total subscriptions divided by the total population²⁵¹. Since April 2017, the 2G (second generation) cellular network was permanently shut down in Singapore to allow for a transition to the 4G (fourth generation) wireless mobile telecommunications technology network²⁵². Users of 2G phones, who were mainly elderly, were required to switch to a 3G or 4G phone²⁵³.

With the smart nation initiative, the use of smartphone apps or health apps for lifestyle management is no longer a foreign concept to many Singaporeans. As the younger and more educated members of the population age in the future, concerns about technological barriers will lessen, and technology will continue to advance for disease management.

In addition to the smart nation initiative, the government is also supporting initiatives to prevent the onset of T2D and to help T2D patients better self-manage their condition, as mentioned in earlier sections. The intersection of smart nation initiatives and T2D prevention/management, coupled with a multi-ethnic society, provides excellent opportunities for Singapore to test-bed digital innovations for T2D care. Healthcare institutions and patients may be more willing to accept and integrate new digital solutions into their routine care as they become more familiar with T2D research.

2.3 Study rationale and research design

This section describes the rationale for research decisions, study design and analytical approach to address the objectives outlined in section 1.6. I conducted three research studies: (1) an assessment of the clinical relevance of DM self-management apps in ten languages spoken by countries with the most number of people with DM; (2) a systematic assessment of the medication management features of apps for people with T2D against (i) its congruence with international T2D and medication management guidelines, and the (ii) transparency and reliability of information

disseminated via the apps; and (3) a pilot trial assessing the feasibility and impact of a smartphone app in improving medication adherence in people with T2D in Singapore.

A funnel approach was taken for the sequence of the studies; beginning with global smartphone apps for people with DM and narrowing to focus on English language medication adherence apps for people with T2D. The systematic app assessments in study 2 were necessary to select a suitable medication management app for the feasibility study in Study 3.

2.3.1 Rationale for systematic app assessments

The number of apps and consumer choices has increased rapidly due to the growing amount of positive evidence on the clinical efficacy of smartphone apps for T2D self-management. As mentioned in Section 1.4.1, IQVIA estimated the global number of apps to have increased from 165,000 in 2015 to 318,000 in 2017^{62, 117}. The number of DM apps has also increased rapidly from six in 2008 to 267 in 2012²⁵⁴. By 2016, there were over 1000 DM apps (for patient and providers) in the Google and Apple app stores²⁵⁵. Apart from the small number of apps with evidence of efficacy, the quality and applicability of the remaining apps were unknown and unregulated. For example, independent evaluations have identified areas of health apps that could potentially harm users^{173, 175, 179}. One study found that insulin dose calculator apps could potentially make incorrect recommendations that may put the user at risk¹⁷⁹. Prior to this study, Pfitzer and Sanofi Aventis have recalled Rheumatology and Insulin calculator apps that were generating mistakenly high and low scores¹⁷⁵. Another study found that apps accredited by the UK NHS Health Apps Library offered limited data protection (risk of identity leak were present) to users²⁵⁶. Therefore, an understanding of the overall app landscape is imperative to identify gaps that are relevant for improvement prior to app implementation.

A systematic approach (i.e. app search, app assessments) is required to ensure the validity of the results. As the apps in the app stores change frequently, systematic app

assessments must be quick and well-coordinated. Many studies in existing literature assess apps based on random searches which are often biased towards apps with higher user ratings.

The app assessments in my PhD are part of a larger study assessing the features of T2D self-management apps and their congruence with international T2D guidelines. The study includes blood glucose monitoring, medication adherence, physical activity, diet modifications, and other important T2D self-care behaviours and app attributes (i.e. data transfer, privacy and security, disclosure of developers' information). I focus on the medication management aspects of T2D apps, and the transparency and reliability of information disseminated via these apps.

Rationale for global app assessment

While conducting a literature review on this topic, I found a disproportionate number of app studies focusing on English speaking populations despite a large number of people with DM who speak other native languages. The assessment of apps in other languages will provide a better representation of the global app landscape. Therefore, I conducted a global app assessment study to obtain a broad overview of the global app landscape before narrowing down to focus on English language apps.

2.3.2 Rationale for a randomised feasibility trial

There is a paucity of RCTs focusing on the impact of a smartphone app on improving medication adherence, especially in Asian populations. With this gap in mind, I designed and conducted a pilot study to determine the feasibility, acceptability, and clinical outcomes of using a smartphone app to improve medication adherence in T2D patients.

I chose to conduct a pilot study due to the uncertainties surrounding smartphone app RCTs (i.e. participants' digital literacy, the possibility of contamination, non-adherence to trial, acceptability of medication management app interventions among Asian populations, etc.) and recommendations from the UK MRC that feasibility

studies should precede full-scale RCTs²⁵⁷. A registered RCT of a self-developed smartphone app designed to improve medication adherence among T2D patients in Singapore was withdrawn due to poor patient recruitment²⁴⁵. As there was no prior baseline information on recruitment rates and patient willingness to participate in a smartphone app study in Singapore, a pilot trial was deemed more suitable in identifying and rectifying problems prior to a full trial.

The systematic app assessments helped me to select a suitable app for the feasibility trial. I chose a free-to-download commercial app (Medisafe®) with evidence supporting its effectiveness for the study (elaborated in [Section 6.3.5](#)) instead of developing my app, as the purpose of the study was to analyse patients' acceptability of the intervention and app usage behaviour rather than the attributes of the app. Selecting a highly downloaded app also reduced the need to develop, test and validate the app.

I employed a pre-post two-arm study design to reduce biases in self-reporting instruments. For example, patients who tend to over- or under-report their health status are likely to do so for both the pre- and post-surveys. The average follow-up interval was between three to six months. Therefore, a 12-week follow-up period was adopted for a feasibility trial, although health outcomes specific to certain aspects such as HbA1c are unlikely to change over a short period. Intermediate (monthly) surveys were sent to “remind” participants to continue to use the app and to assess changes in attitude towards app usage over time. Small participant incentives (grocery vouchers) were offered to reduce the dropout rate. This feasibility trial will produce a baseline for planning future studies.

Chapter 3

Clinical relevance of smartphone apps for diabetes management: A global overview

This chapter is published as

Huang Z, Soljak M, Boehm BO, Car J. Clinical relevance of smartphone apps for diabetes management: A global overview. Diabetes Metab Res Rev. 2018; e2990. <https://doi.org/10.1002/dmrr.2990>

The contributions of the co-authors are as follows:

- I (ZH) conceived the idea, conducted the analysis, wrote and revised the manuscript.
- Dr Michael Soljak (MS), Prof. Bernhard Boehm (BB) and Assoc Prof. Josip Car (JC) revised, commented on the manuscript and provided guidance to ZH.
- I would also like to acknowledge Tan Guan Zhong, Chua Kee Leng, Janis Lee, Wang Hua Xian, Laura Beatriz Martinengo, Tarig Osman, Geronimo Jimenez Larrain, Aspembitova Ayana, Monika Semwal and Shoko Dauwels-Okutsu for their contributions in screening the app titles and assessing the apps; and Dr Elaine Lum Pooi Ming for providing a critical review of this manuscript.

*Rights to reuse this article in my dissertation was obtained from the publisher

Chapter 3

Clinical relevance of smartphone apps for the management of diabetes mellitus: A global overview

This chapter provides a global overview of the clinical relevance of diabetes DM self-management apps for people with DM. Apps in widely spoken languages of ten countries with the highest numbers of people with DM were first screened for relevance to DM self-management. Eighteen apps in the ten languages were then downloaded and assessed for clinical relevance to T2D self-management with reference to current clinical guidelines. A broad inclusion criterion was used at the screening stage to include all types of apps for DM self-management, as many apps have features that can be used for all types of DM (e.g. blood glucose monitoring). This criterion was narrowed to focus on adult T2D cases at the app assessment stage to align with the focus of the thesis.

3.1 Motivation of the study

Diabetes mellitus is a complex chronic disease characterised by the body's failure to use and store glucose properly²⁵⁸. Over 400 million adults currently have DM, and this number is expected to increase by 50% in the next 25 years^{2, 259}. Over 90% of DM cases are T2D². Although interventions such as medications and lifestyle changes can facilitate good glycaemic control, there is no fixed approach to DM management. Individual responses to DM management are unique to the duration and stage of the disease, life expectancy, and predisposition to DM complications⁷. With the large number of people with DM, innovative solutions utilising digital interventions can enable better DM care as part of multifaceted interventions following validated treatment guidelines. Innovative solutions for DM care are critical for Lower- and Middle-Income Countries (LMICs) where deficiencies of healthcare services and shortage of healthcare professionals are particularly grave.

Studies have demonstrated the utility of smartphone apps in complementing DM care⁶³. The number of smartphone users has surpassed 2 billion in 2016 and is expected to increase to 2.86 billion by 2020²⁶⁰. Currently, the Android and Apple markets represent 80% and 15% of the apps market share, respectively. The number of health apps worldwide has also increased from 165,000 to 318,000 in 2017 in a span of 2 years⁶². As described in section 1.4.1, the clinical effectiveness of smartphone apps in HbA1c reductions have been demonstrated through patient education, telemonitoring and interventions eliciting behavioural change^{63, 119-121}. With increasing evidence in the clinical effectiveness of apps for DM care^{62, 261}, the number of DM management apps are expected to further increase in magnitude and capabilities to help meet the unmet needs of patients.

While health app developments are advancing rapidly, the number of apps intended for DM (including T2D) self-management is unknown. Studies of health apps are also generally limited to English language apps. Disparities in health app access and usage exist within and between health systems^{208, 209}. With a large number of non-English speaking people with DM worldwide, it is imperative to understand the global DM apps landscape and appreciate the applicability of high-quality mobile health (mHealth) apps for different populations and contexts.

3.2 Objectives

The objectives of this study were to assess (1) the number and proportion of DM self-management apps in major languages spoken in ten countries with the largest numbers of people with DM; and (2) clinical relevance of selected apps in each language.

3.3 Methods

3.3.1 Selection of apps

The method of app selection and identification was similar to the process of a systematic literature review²⁶². In brief, China, India, USA, Brazil, Russian Federation, Mexico, Indonesia, Egypt, Japan and Pakistan were identified as the ten countries with the largest numbers of people with DM based on the latest NCD-RisC publication²⁶³. App users were assumed to prefer to use apps in their mother tongue. Hence, the languages spoken and used most frequently in these countries were included in this study. These languages were Chinese for China, Hindi for India, English for the USA, Portuguese for Brazil, Russian for the Russian Federation, Spanish for Mexico, Bahasa Indonesia for Indonesia, Arabic for Egypt, Urdu for Pakistan, and Japanese for Japan. Hindi and English were used for India as they are the official languages in India. Although only approximately 12% of the Indian population speaks English, India has the second-largest English-speaking population after the USA. Apps in Indian vernacular languages were identified from screening the English search results as searches in Indian vernacular search terms returned close to zero results. These apps would either have partial descriptions in a vernacular language or English descriptions indicating that the app is in a vernacular language. In addition, a search was conducted for apps in German, French, Tamil, Bengali, Danish, Korean, Norwegian, Polish, Malay, Filipino and Swedish to cover major international languages.

The titles and descriptions of Android and iOS smartphone apps were extracted in ten languages with a search strategy. All extracted app titles and descriptions were checked for language relevance on Google Translate and sorted by their identified languages. Other unspecified languages were dropped from the analysis. Duplicated apps in the same language and on the same app platform were removed before being screened for relevance to DM self-management by trained reviewers.

3.3.2 Search strategy

Diabetes mellitus related search terms such as “Diabetes”, “Glucose”, “Insulin” and variations of these words were searched on the Android and iOS platforms in June 2017 in ten languages. A search for Chinese language (Mandarin) apps in the Android market was additionally conducted on third-party platforms such as “Baidu”, “Wandoujia” and “360 Zhushou” due to Google restrictions in China. Native speakers translated the terms from English to Chinese, Arabic, Spanish, Portuguese, Russian, Japanese, Hindi, Urdu and Bahasa Indonesia.

3.3.3 App screening

App titles and descriptions were screened in English, Chinese, Arabic, Spanish, Portuguese, Russian, Japanese, Bahasa Indonesia and Urdu. The purpose of app screening was to identify the number of apps relevant to DM self-management based on the search terms to enable a more accurate assessment of the proportion of apps in different languages. Self-management, in this context, refers to behaviour or actions an individual can partake to manage DM without the presence of a healthcare professional. Apps in all languages were correctly classified by the Google language detector except for English language apps, as a mixture of English and other languages are mentioned in some app descriptions. These apps were checked and reclassified into their appropriate language. Approximately 1% of the apps were translated into multiple languages and duplicated across the languages covered by this study. All apps were screened by native speakers.

Prior to the full screening, 100 English apps were selected randomly for adjustments of the inclusion and exclusion criteria by six reviewers independently. The six reviewers included me (the PhD candidate) and five second- and third-year undergraduate medical students from Lee Kong Chian School of Medicine, Singapore. The students were selected based on their interest in global health and were trained to conduct systematic app assessments. Fleiss’s generalised kappa coefficient, an adaptation of Scott’s pi was used to calculate the inter-rater agreement

among all reviewers²⁶⁴. An agreement between 60–80% represents a reasonably good agreement among the reviewers²⁶⁵. Disagreements were discussed, and the apps were rescreened until a good agreement was achieved between the reviewers. The final inclusion and exclusion criteria are shown below:

Inclusion criteria:

- Targeted at people with all types of DM
- For self-management or informal caregivers of people with DM
- Recipes specifically for DM

Exclusion criteria:

- Apps intended solely for healthcare provider's use
- Medical dictionaries for doctors or patients
- Apps for T2D prevention or prediction of DM risk
- Apps promoting pharmaceutical products without any DM self-management components
- Apps for general well-being without a specific focus on DM
- Apps intended for other chronic diseases other than DM
- Apps espousing traditional cure
- Demonstration/trial apps

3.3.4 App assessments

The inclusion criteria were narrowed to focus on adults with T2D for the app assessments, as a large number of DM self-management apps users are expected to be people with T2D¹¹⁸. Selected apps were downloaded and assessed against a checklist developed with reference to the 2017 ADA clinical guidelines⁸. A clinically relevant app should reliably facilitate T2D self-care through knowledge empowerment, self-awareness promotion, added convenience, and goal setting. Apps should also cover essential domains such as physical activity, nutrition, weight, medicines management, smoking cessation, foot and eye care, psychosocial care, and lipids and blood pressure management. Up to three apps in each language were

selected from the list of apps screened and determined to be suitable for T2D self-management based on availability, downloads and popularity. Selected apps must be suitable for adults with T2D, and at least have information or a functionality supporting blood glucose monitoring, as optimal blood glucose control is often the primary outcome of DM (including T2D) management. A criterion is considered to have been met if the app contains content or any functionality in the DM care domains listed in Table 3.1.

3.3.5 Data analysis

Apps were profiled according to the app platform and language. Descriptive summary statistics were used to collate the number and proportion of apps according to languages. Excel 2016 was used to conduct all analyses.

Table 3.1 Selected ADA standards mapped with possible diabetes mellitus self-management app functions

Selected ADA standards of medical care in diabetes ^d	Self-care domain	How apps can complement care
<p>Successful diabetes care requires a systematic approach to support patients' behaviour change efforts, including the following:</p> <ol style="list-style-type: none"> 1. Healthy lifestyle choices (healthy eating, physical activity, tobacco cessation, weight management, and effective strategies for coping with stress) 2. Disease self-management (taking and managing medications and, when clinically appropriate, self-monitoring of glucose and blood pressure) 3. Prevention of diabetes complications (self-monitoring of foot health; active participation in screening for eye, foot, and renal complications; and immunizations) 4. Identification of self-management problems and development of strategies to solve those problems, including self-selected behavioural goal setting 	<p>Identification of essential domains that facilitate behavioural change</p>	<p>Apps should incorporate components that can support behavioural change in people with diabetes</p>
<p>Diabetes self-management education (DSME) is recommended to facilitate knowledge, skills, and ability necessary for diabetes self-care and in diabetes self-management support to assist with implementing and sustaining skills and behaviours needed for ongoing self-management, both at diagnosis and thereafter.</p>	<p>All</p>	<p>Provide accurate information to facilitate diabetes self-care through knowledge empowerment</p>

^dDiabetes here refers to all types of diabetes, as the ADA guidelines incorporated all types of diabetes.

3. Clinical relevance of smartphone apps for the management of diabetes mellitus: A global overview

Most adults with Type 1 and Type 2 diabetes should engage in moderate-to-vigorous intensity physical activity for 150 min or more per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 mins/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.	Physical activity	Provide information on the importance and recommended amount of physical activity. Tracking of exercise levels will help to guide treatment decisions and promote self-awareness on the progress of diabetes management
Nutrition therapy has an integral role in overall diabetes management, and each person with diabetes should be actively engaged in education, self-management, and treatment planning with his or her health care team, including the collaborative development of an individualised eating plan. All individuals with diabetes should receive individualised medical nutrition therapy (MNT), preferably provided by a registered dietitian who is knowledgeable and skilled in providing diabetes-specific MNT.	Nutrition therapy	Provide information on healthy food choices and food to avoid. A food database with nutritional information should be provided for reference. Meal logging will also guide treatment decision and promote self-awareness of the dietary patterns
In overweight and obese patients with Type 2 diabetes, modest weight loss, defined as sustained reduction of 5% of initial body weight, has been shown to improve glycaemic control and reduce the need for glucose-lowering medications. For many obese individuals with Type 2 diabetes, weight loss >5% is needed to produce beneficial outcomes in glycaemic control, lipids, and blood pressure, and sustained weight loss of ≥7% is optimal.	Weight management	Provide information on the importance of weight loss in obese people with diabetes. BMI and weight tracking can guide treatment decisions and promote self-awareness in the progress of weight loss
Advise all patients not to use cigarettes and other tobacco products or e-cigarettes. Include smoking cessation counselling and other forms of treatment as routine component of diabetes care.	Smoking cessation	Provide information on the importance of smoking cessation in people with diabetes

3. Clinical relevance of smartphone apps for the management of diabetes mellitus: A global overview

The care team, which includes the patient, should prioritise timely and appropriate intensification of lifestyle and/or pharmacological therapy for patients who have not achieved the recommended metabolic targets. To inform this process, providers should routinely assess medication adherence.	Medicine management	Provide information on common diabetes medications and the importance of medication adherence. Tracking of medication can guide treatment decisions (i.e. whether to increase medication dosage) and promote self-awareness in people with diabetes
Psychosocial care should be integrated with a collaborative, patient-centred approach and provided to all people with diabetes, with the goals of optimising health outcomes and health-related quality of life. Providers should consider assessment for symptoms of diabetes distress, depression, anxiety, disordered eating, and cognitive capacities using patient-appropriate standardised and validated tools at the initial visit, at periodic intervals, and when there is a change in disease, treatment, or life circumstance.	Psychosocial issues	Tracking of the patient's mood at different time points of the day can alert the healthcare provider of coping issues and factors that may cause irregular blood glucose levels
Optimise glycaemic control, blood pressure and serum lipid to reduce the risk or slow the progression of retinopathy. Patients with Type 2 diabetes should undergo an initial dilated and comprehensive eye examination by an optometrist at the time of diabetes diagnosis.	Diabetic retinopathy	Provide information on the importance of glycaemic control in delaying the progression of retinopathy and ways to perform eye care
Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputation. All patients with diabetes should have their feet inspected at every visit.	Foot care	Provide information on the importance and ways to perform foot care

Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of 140 mmHg and a diastolic blood pressure goal of 90 mmHg. Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease if they can be achieved without undue treatment burden.	Hypertension/ Blood pressure control	Blood pressure tracking and monitoring will help the user and healthcare provider to predict and understand the risks of cardiovascular diseases
For adults that do not take statins, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter, or more frequently if necessary. Obtain a lipid profile at initiation of statin therapy and periodically thereafter as it may help to monitor the response to therapy and inform of adherence.	Lipid management	Cholesterol level tracking can assist in formulating personalised nutritional therapies
When prescribed as part of a broad educational program, SMBG may help to guide treatment decisions and/or self-management for patients taking less frequent insulin injections or noninsulin therapies. When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique, SMBG results, and their ability to use SMBG data to adjust therapy. When prescribing Continuous Glucose Monitoring (CGM), robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use.	Self-monitoring of Blood Glucose	Provide information on the importance of SMBG and ways to perform SMBG. Monitoring/tracking of blood glucose levels and insulin intake will help to guide treatment decisions and promote self-awareness in the control of blood glucose levels

Table 3.1 Statements relevant to the self-management of Type 2 Diabetes (T2D) were extracted from the 2017 ADA clinical guidelines and grouped into self-care domains. The potential app functionalities in complementing T2D self-care were described under each self-care domain. A clinically relevant app should reliably facilitate diabetes self-care through knowledge empowerment, self-awareness promotion, added convenience, and goal setting. Apps should also cover essential domains such as physical activity, nutrition, weight, medicines management, smoking cessation, foot and eye care, psychosocial care, and lipids and blood pressure management. A criterion is considered to have been met if the app contains content or any functionality in the domains listed in the table.

3.4 Results

Overall, the DM-related search terms identified 3374 Android (inclusive of Mandarin apps) and 4477 iOS apps from the respective app markets. After screening, 1019 Android and 1303 iOS apps were screened and determined to be relevant to DM self-management. Of the included apps, 193 apps were duplicated across the Android and iOS platforms. Although the English language search terms returned the highest number of results compared to all other languages, approximately half to a third were reclassified as apps of other languages. Reclassified apps in languages that were not in the scope of this study were excluded from the analysis.

3.4.1 Proportion of apps by languages

The app description screening classified 27.6% more iOS apps that were relevant to DM self-management compared with Android apps. English and Mandarin apps constitute over 80% of apps for DM self-management among the ten languages spoken by countries with the largest numbers of people with DM on both app platforms (refer to Figure 3.1). The inclusion of eleven other languages and dialects prior to screening did not alter the proportion of English and Mandarin apps significantly. Mandarin apps have the largest proportion of relevant DM self-management apps on the Android platform, possibly due to the large app user base and low barriers of entry to the many third-party Android app platforms. English language DM apps dominate the iOS market.

Figure 3.1 Number and proportion of diabetes apps suitable for diabetes mellitus (DM) self-management after app description screening

English and Mandarin apps constitute over 80% of apps for DM self-management among the ten languages spoken by countries with the largest numbers of people with DM on both app platforms.

3.4.2 Relevance of apps from DM-related search terms to DM self-management

The proportion of apps relevant to DM self-management was determined by computing the percentage of apps included after screening the list of apps obtained from the searches. Overall, the searches conducted using the DM-related search terms returned with apps that were of low relevance to DM self-management (refer to Figure 3.2). It was also observed during the apps screening that many apps provided recommendations or claimed to “cure diabetes” without any supporting evidence.

The iOS apps in Urdu and Hindi were all identified from the English search terms, as the search terms in these languages did not return any results. There were five or fewer apps identified for DM self-management in these two languages on each

platform, and the apps were mainly focused on diet and education. Despite the high number of apps found using the English search terms, only approximately a quarter of the apps were determined to be relevant for DM self-management. Mandarin Android apps have the highest proportion (55.6%) of apps relevant for DM self-management, possibly due to the additional searches conducted on third-party platforms that dominate the app market in China, such as Baidu, Wandoujia and 360 Zhushou.

Figure 3.2 Proportion of apps relevant to diabetes mellitus (DM) self-management by language

Overall, the searches conducted using the DM-related search terms returned with apps that were of low relevance to DM self-management. Mandarin Android apps have the highest proportion (55.6%) of apps relevant for DM self-management. Only a quarter of English language apps were determined to be relevant for DM self-management despite the high number of apps found with the English search terms.

3.4.3 Clinical relevance of DM apps

The profile of apps checked against the list of criteria extracted from the ADA guidelines is shown in Figure 3.3. The criteria were grouped according to information provision and app functionality, and apps were colour coded according to language. Each fulfilled criterion was subsequently coded in the colour corresponding to the language of the app. The row height of each column shows the logarithm of the number of Android downloads of the app. The majority of the apps assessed were

available on both the Android and iOS platforms, but Android apps were assessed due to the existence of third-party Android platforms in China. Eighteen apps were assessed across all languages. Except for English, Mandarin and Japanese apps, I could not find more than two apps with at least information provision or recording functionality of blood glucose level in other languages. Only one app available in various Indian vernacular languages (including Hindi and Urdu) met the criteria for app assessment.

The apps in English and Mandarin had many more users and possessed more comprehensive DM management functionalities in general, compared with the apps in other languages. None of the apps assessed met all the criteria for information provision and app functionalities. Although the English apps were very close to meeting all of the criteria relating to app functionalities, none of these top downloaded apps had any form of information provision. Two of the three Mandarin apps assessed had full information provision, but both apps contained online retail services and dubious information sources for users. It is also noteworthy that of the apps with information provision, none of the apps assessed had information cited from accredited sources.

As blood glucose level information or functionality was set as the basis for selecting apps for assessment, all of them except for one app had a blood glucose management functionality. Insulin, food and oral medication logging were found in two thirds of the apps assessed. Only five out of the eighteen apps allowed the user to set blood glucose level goals, and only three apps had mood tracking functions.

3. Clinical relevance of smartphone apps for the management of diabetes mellitus: A global overview

Figure 3.3 Profile of apps assessed in ten languages against an American Diabetes Association clinical guideline derived checklist.

†The app in Hindi and Urdu are the same

The criteria were grouped according to information provision and app functionality, and apps were colour coded according to language. Each fulfilled criterion was subsequently coded in the colour corresponding to the language of the app. The row height of each column shows the logarithm of the number of Android downloads of the app.

3.5 Discussion

The systematic screening identified more than 2000 apps for DM (including T2D) self-management across ten languages, covering more than half of the world's population. These apps are not distributed proportionately across app operating platforms and the languages assessed. English and Chinese speaking populations have a greater variety, and more clinically relevant apps to choose from, while other populations may not have an app of clinical relevance. Despite the large variety of apps for T2D self-management, none of the apps assessed for clinical relevance covered all the essential app functionalities and provided information from accredited sources. Several observations can be derived from our findings.

3.5.1 Perception of health apps influences its adoption

There is potential for mHealth to improve the quality of healthcare in all countries. However, adoption of this innovation in healthcare lags behind other industries, which undermines any benefit mHealth can bring to population health. For the technologically astute smartphone user, health apps can assist in relieving stress from the demands of managing a newly diagnosed or long-standing chronic disease. A useful app will enable better collection, organisation, dissemination, and management of information, which brings convenience and helps in the adjustment of lifestyle changes. However, the adoption of a health app is dependent on patients' and clinicians' perception of its utility. For example, less than a third of the apps assessed in our study provided information on T2D management, which may imply either a lack of demand for T2D education or perceived low importance of T2D education by app developers.

Poor perception of health apps usually arises from a lack of trust in obtaining information and managing one's health condition via a piece of software developed by a third party. Health policymakers should engage the right stakeholders early in the app development process. For example, involving both patients and clinicians in

the design of an app can increase the possibility of creating a more clinically relevant, patient-centred, and user-friendly app.

Improper information dissemination and use of apps can be detrimental to the user. Miscalculation of insulin doses by an app can potentially be fatal to people with DM^{175, 179}. For example, the observation that many apps provided recommendations or claimed to “cure diabetes” without any supporting evidence could mislead the user to act inappropriately. Therefore, elements that ensure patients’ and clinicians’ trust in the use of apps for DM management, such as government support in implementation, funding, quality assessment, regulation, and interoperability, should be addressed to improve perceptions of health apps and to drive mHealth adoption.

3.5.2 Health app recommendations should be incorporated into clinical guidance

The role of the medical professional evolves with technological advancements. With the easy accessibility of online information, patients are empowered to take a more active role in healthcare partnership with the physician^{266, 267}. For example, patients can search for medical information online before the consultation and discuss their newly acquired health knowledge with the physician instead of passively waiting for the physician to explain the health symptoms. Patients may even ask the doctor for advice on the use of new technologies (e.g. apps). Therefore, having clinical guidance would provide physicians with more confidence in recommending relevant technologies for patients to use outside the clinical setting.

There is a lack of mHealth regulation regardless of the number of apps in a language. This problem is intensified in countries with a range of health apps for consumers to choose from. Support from an authoritative body, provision of more guidance on app selection, and communication between patients and clinicians will enhance the incorporation of app use into the clinical pathway. Recommendations should minimally be made based on an available, accredited and clinically relevant app. App functionalities and content should be assessed to identify potential ‘useful’ attributes

for the different types of DM self-management, and this information could be used to create a trusted platform to guide app selection. For example, the US FDA has issued a consultation on draft guidance for industry and FDA staff²⁶⁸, and a digital innovation action plan to commit to the regulation of digital health products. The United Kingdom National Health Service launched a beta digital Apps Library in April 2017 to host approved (from a technical perspective) healthcare apps that can be trusted by the public²⁶⁹. Apps that were listed on the NHS platform were assessed using a set of tools to ensure its safety and validity.

3.5.3 Populations most in need often do not have access to technology

The inverse care law, which states that “the availability of good medical care tends to vary inversely with the need for it in the population served” was observed in the use of mHealth^{209, 270}. Rural populations, and those living in LMICs, have lower access to medical resources and have a greater need for alternative solutions such as health apps. Our study, however, showed that their needs were not catered for. For example, there were very few DM (and T2D) self-management apps in Hindi, Urdu and Bahasa Indonesian despite a large number of people with T2D residing in these countries. The most highly downloaded apps in these languages were also not as comprehensive as English language and Mandarin apps. Although studies have demonstrated the ability of technology to improve access to care, inequality is still high between the young and old, and more and less deprived populations²⁰⁹. Apps with elderly-friendly features are needed²⁷¹, as the elderly population is capable of adopting mHealth. While e- and m-commerce have grown tremendously in China, mHealth presents more challenges in terms of pricing and regulations²⁷².

Under-developed app markets can focus on creating high-quality apps through partnerships, learning from examples, and translation of high-quality apps to context-specific content and languages for the population of interest. As only 12% of the Indian population speak English, most of the older and rural Indian population rely on vernacular language for communication. However, most Indian apps for DM self-

management only have an English description, which implies that the app user has to be proficient in English to use an app in a vernacular language. The lack of apps in vernacular languages presents a significant gap as future internet and smartphone populations in India will be older, more rural, more gender-balanced and more vernacular. There were a few apps that were translated into various Indian vernacular languages, but no single or combination of apps covered the full spectrum of DM self-management. An example is the 'Humrahi' app (identified from the app screening and app assessment) which educates patients and caregivers on DM care. Translation of app languages will improve the adoption of apps and enable broader population coverage.

3.5.4 Future directions

As DM is a complex disease, a stand-alone app is less likely to be effective in helping the patient achieve good DM treatment outcomes. A good app should be tailored to users' requirements and supported by healthcare-affiliated systems. In addition, governments or insurers can consider reimbursing health apps that have shown to be effective in disease management to better integrate apps into the overall care path.

With continuous technology advancements, healthcare professionals have to keep abreast of the latest health technologies to relate to different segments of the population. Medical schools will also have to continuously update their curriculum and teaching pedagogies to prepare future healthcare professionals for the digitised world^{273, 274}. Medical students should be familiarised with technology use, be taught to communicate effectively with empowered patients, and be informed of the latest regulatory updates on the use of these technologies.

Moving forward, mHealth in DM care should focus more on the safety and effectiveness of apps in DM care. Frameworks should be in place to control the quality of apps used for chronic disease management. The reliability of the educational content or advice given by the app is of paramount importance, as such information can potentially elicit behavioural change¹⁷¹. For example, DM apps can

be checked for the advice given on acute complications surrounding blood glucose fluctuations, and the prevention and management of complications and multimorbidities. These frameworks should also be regularly updated according to accepted DM guidelines to keep up with the evidence base. I have since developed a tool to systematically assess the content, features and reliability of T2D apps, which will be discussed in Chapters 4 and 5.

3.5.5 Limitations

There are some limitations to this study. First, description screening enables the identification of potential apps for DM self-management, but not the utility of the app, as the usability and content of the apps were not assessed. Second, the number of apps in the market increases quickly, limiting any precise estimation of app numbers. Third, apps with multiple language versions may be counted more than once. Apps intended for the Indian or Pakistani population may also be described in English, but the screening does not enable the identification of the country of origin of the developer, thus limiting the classification of the apps by country. Lastly, relevance to DM self-management is context-specific and dependent on individual needs, but this study covered a broader range of apps to account for different needs.

3.6 Conclusion

In conclusion, every patient with DM who has a smartphone and speaks one of the above ten languages can access an app for DM self-management. English and Mandarin literate people with DM will have more app choices to self-manage DM but may face challenges in selecting the most suitable app. A larger variety of health apps can cater to more diverse user needs, but too many unregulated apps that do not meet user expectations may lead to app fatigue and erosion of trust in this mode of support for DM care. In low resource settings, one high-quality app for a specific population may suffice to complement DM care. While there is an app for everyone, not everyone can have an app. The future of mHealth is rosy with the rise in smartphone ownership and an increase in positive evidence. The onus is on

3. Clinical relevance of smartphone apps for the management of diabetes mellitus: A global overview

governments and regulators to develop minimum quality standards and quality assurance processes (e.g. through curation, certification, etc.) to assist the industry, clinicians and patients alike and drive mHealth adoption.

Chapters 4 & 5

(Two articles comprise Chapters 4 & 5)

Medication management support in diabetes: A systematic assessment of diabetes self-management apps

This article has been published as

Huang Z, Lum E, Jimenez G, Semwal M, Sloat P, Car J. Medication management support in diabetes: a systematic assessment of diabetes self-management apps. BMC Medicine. 2019;17(1):127. <https://doi.org/10.1186/s12916-019-1362-1>

The contributions of the co-authors are as follows:

- I (ZH) conceptualised, developed and refined the medication management diagram and app assessment criteria; screened and assessed apps; cleaned, analysed and interpreted data; drafted and revised the manuscript.
- Dr Elaine Lum (EL) co-conceptualised the medication management diagram; provided critical input into the developed app assessment criteria; assessed apps; interpreted data; revised the manuscript.
- Mr Geronimo Jimenez (GJ) refined the app assessment criteria; assessed apps; obtained access to restricted apps; interpreted data; revised the manuscript.
- Dr Monika Semwal (MS) contributed to the development of app assessment criteria; assessed apps; reviewed the draft manuscript.
- Prof Peter Sloat (PS) provided critical input to the study and draft manuscript.
- Assoc Prof Josip Car (JC) conceptualized the overall study; obtained the funding; supervised the team; provided critical input into all stages of the study; critically reviewed the draft manuscript.
- I would also like to acknowledge Dr Ming Keat Sng (MKS), Dr Li Li (LL), and Ms My Linh Thai (MLT) for their input in piloting and refining the app assessment criteria; Ms Christina Tan (CT) and MLT for their assistance in app assessment.

*Rights to reuse this article in my dissertation was obtained from the publisher

Medication management apps for diabetes: Systematic assessment of the transparency and reliability of health information dissemination

This article has been published as

Huang Z, Lum E, Car J. Medication management apps for diabetes: Systematic assessment of the transparency and reliability of health information dissemination. JMIR Mhealth Uhealth 2020;8(2):e15364. <https://doi.org/10.2196/15364>

The contributions of the co-authors are as follows:

- I (ZH) conceptualised, developed and refined the adapted HONcode app assessment criteria; screened and assessed apps; cleaned, analysed and interpreted data; drafted and revised the manuscript.
- Dr Elaine Lum (EL) co-conceptualised and provided critical input into the developed app assessment criteria; assessed apps; interpreted data and revised the manuscript.
- Assoc Prof Josip Car (JC) conceptualised the overall study; obtained the funding; supervised the team; provided critical input at all stages of the study; and critically reviewed the draft manuscript.
- I would also like to acknowledge Mr Geronimo Jimenez (GJ) for his input in piloting and refining the app assessment criteria; and Ms Christina Tan (CT), Ms My Linh Thai (MLT) and GJ for their assistance in app assessment.

Chapter 4

Medication management support in Type 2 diabetes: A systematic assessment of diabetes self-management apps (Study methods)

This chapter describes the motivation, objectives and method employed for the systematic assessment of medication management features in T2D self-management apps. Searches for English language apps were conducted in the Apple and Google Play stores using diabetes search terms, and those with both medication and blood glucose management features were downloaded and evaluated against assessment criteria: (1) derived from international medication management and diabetes guidelines, and (2) adapted from the Health on the Net code of conduct (HONcode) principles. Apps were then grouped by platform (i.e. Android, iOS) and profiled according to each criterion using descriptive statistics.

4.1 Motivation for the study

Medication adherence, broadly understood as the act of taking medicines as prescribed by the healthcare provider, is paramount for achieving treatment goals²⁷⁵ for chronic diseases such as T2D. However, studies have shown that approximately 33% of oral medications and 38% of insulin for T2D were not taken prescribed^{73, 79} due to forgetfulness, inconvenience, negative treatment beliefs, fear of injections and a myriad of other personal and health system factors⁸¹.

Medication management strategies have been developed and implemented to assist people in adhering to their medications. Successful strategies for T2D include education on disease management¹⁰⁷, simplification of dosing regimen¹⁰⁶, counselling, reminders, or a combination of these methods^{78, 112}. Despite having these strategies in place, success rates vary according to the duration of the disease, ease of implementing the strategies, and the reason for medication non-adherence^{73, 276}. The appropriate strategy has to be applied to tackle different reasons for medication non-

adherence. Unintentional non-adherence such as forgetfulness can be tackled by reminding patients to take their medication, while intentional non-adherence requiring behavioural change can be tackled with knowledge transfer and effective communication²⁷⁶. On top of that, the social environment exerts considerable influences on patients' medication-taking behaviour^{53, 277}. Being in a supportive network can improve the motivation, coping, and psychological well-being of a person with chronic illness, which indirectly translates to better self-management²⁷⁷. For example, a supportive spouse can provide verbal encouragement and help to facilitate medication adherence. However, social interactions may also influence negative behaviour in chronic illness management. Friends and family members may behave in an unsupportive way (e.g. discarding the patient's medications), offer advice that conflicts with self-management due to misconceptions, or promotes unhealthy behaviour (e.g. encouraging excessive alcohol intake)²⁷⁷.

Digital solutions have been studied in the past 20 years to assist in medication adherence. Although research has shown that mobile text messaging can double the odds of medication adherence in chronic diseases¹⁴¹, more successful interventions often involved the use of two-way communication¹⁴⁶ and were tailored to individual needs^{142, 144}. One-way communication in this context refers to the patient receiving the reminder only, while two-way communication refers to the patient receiving the reminder and replying to confirm whether the medication was taken. A meta-analysis found that two-way text messaging were significantly better at improving medication adherence compared with one-way text messaging¹⁴⁶. These studies suggest the need for innovation and a combination of measures that go beyond basic reminders to improve medication adherence.

Smartphone apps have gained popularity in T2D self-management in recent years. Compared with SMS reminders, smartphone apps have the advantage of performing more sophisticated medication management functions such as pill organisation, tracking of medication-taking, information provision, and adherence assessment¹¹². For example, smartphone apps can help the user to access medication information at the point of care conveniently¹¹⁹, track missed and skipped doses, and reduce the cost

of traditional medication adherence interventions¹¹². These features were not available with SMS reminders.

With the rise in the number of smartphone users^{62, 278} and integration of smartphone apps in daily living¹¹⁹, a myriad of apps were developed to assist people in adhering to their medications. Despite the large number (approximately 400) of accessible and free apps for medication self-management in the app market in recent years¹⁴⁸, the majority of these apps lacked useful and desirable features for medication adherence¹⁴⁹. According to national digital health consumer surveys, only 11% of respondents tracking health goals tracked their medications¹¹³. Medication adherence is also least likely to be tracked in an app (10%) amongst other trackable health-related metrics like physical activity, heart rate and sleep¹¹⁴.

Motivation for assessing the medication management features of T2D apps

Currently, the large number of available T2D management apps provides an opportunity to support medication management but also represents missed opportunities to improve care for people with T2D with the gaps that fall short of users' needs²⁷⁹. It is unclear if T2D apps are adequately incorporating medication management strategies and if app features are aligned with best-practice evidence-based recommendations²⁸⁰. Improvements in app quality and utility can only be realised if gaps in-app features are identified.

Motivation for assessing the reliability and transparency of T2D apps

While conducting the global DM app assessment study, I encountered apps that claimed to “cure” or “reverse” diabetes. Although the two major app stores (i.e. Apple and Google Play) review apps prior to publication (refer to [Appendix 2](#) for pre-review app publication checklists of Apple and Google Play app stores), many apps that do not conform to the pre-review checklist fall through the net and are published.

The regulation of app stores also falls outside the purview of governmental agencies such as the U.S. FDA²⁸¹. Only a small subset of apps that pose higher risks to patients and meet the regulatory definition of “device” are regulated by the FDA^{175, 180, 181}. Therefore, apps with inaccurate content or inappropriate advertisements may still be

published and be available to consumers^{179, 282, 283}. For example, a 2019 study assessing the content of suicide and depression apps found six apps that offered incorrect crisis helpline numbers, which may pose a serious risk to users²⁸⁴. Another earlier study assessing the content of asthma apps found that 77% of apps with advertisements advertised products that were unrelated to health²⁸². The lack of transparency regarding an app's source of content may cast doubt on the reliability of the information it disseminates^{180, 182, 183}, and can potentially mislead or bring harm to patients who have lower health literacy¹⁸⁴.

Concerns over the credibility and reliability of online health information sources began to surface in the early days of Internet usage^{285, 286}. The Health On the Net code of conduct (HONcode), with eight principles (i.e. Authoritative, Complementarity, Privacy, Attribution, Justifiability, Transparency, Financial disclosure and Advertising policy) for website certification, was developed to help guide and standardise the reliability of health and medical information published on the Internet²⁸⁷. As the current reliability and transparency of information disseminated via these apps are unknown, adapting these principles for app assessment will provide an overview, and help to identify gaps in this area.

4.2 Objectives

The objectives of this study are (1) to construct a diagram linking good medication management practice with possible app features; (2) systematically assess and characterise the medication management features in T2D self-management apps and their congruence with best-practice evidence-based criteria; and (3) systematically assess the transparency of information disseminated via these apps against the eight criteria adapted from the HONcode principles.

4.3 Methods

4.3.1 Development of app assessment criteria and diagram

Statements from international medication management guidelines and literature were extracted based on their applicability to chronic disease self-management^{86, 101, 288-295}. As app use was not recommended in any medication management guidelines, app features that were deemed to be desirable for a medication management app (e.g. allowing the medication-taking schedule to sync with the phone calendar), but were not found in international medication management guidelines were included in the classification.

Similar concepts (i.e. factors) were grouped, mapped with possible app features and assigned a group heading for classification purposes. The groups of app features were then linked by adapting the diagram from Stowasser's medication management pathway²⁹⁶, which describes consumer-focused cognitive and physical steps involved in the use of medicines²⁹⁶. For example, the process "Monitor for response" in Stowasser's diagram was termed as "Adherence and Monitoring" in my diagram. Possible app features that can support medication adherence and monitoring were listed and classified under this category. The development of this diagram was an iterative process as new features of medication management apps were identified and added through the app assessment process. Figure 4.1 illustrates the relationship between the factors for good medication management practice and possible app features.

4. Systematic assessment of Type 2 diabetes self-management apps (Study methods)

Figure 4.1 Diagram of app features mapped with factors for good medication management practice

Statements from international medication management guidelines and literature were grouped according to adaptations from Stowasser's medicines management pathway. App features were then mapped with the groupings to link the features into a medication management pathway. The mapped features were used to develop evidenced-based criteria for app assessment. Different box colours were used to differentiate layers of the medication management app pathway.

The possible app features for T2D self-management (from Figure 4.1) were developed into app assessment criteria (Table 4.1). Each assessment criterion was mapped back to medication management guidelines. For example, the assessment criterion “The app allows users to assess medication adherence by comparing planned and actual medication-taking”, operationalised through the app’s logging and tracking features, was mapped to guidelines recommending clinicians to “Routinely assess adherence during prescribing, dispensing, and reviewing medicines” for medication adherence.

The eight HONcode principles (i.e. Authoritative, Complementarity, Privacy, Attribution, Justifiability, Transparency, Financial Disclosure and Advertising Policy) were adapted and termed the App-HONcode criteria to suit the context of health apps and app assessment.

All app assessment criteria had binary responses (Yes/No) for consistency, except for App-HONcode criteria “Attribution” and “Justifiability”. The “not applicable” option was included for these two criteria to account for apps that did not provide health information within the app.

I developed the initial version of the app assessment criteria and Figure 4.1 with detailed input from two pharmacists (EL and MS) with extensive research experience in medication adherence. EL also had more than ten years of experience working as a hospital and community pharmacist in Singapore and Australia. The earlier versions of the criteria were subsequently piloted among the app assessment team members with highly downloaded (>100,000 downloads) apps for T2D management to refine and improve the clarity of the assessment criteria. The app assessment team comprises members with medical, pharmacy, psychology, bioethics, health economics, and public health background. Unclear statements were discussed among app assessment team members until a consensus was reached (refer to section 4.3.2 on the procedures of app assessment). The refined criteria then received input from by a range of healthcare professionals and academics from various healthcare disciplines and nationalities.

The final assessment criteria are shown in Tables 4.1(Criteria developed from international diabetes and medication management guidelines and literature) and 4.2 (App-HONcode criteria).

Table 4.1 App assessment criteria with the corresponding guidance/evidence extracted from international diabetes and medication management guidelines and literature. This set of assessment criteria focuses on but is not limited to Type 2 diabetes.

S/N	App Assessment Criteria	Excerpt of extracted guidance/ Justification	Supporting references
1	Planning and organisation		
1.1	The app has a feature that allows the user to display scheduled medications as different visual compartments (e.g. visual pillbox in the app)	<u>Reduce dosing complexity</u> Use blister or compartmentalised boxes to reduce dosing complexities	86, 289, 293, 295
1.2	The app has a feature that allows the user to switch between daily and weekly medication schedule displays		
1.3	The app has a feature that allows the user to schedule medication-taking on alternate days (e.g. Pill A on Monday, Wednesday, Friday; Pill B on Tuesday, Thursday, Saturday etc.)		
1.4	The app has a feature that enables the user to enter the purpose of the medication	<u>Planning and organisation</u> Develop an individualised, documented self-management plan including the plan's start and review date, conditions being managed, description of the medication (frequency, dose, strength, instructions, known reactions, allergies, and length of treatment)	86, 288, 289, 293, 295
1.5	The app has a feature that allows the user to enter special instructions for the medication (e.g. to be taken before food)		
1.6	The app has a feature that allows the user to organise "take as needed" medications in a separate section from medicines with a fixed regimen		
1.7	The app has a feature that allows the user to enter/log at least 4 different medications at any given time		
1.8	The app has a variety of dosage input options (e.g. subcutaneous insulin for diabetes, oral medications)		
1.9	The app has a feature that allows the user to document allergies (i.e. via prompts/greyed out instructions or a separate tab)		
1.10	The app has a feature that allows the user to sync the medication-taking schedule with their phone calendar	For user convenience, eliminating the need to open a separate calendar to view the medication schedule.	

4. Systematic assessment of Type 2 diabetes self-management apps (Study methods)

2	Adherence and monitoring		
2.1	The app has a feature that allows the user to record the fraction of an actual pill or volume of a liquid medication prescribed (i.e. ½ pill or 5 ml of syrup) to be recorded.	Oral tablets may be prescribed as a fraction of one and liquids are prescribed as a specified volume. Apps that do not allow this will be less helpful and could introduce errors.	
2.2	The app has a feature that allows users to document medication-intake	<u>Monitoring</u> Record medicines taken, self-monitor the condition and report all adverse reactions.	86, 288, 289, 293, 295
2.3	The app has a feature that allows users to record notes on any medication event (i.e. a “note/comment” section at the logging page or as a separate tab)		
2.4	The app has a feature that allows users to document medication side-effects (i.e. via prompts/greyed-out instructions or a separate tab)		
2.5	The app has a feature that assesses medication adherence by comparing planned and actual medication-taking (e.g. the app generates a weekly percentage of adherence or has a visual display).	<u>Adherence assessment</u> Routinely assess adherence during prescribing, dispensing, and reviewing medicines.	86, 289, 292, 293, 295
3	Information provision		
3.1	The app has a feature that provides users with information about the prescribed medication	<u>Information provision</u> Repeatedly offer clear, understandable, and relevant information about the medication prescribed. Provide resources to enable information about medication to be obtained.	288, 292, 293, 295
3.2	The app has a feature that provides users with resources (in-app or external link) to access information about the prescribed medication		
4	Complementary medicines		
4.1	The app has a feature that asks users about the use of complementary medicines	<u>Complementary medicine</u> Take into account all complementary medicines the person is taking or using, and its purpose.	288, 292, 293, 295
4.2	The app has a feature that flags possible contraindications with the use of complementary medicines		

4. Systematic assessment of Type 2 diabetes self-management apps (Study methods)

5	Reminders		
5.1	The app has a feature that allows users to set up reminders for taking medications	<u>Reminders</u> Reminders have shown to improve adherence to medicines despite inconclusive evidence.	288, 292, 293, 295
5.2	The app has a feature that allows users to set up reminders to refill prescriptions	<u>Refill medication</u> Prescription refill is an indirect method for measuring medication adherence and could alert prescribers and pharmacists to problems of adherence.	
6	Motivation		
6.1	The app has a feature that motivates users through statements on the importance of medication adherence	<u>Behavioural change</u> Positive reinforcements are important in sustaining behavioural change (Guidelines). Providing consequences and benefits of effective medication adherence helps the patient to understand the need and to establish motivation to adhere to medication. Positive reinforcements are important in sustaining behavioural change.	289, 292
6.2	The app has a feature that provides encouragement when medication is taken on schedule (i.e. encouraging messages, “badges or awards”)		
7	Caregiver’s involvement		
7.1	The app has a feature that allows users to sync medication-taking schedule with caregiver’s phone	<u>Carer’s involvement:</u> Keep an up-to-date list of all medicines the patient is taking and take note of any allergic or adverse reactions to medicines.	86, 289, 293, 295
7.2	The app has a feature that supports multiple user profiles (e.g. for family members or carers)		
8	Communication with a healthcare provider		
8.1	The app has a feature that allows users to contact a healthcare provider regarding queries on medication	<u>Communication with a health provider</u> Establish the most effective way of communicating with each patient.	86, 289, 292, 293, 295

4. Systematic assessment of Type 2 diabetes self-management apps (Study methods)

9	Communication with the health system		
9.1	The app has a feature that supports data export	<p><u>Communication within/across health settings</u></p> <p>Health and social care practitioners should share relevant information about the person and their medicines when a person transfers from one care setting to another. Use the most effective and secure way with one or multiple approaches, such as secure electronic communication.</p>	86, 288, 289, 293, 295

Legend: **CG76:** Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence⁸⁶; **NG5:** Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes²⁸⁸; **NCCPC:** medicines and supporting adherence [Full guideline and evidence]²⁸⁹; **King's fund:** Polypharmacy and medicines optimisation: Making it safe and sound²⁹³; **AHRQ** (Evidence Report)²⁹²; **APAC:** Australian Pharmaceutical Advisory Council Guiding principles for medication management in the community²⁹⁵

Table 4.2 Adapted HONcode (App-HONcode) criteria for health app assessment

Attribute	HONcode	App-HONcode criteria	Options
Authoritative	The qualifications of the authors are indicated	Does the app indicate the qualifications of specific individuals who developed or contributed to the development of the app?	Yes/No
Complementarity	Information should support, not replace, the doctor-patient relationship	Is there a disclaimer stating or which implies that the information provided and/or app functions do not replace the healthcare provider's advice?	Yes/No
Privacy	Respect the privacy and confidentiality of personal data submitted to the site by the visitor	Is there a privacy and confidentiality clause in the app?	Yes/No
Attribution	Cite the source(s) of published information, date medical and health pages	Are information sources in the app cited?	Yes/No/NA

4. Systematic assessment of Type 2 diabetes self-management apps (Study methods)

Justifiability	Justifiability: Site must back up claims relating to benefits and performance	Are the claims relating to benefits and performance in the app description backed up by evidence? (Answer "NA" if there are no claims)	Yes/No/NA
Transparency	Accessible presentation, accurate email contact	Are the developers contactable by email?	Yes/No
Financial disclosure	Identify funding sources	Does the app indicate any funding sources? ("Yes" if the app is managed by a registered commercial company)	Yes/No
Advertising policy	Clearly distinguish advertising from editorial content	Are adverts distinguishable from the content of the app?	Yes/No/No advertising

4.3.2 Apps selection and assessment

The methods in this study were adapted from principles of a systematic review to minimise bias. A systematic review uses systematic methods to appraise or synthesise findings. Steps to conduct a systematic review include framing the research question, devising a search strategy, screening and selecting studies with pre-defined criteria, extracting data from selected studies and summarising and evaluating the quality of extracted data^{297, 298}.

Search strategy

Diabetes terms were searched to capture apps marketed as DM self-management apps. The Google Play and Apple app stores were searched in June 2018 via an app market explorer (<https://42matters.com/>), which covers both app stores in 55 countries. The search terms used in the English language were “(Diabetes OR Diabetic OR Diabetics) OR (glucose OR glycaemic OR glycemic OR blood sugar OR HbA1c OR A1c) OR insulin”. A list of app titles and descriptions was produced for screening.

Screening

The inclusion and exclusion criteria were scoped to fit the aim and objectives of the study. App titles and descriptions were screened for inclusion and exclusion using the following process: a random sample of 100 apps were first screened by two researchers to ensure consistency in the interpretation of the inclusion and exclusion criteria. Differences in interpretation were resolved via consensus discussions. The list of 100 apps was re-screened until an inter-rater agreement of above 80% was achieved. Disagreements that cannot be resolved during between the two reviewers were discussed with all team members. Unclear titles and descriptions were conservatively included for downloading and re-screening. Apps available on both the iOS and Android platforms were treated as unique apps due to possible differences in versions across platforms.

The following inclusion and exclusion criteria were used:

Inclusion criteria:

- Apps with medication self-management features
- Apps with any blood glucose logging features
- Apps in the English language
- Free apps and apps requiring payment

Exclusion criteria:

- Patient health portals linked to patients' electronic health records
- Apps that were not updated after January 1, 2017
- Apps intended for healthcare professionals
- Apps including insulin calculators/bolus correctors only
- Apps requiring exclusive blood glucose monitoring device tie-in
- Apps duplicated on the same platform
- Apps with regional restrictions
- Technical problems (e.g. crashes, screen hangs, unable to login, unable to download)

App assessments

The medication management features of selected apps were evaluated against the app assessment criteria. Three apps with extensive features were selected to pilot app assessment and refine the assessment criteria. Daily hands-on sessions (2 weeks) together with weekly meetings were used to refine the criteria, to resolve divergent/different interpretation of criteria when assessing the apps, and to calibrate app assessment between six team members. The pilot was concluded when at the end of 2 weeks and team members were highly consistent in the app assessments (over 90% agreement) using the refined criteria.

All apps that were screened to be eligible based on their title and description were then downloaded for re-screening. This step was split among six team members (refer to [Appendix 3](#) for the list of smartphones and their OS systems). Reasons for excluding the re-screened (downloaded) apps were noted by individual team members and discussed for consensus during team meetings. These discussions were documented in a codebook to ensure consistency in the app assessment process. App developers were contacted for access to restricted apps that were free to download. Apps that could not be accessed within a month of contact were excluded from the study. Free apps which offered additional features upon payment were evaluated with the additional features.

4.3.3 Statistical analysis

Screening

Cohen's Kappa was used to calculate the inter-rater agreement between two researchers during the screening process. An agreement score between 0.6 – 0.8 represents a reasonably good agreement between the reviewers²⁶⁵; a cut-off score of 0.8 was used in this study due to the broad inclusion criteria.

App assessments

Apps were grouped by platform (i.e. Android, iOS) and profiled according to their features (i.e. reminders, tracking, monitoring) and each App-HONcode criterion

using descriptive statistics. Only Android apps were further classified by the number of downloads (i.e. $\geq 100,000$ downloads, $< 100,000$ downloads) as information on the number of downloads were not available for iOS apps. The cut-off was set at $\geq 100,000$ downloads as approximately 5% of Android apps achieved more than 100,000 downloads. Pearson's Chi-Square test was used for comparisons between groups, and a two-tailed Fisher's exact test was used where the expected count is less than five in a group. Statistical significance was set at P-value < 0.05 . All analyses were performed using SPSS version 22²⁹⁹.

Chapter 5

Medication management support in Type 2 diabetes: A systematic assessment of diabetes self-management apps (Results and Discussion)

Following a description of the motivation, objectives, and methods employed for app assessment in Chapter 4, this chapter describes the results of app selection, characteristics of included apps and additional findings (i.e. issues observed) from the app assessments. The main results are then discussed with prior work comparisons, followed by discussions about study limitations, implications and recommendations for future work. Finally, this chapter ends with a conclusion of the app assessment study detailed in Chapters 4 and 5.

5.1 Results

The search terms yielded 3369 Android and 1799 iOS apps. After title and description screening, 191 (5.7%) Android and 160 (8.9%) iOS apps remained for downloading. Apps were further excluded due to their unavailability, exclusive device tie-in requirement, technical issues, failure to meet the inclusion criteria (i.e. non-English), and duplication on the same platform. Restricted apps that were inaccessible due to non-response from the developers were also excluded from the study. Finally, 143 apps (81 Android, 62 iOS) were downloaded and assessed against the app assessment criteria (Figure 5.1).

Figure 5.1 Flowchart for app selection

The search terms “(Diabetes OR Diabetic OR Diabetics) OR (glucose OR glycaemic OR glycemic OR blood sugar OR HbA1c OR A1c) OR insulin” yielded 4876 results from the app market explorer (<https://42matters.com>). After screening the app descriptions for relevance*, 351 apps were downloaded for assessment; 208 of these apps were excluded due to (i) technical issues, (ii) device tie-in, (iii) non-availability at time of app assessment, (iv) regional restriction, (v) failure to meet inclusion criteria on second screening, and (vi) duplication of apps on the same platform. Finally, 143 apps (81 Android; 62 iOS) were fully assessed against the app assessment criteria in Table 5.1.

*Relevance refers to meeting the inclusion and exclusion criteria listed in Section 4.3.2 (i.e. apps intended for T2D medication management, targeted at people with limited healthcare knowledge).

5.1.1 Characteristics of included apps (medication management features)

The frequency of app features grouped by each platform is shown in Table 5.1 below.

Planning and organisation

More than two-thirds of the apps allowed users to input insulin doses (86.0%, 123/143) and record multiple medications (68.5%, 98/143), while less than half of the apps allowed users to input special instructions (39.9%, 57/143) or the purpose (29.4%, 42/143) of the medication. A low proportion of the apps supported users in managing dosing complexities with digital visual compartments (4.9%, 7/143), toggling between daily and weekly displays (2.8%, 4/143), and pre-setting complex medication schedules (25.9%, 37/143). Few apps also specifically asked the user to document allergies (3.5%, 5/143) or allowed the user to sync medication schedules with the smartphone's calendar (4.9%, 7/143). No differences in the app features were observed between the operating platforms.

Monitoring and adherence

A significantly higher proportion of iOS apps had a basic medication tracking feature (Android: 70.4%, 57/81; iOS: 88.7%, 55/62; $p=0.008$) compared with Android apps. Although the note-taking feature of the apps (49.0%, 70/143) allowed free text entry, very few specifically asked the user to document medication side-effects (3.5%, 5/143). More than half of the apps allowed the recording of dose fractions (58%, 83/143), but 16.8% (24/143) allowed the user to review medication adherence by comparing planned and actual medication-taking.

Medication information

Few apps provided in-app medication information (8.4%, 12/143) or external resources to medication information (5.6, 8/143%). Two iOS apps prompted the user on the use of complementary medicine, but none of these apps was able to flag possible contraindications with the use of complementary medicines.

Reminders, motivation and caregiver's involvement

Slightly more than half of the apps (58.0%, 83/143) had a medication reminder feature. Few apps were able to remind the user to refill their medication (11.1%, 9/143); reinforced the importance of medication adherence (5.6%, 8/143); or encouraged medication-taking as scheduled with motivational messages (4.2%, 6/143). There were also very few apps that supported caregiver's involvement, such as supporting multiple user profiles (15.4%, 22/143) or enabling data syncing with a caregiver's phone (6.3%, 9/143).

Communication with provider and health system

Few apps allowed the user to ask a health professional questions about medications (11.2%, 16/143). For one-way data sharing, a significantly higher proportion of iOS apps had data export features (Android: 55.0%, 44/81; iOS: 72.6%, 45/62; $p=0.036$).

Table 5.1 Frequency of app features grouped by platform

	S/N	App features	All apps (n = 143) (%)	Android (n = 81) (%)	iOS (n = 62) (%)	p-value
Planning and Organisation	1.1	The app has a feature that allows the user to display scheduled medications as different visual compartments (e.g. visual pillbox in the app)	7 (4.9)	4 (4.9)	3 (4.8)	1.000^
	1.2	The app has a feature that allows the user to switch between daily and weekly medication schedule displays	4 (2.8)	3 (3.7)	1 (1.6)	0.633^
	1.3	The app has a feature that allows the user to schedule medication-taking on alternate days (e.g. Pill A on Monday, Wednesday, Friday; Pill B on Tuesday, Thursday, Saturday etc.)	37 (25.9)	24 (29.6)	13 (21.0)	0.241
	1.4	The app has a feature that enables the user to enter the purpose of the medication	42 (29.4)	22 (27.2)	20 (32.3)	0.507
	1.5	The app has a feature that allows the user to enter special instructions for medication (e.g. to be taken before food)	57 (39.9)	33 (40.7)	24 (38.7)	0.806
	1.6	The app has a feature that allows the user to organise "take as needed" medications in a separate section from medicines with a fixed regimen	12 (8.4)	6 (7.4)	6 (9.7)	0.628
	1.7	The app has a feature that allows the user to enter/log at least 4 different medications at any given time	98 (68.5)	56 (69.1)	42 (67.7)	0.859
	1.8	The app has a variety of dosage input options (e.g. subcutaneous insulin for DM, oral medications)	123 (86.0)	66 (81.5)	57 (91.9)	0.074
	1.9	The app has a feature that allows the user to document allergies (i.e. via prompts/greyed out instructions or a separate tab)	5 (3.5)	4 (4.9)	1 (1.6)	0.389^
	1.10	The app has a feature that allows the user to sync the medication-taking schedule with their phone calendar	7 (4.9)	2 (2.5)	5 (8.1)	0.239^

5. Systematic assessment of Type 2 diabetes self-management apps (Results and Discussion)

Monitoring and Adherence	2.1	The app has a feature that allows the user to record the fraction of an actual pill or volume of a liquid medication prescribed (i.e. ½ pill or 5 ml of a syrup) to be recorded.	83 (58.0)	45 (55.6)	38 (61.3)	0.491
	2.2	The app has a feature that allows users to document medication-intake	112 (78.3)	57 (70.4)	55 (88.7)	0.008*
	2.3	The app has a feature that allows users to record notes on any medication event (i.e. a “note/comment” section at the logging page or a as a separate tab)	70 (49.0)	35 (43.2)	35 (56.5)	0.116
	2.4	The app has a feature that allows users to document medication side-effects (i.e. via prompts/greyed-out instructions or a separate tab)	5 (3.5)	4 (4.9)	1 (1.6)	0.389^
	2.5	The app has a feature that assesses medication adherence by comparing planned and actual medication-taking (e.g. the app generates weekly percentage of adherence or has a visual display).	24 (16.8)	17 (21.0)	7 (11.3)	0.175
Information provision	3.1	The app has a feature that provides users with information about the prescribed medication	12 (8.4)	6 (7.4)	6 (9.7)	0.628
	3.2	The app has a feature that provides users with resources (in-app or external link) to access information about the prescribed medication	8 (5.6)	4 (4.9)	4 (6.5)	0.727^
Complementary medicines	4.1	The app has a feature that asks users about the use of complementary medicines	2 (1.4)	0 (0.0)	2 (3.2)	0.186^
	4.2	The app has a feature that flags possible contraindications with the use of complementary medicines	0 (0.0)	0 (0.0)	0 (0.0)	1.000^
Reminders	5.1	The app has a feature that allows users to set up reminders for taking medications	83 (58.0)	47 (58.0)	36 (58.1)	0.996
	5.2	The app has a feature that allows users to set up reminders to refill prescriptions	9 (11.1)	6 (9.7)	15 (10.5)	0.782

5. Systematic assessment of Type 2 diabetes self-management apps (Results and Discussion)

Motivation	6.1	The app has a feature that motivates users through statements on the importance of medication adherence	8 (5.6)	3 (3.7)	5 (8.1)	0.293^
	6.2	The app has a feature that provides encouragement when medication is taken according to schedule (i.e. encouraging messages, “badges or awards”)	6 (4.2)	3 (3.7)	3 (4.8)	1.000^
Caregiver's involvement	7.1	The app has a feature that allows users to sync their medication-taking schedule with a caregiver's phone	9 (6.3)	5 (6.2)	4 (6.5)	1.000^
	7.2	The app has a feature that supports multiple user profiles (e.g. For family members or carers)	22 (15.4)	11 (13.6)	11 (17.7)	0.494
Communication with healthcare provider	8.1	The app has a feature that allows users to contact a healthcare provider regarding queries on medication	16 (11.2)	7 (8.6)	9 (14.5)	0.269
Communication with health system	9.1	The app has a feature that supports data export	89 (62.7)	44 (55.0)	45 (72.6)	0.036*

*Statistical significance $P < 0.05$ in the comparison between Android and iOS app features

^Two-tailed p-value calculated using Fisher's-exact test as the expected count is less than 5 in at least a group

5.1.2 Characteristics of included apps (App-HONcode criteria)

Figure 5.2 shows the number and proportion of the assessed apps meeting the App-HONcode criteria. The number of “Yes” responses were summed up for each app to determine the number of App-HONcode criteria met. “NA” responses for “Attribution” and “Justifiability” were treated as “not meeting the criteria” for a more conservative approach, while the “No advertising” response for “Advertising policy”

was treated as a “Yes” (conforming to this principle). Most of the apps on both the Android and iOS platforms fulfilled between two to six criteria; one Android app met all eight criteria while another did not meet any of the criteria. A higher proportion of apps published on the iOS platform seemed to meet more App-HONcode criteria compared with apps on the Android platform. For example, 43.6% of iOS apps met at least 5 App-HONcode criteria compared with 28.3% Android apps.

Figure 5.2 Number and Proportion of diabetes apps meeting the App-HONcode app criteria.

The number of “Yes” responses were summed up for each app to determine the number of App-HONcode criteria met. “NA” responses for “Attribution” and “Justifiability” were treated as “No” while the “No advertising” response for “Advertising policy” was treated as a “Yes”.

Table 5.2 shows the profile of app attributes grouped by each platform. Few apps mentioned the qualifications of individuals who contributed to app development (14.0%, 20/143). Less than half of the apps have a disclaimer stating that the information provided/app functions do not replace a healthcare provider's advice (39.2%, 56/143) and approximately two-thirds of apps have a privacy and confidentiality clause (65.0%, 93/143). Of the apps providing health or medical information or made claims on its efficacy, only a third cited their information sources (35.7%, 15/42) and/or backed up the claims relating to benefits and performance in the app by evidence (30.4%, 7/23).

There were no significant differences between the Android and iOS platforms in the proportion of apps fulfilling each criterion except for the principle on "Transparency". Android apps have a significantly higher proportion of apps with the developer's email listed on the Google play store compared with apps listed on the Apple store (Android: 97.6%, 75/81; iOS: 83.9%, 52/62; $P=0.005$). Over half of the apps disclosed funding sources (61.5%, 88/143). Lastly, most of the assessed apps do not have advertisements (83.2%, 119/143). Of the apps with advertisements, three-quarters were distinguishable from the content of the app (75.0%, 18/24).

Table 5.2 Profile of app attributes grouped by platform

HONcode principle	App-HONcode criteria	All apps (n = 143) (%)	Android (n = 81) (%)	iOS (n = 62) (%)	P-value
Authoritative	Does the app indicate the qualifications of the specific individuals who developed or contributed to the development of the app?	20 (14.0)	9 (11.1)	11 (17.7)	0.332
Complementarity	Is there a disclaimer which states or implies that the provided information and/or app functions do not replace the healthcare provider's advice?	56 (39.2)	27 (33.3)	29 (46.8)	0.121
Privacy	Is there a privacy and confidentiality clause in the app?	93 (65.0)	48 (59.3)	45 (72.6)	0.113
Attribution	Are information sources in the app cited?	15/44 (34.1) ^a	8/22 (36.4) ^a	7/22 (31.8) ^a	1.000 [^]
Justifiability	Are the claims relating to benefits and performance in the app description backed up by evidence? (Answer "NA" if there are no claims)	7/24 (30.4) ^a	4/14 (28.6) ^a	3/9 (33.3) ^a	1.000 [^]
Transparency	Are the developers contactable by email?	131 (91.6)	79 (97.5)	52 (83.9)	0.005*
Financial disclosure	Does the app indicate the qualifications of the specific individuals who developed or contributed to the development of the app?	88 (61.5)	46 (56.8)	42 (67.7)	0.225
Advertising policy	Is there a disclaimer which states or implies that the provided information and/or app functions do not replace the healthcare provider's advice?	119 (83.2)	64 (79.0)	55 (88.7)	0.175
	Is there a privacy and confidentiality clause in the app?	18/24 (75.0) ^b	12/17 (70.6) ^b	6/7 (85.7) ^b	0.629

*Statistical significance $P < 0.05$ in the comparison between Android and iOS app features[^]Two-tailed p-value calculated using Fisher's-exact test as the expected count was less than 5 in at least a group^a"NA" removed before statistical analysis and percentage computation^bPercentage was computed by dividing (1) the number of apps with distinguishable advertisements with (2) the total number of apps with advertisements

5.1.3 Android apps by downloads

Assessment of medication management features

Android apps with <100,000 downloads were compared against those with higher downloads ($\geq 100,000$) (Table 5.3). Although only a small number (17/81,) of apps were downloaded $\geq 100,000$ times, a significantly higher proportion of these apps have features that allowed the user to separate medications into “take as needed” sections ($\geq 100,000$ downloads: 29.4%, 5/17; <100,000 downloads: 1.6%, 1/64; $P=0.001$), document medication-intake ($\geq 100,000$ downloads: 94.1%, 16/17; <100,000 downloads: 64.1%, 41/64; $P=0.016$), vary dosage input options ($\geq 100,000$ downloads: 100.0%, 17/17; <100,000 downloads: 76.6%, 49/64; $P=0.032$), set up reminders to refill prescriptions ($\geq 100,000$ downloads: 35.3%, 6/17; <100,000 downloads: 4.7%, 13/64; $P=0.002$), sync medication-taking schedule with caregiver’s phone ($\geq 100,000$ downloads: 23.5%, 4/17; <100,000 downloads: 1.6%, 1/64; $P=0.006$), support multiple user profiles ($\geq 100,000$ downloads: 35.3%, 6/17; <100,000 downloads: 7.8%, 5/64; $P=0.009$), support data export ($\geq 100,000$ downloads: 88.2%, 15/17; <100,000 downloads: 45.3%, 29/64; $P=0.002$). The number of downloads were not available from the Apple app store. Hence, iOS apps were not analysed in the same manner.

Table 5.3 Profile of medication management app features grouped by downloads (Android apps only)

	S/N	App features	All apps (n = 81) (%)	<100,000 downloads (n = 64) (%)	≥100,000 downloads (n = 17) (%)	p-value
Planning and Organisation	1.1	The app has a feature that allows the user to display scheduled medications as different visual compartments (e.g. visual pillbox in the app)	4 (4.9%)	3 (4.7%)	1 (5.9%)	1.000^
	1.2	The app has a feature that allows the user to switch between daily and weekly medication schedule displays	3 (3.7%)	1 (1.6%)	2 (11.8%)	0.110^
	1.3	The app has a feature that allows the user to schedule medication-taking on alternate days (e.g. Pill A on Monday, Wednesday, Friday; Pill B on Tuesday, Thursday, and Saturday, etc.)	24 (29.6%)	17 (26.6%)	7 (41.2%)	0.241
	1.4	The app has a feature that enables the user to enter the purpose of the medication	22 (27.2%)	16 (25.0%)	6 (35.3%)	0.540^
	1.5	The app has a feature that allows the user to enter special instructions for medication (e.g. taken before food)	33 (40.7%)	27 (42.2%)	6 (35.3%)	0.607^
	1.6	The app has a feature that allows the user to organise "take as needed" medications in a separate section from medicines with a fixed regimen	6 (7.4%)	1 (1.6%)	5 (29.4%)	0.001^*
	1.7	The app has a feature that allows the user to enter/log at least 4 different medications at any given time	56 (69.1%)	42 (65.6%)	14 (82.4%)	0.184^
	1.8	The app has a variety of dosage input options (e.g. subcutaneous insulin for DM, oral medications)	66 (81.5%)	49 (76.6%)	17 (100.0%)	0.032^*

5. Systematic assessment of Type 2 diabetes self-management apps (Results and Discussion)

	1.9	The app has a feature that allows the user to document allergies (i.e. via prompts/greyed out instructions or a separate tab)	4 (4.9%)	2 (3.1%)	2 (11.8%)	0.192
	1.10	The app has a feature that allows the user to sync the medication-taking schedule with their phone calendar	2 (2.5%)	2 (3.1%)	0 (0.0%)	1.000
Monitoring and Adherence	2.1	The app has a feature that allows the user to record the fraction of an actual pill or volume of a liquid medication prescribed (i.e. ½ pill or 5 ml of a syrup) to be recorded.	45 (55.6%)	35 (54.7%)	10 (58.8%)	0.76
	2.2	The app has a feature that allows users to document their medication-intake	57 (70.4%)	41 (64.1%)	16 (94.1%)	0.016*
	2.3	The app has a feature that allows users to record notes on any medication event (i.e. a “note/comment” section at the logging page or a as a separate tab)	35 (43.2%)	25 (39.1%)	10 (58.8%)	0.144
	2.4	The app has a feature that allows users to document medication side-effects (i.e. via prompts/greyed-out instructions or a separate tab)	4 (4.9%)	2 (3.1%)	2 (11.8%)	0.192^
	2.5	The app has a feature that assesses medication adherence by comparing planned and actual medication-taking (e.g. the app generates weekly percentage of adherence or has a visual display).	17 (21.0%)	12 (18.8%)	5 (29.4%)	0.334^
Information provision	3.1	The app has a feature that provides users with information about the prescribed medication	6 (7.4%)	4 (6.3%)	2 (11.8%)	0.601^
	3.2	The app has a feature that provides users with resources (in-app or external link) to access information about the prescribed medication	4 (4.9%)	3 (4.7%)	1 (5.9%)	1.000^

5. Systematic assessment of Type 2 diabetes self-management apps (Results and Discussion)

Complementary medicines	4.1	The app has a feature that asks users about the use of complementary medicines	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000^
	4.2	The app has a feature that flags possible contraindications with the use of complementary medicines	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000^
Reminders	5.1	The app has a feature that allows users to set up reminders for taking medications	47 (58.0%)	37 (57.8%)	10 (58.8%)	0.94
	5.2	The app has a feature that allows users to set up reminders to refill prescriptions	9 (11.1%)	3 (4.7%)	6 (35.3%)	0.002^*
Motivation	6.1	The app has a feature that provides statements to motivate users about the importance of medication adherence	3 (3.7%)	2 (3.1%)	1 (5.9%)	0.512^
	6.2	The app has a feature that provides encouragement when medication is taken according to schedule (i.e. encouraging messages, “badges or awards”)	3 (3.7%)	1 (1.6%)	2 (11.8%)	0.110^
Caregiver's involvement	7.1	The app has a feature that allows users to sync their medication-taking schedule with a caregiver's phone	5 (6.2%)	1 (1.6%)	4 (23.5%)	0.006^*
	7.2	The app has a feature that supports multiple user profiles (e.g. for family members or carers)	11 (13.6%)	5 (7.8%)	6 (35.3%)	0.009^*
Communication with healthcare provider	8.1	The app has a feature that allows users to contact a healthcare provider regarding queries on medication	7 (8.6%)	4 (6.3%)	3 (17.6%)	0.157^

Communication with health system	9.1	The app has a feature that supports data export	44 (54.3%)	29 (45.3%)	15 (88.2%)	0.002 ^{^*}
----------------------------------	-----	---	---------------	---------------	---------------	---------------------

*Statistical significance $P < 0.05$ in the comparison of app features between Android apps with $< 100,000$ downloads and $\geq 100,000$ downloads.

[^]Two-tailed p-value calculated using Fisher's-exact test as the expected count is less than 5 in at least one group

Assessment with App-HONcode criteria

Table 5.4 shows the profile of app attributes for Android apps, grouped by the number of downloads ($< 100,000$ downloads and $\geq 100,000$ downloads). There were no significant differences between the apps with $< 100,000$ downloads and the apps with $\geq 100,000$ downloads in terms of the “Authoritative”, “Complementarity”, “Attribution”, “Justifiability”, “Transparency” and “Advertising policy” principles. A significantly higher proportion of the apps with $\geq 100,000$ downloads have a privacy and confidentiality clause ($\geq 100,000$ downloads: 88.2%, 15/17; $< 100,000$ downloads: 51.6%, 33/64; $P = 0.006$) and are more likely to discuss their funding sources ($\geq 100,000$ downloads: 82.4%, 15/17; $< 100,000$ downloads: 50.0%, 32/64; $P = 0.026$) compared with less downloaded apps.

Table 5.4 Profile of App-HONcode criteria grouped by number of downloads (Android apps only)

HONcode principle	App-HONcode criteria	All Android apps (n = 81) (%)	<100,000 downloads (n = 64) (%)	≥ 100,000 downloads (n = 17) (%)	P-value
Authoritative	Does the app indicate the qualifications of the specific individuals who developed or contributed to the development of the app?	9 (11.1)	8 (12.5)	1 (5.9)	0.676 [^]
Complementarity	Is there a disclaimer which states or implies that the provided information and/or app functions do not replace the healthcare provider's advice?	27 (33.3)	18 (28.1)	9 (52.9)	0.081
Privacy	Is there a privacy and confidentiality clause in the app?	48 (59.3)	33 (51.6)	15 (88.2)	0.006 [*]
Attribution	Are information sources in the app cited?	8/22 (36.3) ^a	7/19 (36.8) ^a	1/3 (33.3) ^a	1.000 [^]
Justifiability	Are the claims relating to benefits and performance in the app description backed up by evidence? (Answer "NA" if there are no claims)	4/14 (28.6) ^a	3/10 (30.0) ^a	1/4 (25.0) ^a	1.000 [^]
Transparency	Are the developers contactable by email?	79 (97.5)	63 (98.4)	16 (94.1)	0.378
Financial disclosure	Does the app indicate the qualifications of the specific individuals who developed or contributed to the development of the app?	46 (56.8)	32 (50.0)	14 (82.4)	0.026 [*]

5. Systematic assessment of Type 2 diabetes self-management apps (Results and Discussion)

Advertising policy	Is there a disclaimer which states or implies that the provided information and/or app functions do not replace the healthcare provider's advice?	64 (79.0)	50 (78.1)	14 (82.4)	1.000 [^]
	Is there a privacy and confidentiality clause in the app?	12/17 (70.6) ^b	11/14 (78.6) ^b	1/3 (33.3) ^b	0.19 [^]

*Statistical significance $P < 0.05$ in the comparison between apps with $\geq 100,000$ and $< 100,000$ downloads

[^]Two-tailed p-value calculated using Fisher's-exact test as the expected count is less than 5 in at least one group

^a"NA" removed before statistical analysis and percentage computation

^b Percentage is computed by dividing (1) the number of apps with distinguishable advertisements by (2) the total number of apps with advertisements

5.1.4 Additional findings

Several issues were observed during the app assessments. First, the medication logging features of some apps were limited by the absence of features such as timestamp, dosage, measurement unit and medication label. For example, one app restricted oral medications input to a maximum dosage of 99.9 mg despite the much higher dosage of some T2D oral medications. Another app limited medication labels to "Medication 1" and "Medication 2". A few other apps did not allow medication logging to be retrospective, nor allowed the tagging of an event (i.e. physical activity or a meal) to the medication.

Second, some apps had reminder features that did not allow the user to set a recurring alarm or pre-set a medication-taking schedule. In addition, a few apps had hard-to-find reminder features, faulty alarms that did not work or could not be stopped, and delayed notifications. Lastly, one app with inaccurate adherence tracking was observed. The app divided the percentage of medication "taken" and "skipped" in a pie chart without differentiating the type of medication nor the time period of the entry. Other issues include visually distracting advertisements (subjective to assessor's judgement), inability to set up a personal account, poor user interface and functional errors during usage (i.e. crashes).

5.2 Discussion

One hundred and forty-three apps were identified, downloaded and systematically evaluated against criteria derived from international T2D and medication management guidelines, and App-HONcode criteria adapted from the eight HONcode principles. All identified apps were intended for a layperson, had at least one feature that can assist the user in managing his/her medications, and had blood glucose logging features to assist people with T2D in managing their medications. As the descriptions of all apps on the app market explorer were scanned for the existence of the search terms, more than 90% of the results returned from the app store did not fit into the inclusion criteria described in Section 4.3.2. Having a conservative search strategy broadens the search and enabled more accurate identification of the apps of interest.

Strengths of this study include the development of app assessment criteria with reference to evidence-based guidelines and the coverage of a broader scope of medication management compared with other studies^{112, 149, 170}. For example, Dayer et al. did not employ a systematic search and evaluation process in the app assessment¹¹², Santo et al. covered only the Australian app market¹⁵² and Martinez et al. focused only on the iOS market¹⁷⁰. All three studies did not refer to any medication adherence guidelines in formulating the app assessment criteria. Free and paid apps which were not limited to one country's app store, were assessed in my study.

Assessment of medication management features

There were few differences in the app features between Android and iOS apps, except for a higher proportion of iOS apps with medication-intake documentation and data export features. Most of the assessed apps, including apps with higher downloads ($\geq 100,000$), have basic logging and tracking features for T2D medication, but lacked features that could enhance medication adherence and safety. The following gaps were identified from the app assessment.

First, approximately half (46.7%) of the apps for T2D self-management lacked any form of medication management features. This finding concurs with a 2017 study that found only 50% of the highest-rated iOS DM management apps to have medication adherence features¹⁷⁰. The study used a single “diabetes” search term to identify DM management apps on an iPad. Selected apps were assessed on attributes such as rating, number of reviews, price and DM management features. Although the method of identifying apps was different, the proportion of apps with medication adherence (part of medication management) features differed only slightly from my study. A separate study by our team, which employed a similar search strategy, also found that only 43% of the accessible T2D self-management apps had medication management features³⁰⁰. The lack of medication management features in T2D apps may be attributed to a lack of emphasis given to medication adherence in T2D management. Among the assessed apps with medication management features, a large proportion did not have essential features such as a basic reminder feature, the capability to enter medication-taking instructions and medication adherence review. Apps devoid of essential features for enhancing medication adherence are less likely to be useful in helping users adhere to their medications.

Second, less than 10% of the apps provided any information on T2D medication or allowed the user to communicate with a healthcare professional. Although this feature is more important for users adjusting to new medication therapy, the provision of information on medication will be beneficial as T2D is likely to progress over time. This feature was not assessed in other studies, as many medication adherence studies did not specifically focus on any chronic disease^{112, 152, 170, 301}.

Third, only two iOS apps prompted the user about the use of complementary medicine. The use of complementary medicine is common in many cultures and can lead to contraindications³⁰². Stopping conventional medication in favour of complementary medicine can also lead to ineffective or adverse treatment outcomes. It is important for app developers to include a cautionary message or features to alert users to potential contraindications. Documentation of allergies is also necessary to

flag possible medication or food-related contraindication, but only 3.5% of the assessed apps had this capability.

Fourth, less than 5% of the apps had features that provided any form of motivation to the user. A few apps that encouraged medication adherence had interactive features that could possibly increase time spent on the app. Sustained app use may increase medication-taking awareness of users who may otherwise fail to remember to take their medications. Fifth, about 40% of the apps do not allow data export, which can assist the individual or a healthcare provider in reviewing treatment plans and goals.

Lastly, less than a fifth of the apps had features that could facilitate carers' involvement in medication management. Although T2D can largely be self-managed, the support of an informal carer (often a family member) plays an important role in promoting medication adherence in people with T2D^{81, 303}. The relationship between the carer and the patient can be complicated due to dilemmas regarding the sharing of information and decision making, disputes over the control of medication, and differing motivation in disease management³⁰⁴. A balance that respects the autonomy of the patient while providing support for the carer needs to be sought for partnership in medication management. This balance is dynamic and has to be continuously renegotiated with every change in disease stage, treatment plans, and introduction of new technologies¹¹⁹. Apps have the capability to digitise the process of medication-taking and facilitate remote monitoring, but the utility of these capabilities depends on patients' intentions regarding medication management. Enhanced support in medication management may be well-received⁴⁹ or considered as an interference to patients who have other reasons to be intentionally non-adherent to their medications³⁰⁴. Therefore, it is important to negotiate an agreement based on the circumstances of each individual.

External monitoring is a strategy that enables users to send collected personal app data to third parties (such as family, friends, or health care providers)¹⁴⁸. This strategy is important for increasing the involvement of family members and health care providers in the care of patients with chronic conditions, but has been poorly utilised in medication adherence apps; only 5.2% of medication adherence apps employed

this strategy in Ahmed et al.'s study¹⁴⁸. Although my study did not assess this feature, the lack of data export capabilities limits external monitoring in apps.

The absence of involvement from health care providers in the development of the app may be an explanation for the lack of evidence-based features in health apps²⁸⁰. Only 13.6% of the apps for medication adherence were developed with the involvement of a health care provider, and only 1% of the apps were evidence-based according to another study which reviewed the evidence base, medical professional involvement in development, and strategies used to facilitate behaviour change in medication adherence apps¹⁴⁸. Intermittent app use or app intervention failure may sometimes be caused by a lack of useful app features rather than apps being ineffective per se. Many studies on medication adherence app intervention focused on reminding the user to take their medications, but the quality of reminder features and alignment with evidence-based recommendations were unclear^{153, 305}. Assessing the app against a medication management checklist (as illustrated in Figure 4) before the intervention will better align the app for its purpose.

While this study focused on users with T2D, 86% of the assessed apps allow users to log and track insulin doses and can hence also be used by people with T1D. However, adherence to insulin is more challenging than oral medications due to barriers such as fear of injections, embarrassment of administering injections in public, concerns over cost, and side effects such as hypoglycaemia^{79, 306, 307}. These barriers cannot be overcome by solely using a medication management app, although apps could potentially support adherence to insulin therapy by incorporating patient education.

Assessment with App-HONcode criteria

Most apps fulfilled between two to five assessment criteria, and only one Android app fulfilled all eight criteria. Overall, a higher proportion of iOS apps fulfilled more App-HONcode criteria compared with Android apps, although the differences were not significant.

Many apps were not transparent with the content source of the app. More than half of the assessed apps do not fulfil essential criteria, such as indicating the qualifications of individuals involved in the app development and disclaiming that the app does not replace healthcare provider advice. This result concurs with a study assessing eczema apps, where only 15% of the app developers indicated their qualifications and 46% disclaimed that the app does not replace the advice of the healthcare provider³⁰⁸. Although it may be challenging to indicate the qualifications of all individuals involved in the development of a complex app, the qualifications of the main content contributors and a representation of their collaborators should minimally be quoted to account for the content source of the app.

Approximately three-quarters of the assessed apps did not provide any health information. This was not surprising as disease management apps tend to emphasise management aspects rather than educating the patient¹⁶⁷, which presents a missed opportunity for patient education, which can be incorporated into apps. Of the apps that provided health information, only a third cited the source of information. Few of the assessed apps had claims relating to the benefits and performance of the app. However, only a third of these apps backed the claims with evidence. Apps or any consumer products with unsubstantiated claims have the potential to mislead and bring harm to the undiscerning consumer^{184, 309}. Therefore, it is imperative for app stores to check the veracity of the app description prior to its publication on the app stores.

Most apps displayed the email address of the developer, but the email address did not guarantee access to the app developer. App developers of apps that had access restrictions were contacted, and only 10% responded to the emails (two emails sent a week apart). This percentage should be higher for apps that are accessible, but there is a possibility that inoperative email addresses were displayed on the app stores. App stores should ensure the inclusion of a valid email address for all health apps for consumer enquiries.

Privacy breaches can erode consumer trust in the app. Two-thirds of the apps assessed had a privacy and confidentiality clause. This result was an improvement from a study

published six years ago assessing the availability, scope, and transparency of mHealth app privacy policies on 600 commonly used mHealth iOS and Android apps¹⁸³. One explanation for this improvement could be the changes made to the app store policies to improve the quality of apps over the years^{310, 311}. However, stricter scrutiny is required on the part of the app stores given the absence of privacy policies in many of the assessed apps. Although there is an improvement with the inclusion of a privacy policy for the assessed English language apps, those published on other platforms and in other languages may yield different assessment results.

Approximately 40% of the assessed apps did not have their funding sources indicated. The funding source of an app will affect its development, quality and the services provided. The lack of funding source disclosure represents a gap in which app stores can play a role to improve the quality assurance of health apps. Advertisements were not present in 80% of the assessed apps. This proportion may be lower as the best version of apps requiring in-app payments for feature upgrades were assessed. Studies have shown that paid apps were not of higher quality compared with free apps^{312, 313}. Approximately one third of the in-app advertisements were judged as being non-distinguishable from the content of the app. I did not scrutinize appropriateness of the advertising content, which may present an additional gap in the quality and reliability of information disseminated via these apps.

The originators of the HONcode recently published an extension for apps—mHONcode—to cover the certification of health information disseminated on apps³¹⁴. This new certification was only available after the app assessments were completed, but there are minimal conceptual differences between the App-HONcode and mHONcode. The App-HONcode criteria were worded in a manner that minimised subjectivity of assessment by different researchers.

5.2.1 Study limitations

Despite attempts to minimise bias, there were limitations to the study. First, the entire spectrum of medication management apps cannot be covered. Type 2 diabetes was

chosen as the disease focus due to its prevalence and the need for long-term medication management. Second, the assessment also may not reflect the current state of the apps due to constant updates. However, attempts were made to cover all apps at a particular time point. Hence, the findings should remain unchanged as a previous study showed that the quality of apps in terms of alignment with evidence-based guidelines did not improve within a two-year period³¹⁵.

Third, confirmation bias may exist in the app assessment³¹⁶. The app assessment criteria list for this study were selected based on their perceived usefulness to people with T2D that require long-term medication management. Other criteria, such as shared decision-making when medications were not taken as intended, the app's ability to flag medication contraindications, and the content of the medication information provided in these apps were not covered and could be considered for future assessments. Although steps were taken to minimise confirmation bias by getting inputs from academics and health professional experts, confirmation bias was inevitable as our past experiences and our environment shape our opinions. Additionally, the issues surrounding data management and the content of privacy and confidentiality clauses were not assessed. There is a possibility that apps may not accurately disclose details about the sharing of some personal information²⁵⁶.

Fourth, apps that do not provide health information (e.g. medication logging apps) may be underrated. Even so, many apps were not transparent in data privacy and in clearly distinguishing the complementarity of the app (i.e. not replacing the advice of healthcare providers).

Fifth, there was a lack of user input in the development of the app assessment criteria. The regular app user may not fully appreciate an app that fulfils app assessment criteria developed from the perspective of academics and health professional experts. Nevertheless, the development of the app assessment criteria is an essential step in providing a set of standards that benefits the interest of app users. Lastly, app assessments were subjective to researcher interpretation, although attempts were made to reduce researcher bias by piloting the assessment and using a standardised patient profile when interacting with apps.

5.2.2 Implications and future work

A minimum standard (i.e. certification or selection of apps using an evidence-based checklist) could be one way to raise the standard of medication management features of apps. The implementation of the NHS digital library and the FDA “precertification” program for mobile apps are precedents of tools used to objectively evaluate apps, although gaps still exist in the app marketplace in meeting patients’ and clinicians’ needs¹⁸¹.

In addition to certification, health app developers should take active steps to ensure that their apps meet minimum standards by co-designing apps with potential users and continuing to upgrade their apps. Experience-based co-design can provide insights and direction for the design of technologies with useful features³¹⁷⁻³²⁰. These techniques have been used for the design of apps in various healthcare disciplines such as dementia care³²⁰, health failure³¹⁹ and rheumatoid arthritis³¹⁸, although the health outcomes resulting from the use of such apps are yet to be assessed. Health care providers can take a more active role through participating in app co-design and work with their patients to effectively use an app to manage chronic conditions.

This study showed the immaturity of most apps in assisting a user with T2D to self-manage his/her medications. Therefore, researchers planning for studies involving medication adherence app intervention should also be aware of the shortcomings of current apps when evaluating the effectiveness of these apps in improving medication adherence.

The fulfilment of the eight App-HONcode criteria is actionable, but not many developers may be aware of the need to indicate background information nor check the content of advertisements, as their main aim is to get the app published. App developers and consumers would benefit from the availability of a standardised checklist to assess the information quality of health apps. It would be challenging for governments to regulate all health apps due to their ubiquity, pace of development, and ambiguity in their definition. Therefore, app stores should play a greater role in the quality assurance of health/medical apps. For example, app stores could make the

transparency and reliability of information dissemination a basic requirement for app publication. As observed from the app assessments, a larger proportion of apps that fulfilled more of the App-HONcode criteria were from the Apple app store, which was likely due to the higher barriers of entry currently set by the store (refer to [Appendix 2](#)).

The list of assessment criteria is non-exhaustive and should be tailored to patient needs and advancements in technology. Since T2D self-management requires additional self-care activities such as blood glucose monitoring, physical activity and diet modifications, other features of the app should be considered in assessing the overall quality of the app.

Given that these assessment criteria may apply to medication management of other chronic diseases, future studies can explore apps specific to other chronic diseases to determine if similar gaps exist. Studies can also explore the usability of these apps for better patient experience, as well as the efficacy of the medication management features in improving medication adherence in different settings.

As health apps collect a lot more user data than the internet, the consent-seeking process for data collection and data management policies of these apps should be evaluated in future. The appropriateness of advertising content and the clarity of privacy clauses for T2D management and other chronic disease management apps in other languages and on other platforms should also be checked, to provide a complete landscape of the transparency and reliability of information disseminated and collected through these apps.

5.3 Conclusion

The systematic app assessments provide an overview of the medication management features of T2D self-management apps and discovered gaps in the disclosure of the developer's qualification, funding source and the complementary role of the app in these apps. A large proportion of the apps lacked features that were useful for

enhancing medication adherence and safety, such as the capability to enter information on allergies and medication-taking instructions, working reminders, information provision, and prompts for the usage of complementary medicine. These gaps represent missed opportunities for better app quality, which can potentially enhance the utility and usage of digital medication management for people with T2D.

More emphasis should also be given to the inclusion and design of medication management features in apps for T2D self-management. Healthcare providers, app developers and researchers should be involved in the co-design of health apps to improve their quality and be aware of the shortcomings of current apps when making recommendations about their effectiveness. App stores should also play a larger role in scrutinising app publication, as higher barriers of app entry will enable the publication of apps with better disclosure of the app's content source. As the development of the App-HONcode criteria is preliminary, future work can further examine the consent seeking process for data collection, data management policies, and the appropriateness of advertising and clarity of privacy clauses.

Chapters 6 & 7

Medication app-herence for Type 2 diabetes in Asia: a feasibility randomised controlled trial

Chapters 6 & 7 are published as

Huang Z, Tan E, Lum E, Sloot P, Boehm BO, Car J. A Smartphone App to Improve Medication Adherence in Patients With Type 2 Diabetes in Asia: Feasibility Randomized Controlled Trial. *JMIR Mhealth Uhealth*. 2019;7(9):e14914. <https://doi.org/10.2196/14914>

The contributions of the co-authors are as follows:

- I (ZH) conceptualised and set-up the study; created the online surveys; trained the data collectors; collected and analysed data; drafted and revised the manuscript.
- Dr Eberta Tan (ET) co-conceptualized the study; supported study implementation; referred patients; supported extraction of clinical records data; critically reviewed the draft manuscript.
- Dr Elaine Lum (EL) provided critical input into the conceptualization of the study; supported study implementation; reviewed and revised the manuscript.
- Prof Bernhard Boehm (BB) and Prof Peter Sloot (PS) provided critical input to the study; critically reviewed the draft manuscript.
- Assoc Prof Josip Car (JC) obtained funding for the data collectors; provided critical input at all stages of the study; critically reviewed the draft manuscript.
- I would like to thank Dr Tay Tunn Lin (TTL), Dr Soh Shui Boon (SSB), Dr Khoo Joo Ching Joan (JK) and the staff of Changi General Hospital Diabetes Centre for their support in study recruitment.
- I would also like to acknowledge Ms My Linh Thai (MLT) and Ms Audrey Nah for their help in participant recruitment and data collection; and Medisafe® for providing technical support during the study.

*Rights to reuse this article in my dissertation was obtained from the publisher

Chapter 6

Smartphone app for medication adherence: A feasibility trial (Study methods)

The systematic app assessments described in the previous chapters helped me to familiarise with the smartphone app landscape and select a suitable app for a feasibility study. It is essential to understand the acceptance, usage patterns and effectiveness of a smartphone app on people with T2D to improve app adoption. I conducted a pilot study to determine the feasibility, acceptability and clinical outcomes of using a smartphone app to improve medication adherence in a multi-ethnic T2D Asian population. A feasibility study meets the objectives of my PhD research and will likely improve the success rate of future smartphone app studies in the same context. This chapter describes the methods employed for the feasibility trial, including the study motivation, objectives, study design, study procedures, and statistical analyses.

6.1 Motivation for the study

Medication non-adherence is a complex, costly and multi-dimensional problem that involves the patient, their healthcare providers, and the process of taking/using the medication⁷¹. Patient education, medication management, reminders and incentives to promote adherence are interventions that have been shown to improve medication adherence successfully⁸³. However, approximately a third to half of people with T2D worldwide are still not adherent to their medications^{73, 79}. People with T2D have poorer medication adherence if they do not believe in the safety and efficacy of the medication, which is common in asymptomatic diseases⁸⁹. Poor adherence to T2D medication results in suboptimal glycaemic control^{82, 321}, which increases the risk of T2D -related complications^{8, 322} leading to higher hospitalisation rates and emergency department visits^{94, 323}.

Smartphone apps are increasingly used as a complementary tool for T2D self-management (including medication management) in recent years. According to estimates from the IQVIA Institute for Human Data Science, the global number of health apps has almost doubled from 165,000 in 2015 to 318,000 in 2017^{62, 117}. A pooled analysis on the effect of smartphone apps for T2D self-management found an overall 0.5% reduction in HbA1c levels⁶³. Despite having emerging positive evidence on the efficacy of apps in T2D self-management^{62, 324}, gaps still exist in the utility of app features in meeting user needs^{167, 208, 279}. There is a paucity of studies on the efficacy and implementation of smartphone apps in supporting medication-taking¹⁴⁷; with only a small number of randomised controlled trials investigating medication adherence in people with high blood pressure^{154, 325}.

Furthermore, T2D and medication adherence app interventions are not well studied in Asian populations. Asians constitute 60% of people with T2D globally and are likely to have different cultural beliefs towards disease and medication management^{2, 326}. This represents missed opportunities to benefit up to 250 million people with T2D³²⁷. Given the acceleration of mobile connectivity in the Asia Pacific region in recent years³²⁸, it is timely to investigate the receptivity and usage of apps for T2D medication management in Asian populations with high mobile penetration. As Singapore progresses towards a smart nation, the integration of technology (including health apps) with daily living and T2D management is anticipated.

Population-based interventions involving smartphone apps are often complex and multifaceted due to challenges in controlling the environment²⁵⁷. In view of the challenges associated with evaluating complex health interventions, a feasibility and piloting phase to optimise study design and evaluation is warranted^{119, 257}.

6.2 Aim and Objectives

This study aimed to determine the feasibility, effectiveness, acceptability, and clinical outcomes of using a smartphone app to improve medication adherence in a multi-

ethnic T2D Asian population (Singapore) through a pilot. The objectives were to assess the:

1. Recruitment rate to determine the feasibility of implementing the study
2. Profile of randomised patients to determine the feasibility of the study design
3. Participants' interaction with the app to determine the feasibility and effectiveness of the intervention
4. Changes in self-reported barriers to medication adherence to determine the effectiveness of the intervention
5. T2D health outcomes (i.e. HbA1c, Lipid profile) to determine the short-term clinical outcomes of the intervention
6. Perception, attitudes and satisfaction with using an app for medication management to determine the acceptability of the intervention

6.3 Methods

The CONSORT checklist for feasibility trials³²⁹ and the mERA checklist for mHealth³³⁰ were used to report the study methods and findings (refer to [Appendix 4](#) for the checklists).

6.3.1 Study design

A randomised two-arm pre-test post-test control group design with a 12-week follow-up period was used. All participants received usual care, while the participants from the intervention group additionally downloaded and used the Medisafe® app on their personal smartphones during the study.

6.3.2 Study setting

Participants were recruited over ten weeks from September to November 2018 at a tertiary diabetes specialist outpatient centre (part of a 1,000-bed public hospital) in the Eastern region of Singapore. The centre serves both subsidised and private patients, as well as non-residents of Singapore. Patients were either self-referred or referred from primary care general practitioners, other departments in the same hospital or other hospitals. Usual care provided by the centre comprises 3-6 monthly clinic appointments. At each clinic appointment, patients have their blood pressure and body weight taken, undergo blood tests to monitor their blood glucose and lipid levels, review T2D management with their endocrinologist, and collect their prescribed medications from the hospital pharmacy. Consultations with the podiatrist, dietitian or other specialists (i.e. ophthalmologist, cardiologist, renal specialist) were arranged on an ad hoc basis (i.e. usually once a year for foot and eye examination). Patients are expected to self-manage their T2D (following their treatment plan) outside the hospital setting between these scheduled clinic appointments.

6.3.3 Participant recruitment and eligibility criteria

Potential participants were referred by four endocrinologists using a recruitment pamphlet (refer to [Appendix 5](#) for a sample of the pamphlet). To be referred by the endocrinologist, participants were:

- 1) At or above the age of 21 (the legal age for study consent in Singapore)
- 2) Diagnosed with T2D according to American Diabetes Association guidelines
- 3) On insulin or Oral Hypoglycaemic Agents
- 4) English speaking

Participants were excluded from the study if they were:

- 1) Pregnant
- 2) Cognitively impaired and/or diagnosed with psychological issues
- 3) Prisoners
- 4) Diagnosed with T1D
- 5) Bedbound and undergoing tube feeding

6) Prescribed medication for the first time

Referred patients who consented to participate in the study were asked to complete a baseline questionnaire, which also served as a screening tool to identify eligible patients for randomisation. To prevent the “ceiling effect”, participants who were adherent to their medications were screened out of the study. Participants were considered non-adherent to their medication if they answered “Strongly Agree” or “Agree” to the question “I forget to take my medicines some of the time” (ASK-12-Q1)

ASK-12 Q1: I forget to take my medicines some of the time

Options	Meets inclusion criteria?
Strongly Agree	Yes
Agree	Yes
Neutral	No
Disagree	No
Strongly Disagree	No

or if they answered “In the last week/month/3 months” to the question “Have you taken a medicine more or less often than prescribed?”(ask-12-Q8) in the Adherence Starts with Knowledge-12 (ASK-12) questionnaire³³¹.

ASK-12 Q8: Have you taken a medicine more or less often than prescribed?

Options	Meets inclusion criteria?
In the last week	Yes
In the last month	Yes
In the last 3 months	Yes
More than 3 months	No
Never	No

To screen out participants who were not digitally literate, participants must respond “Yes” to the question “Have you used any phone apps in the past two weeks?”. Lastly, to screen out participants who were already using an app to manage their medication, participants must respond “No” to the question “Have you used any smartphone app to manage your medications in the past two weeks?”.

Hence, secondary inclusion criteria for randomisation into the study were:

- 1) Self-reported medication non-adherence
- 2) Digitally literate
- 3) Not using a medication management app in the past two weeks

6.3.4 Study procedures

T2D patients identified to have met the referral inclusion criteria while attending their scheduled clinic appointments were referred to the researchers by their endocrinologist. Interested patients proceeded to provide informed consent for the study. The patient was termed a research participant once the informed consent document was signed. At the point of consent seeking, researchers explained to potential participants that they may or may not be selected for the study, depending on their eligibility which could only be determined after they responded to the baseline questionnaire.

Study data were collected and managed using REDCap electronic data capture tools hosted at Nanyang Technological University^{332, 333}. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. Upon receiving informed consent, REDCap generates a unique survey code linked to each participant's pre-defined email for the baseline and subsequent

follow-up surveys. All data in REDCap were de-identified apart from participants' email address. Baseline data were collected using an iPad on the day of recruitment before randomisation.

6.3.5 Intervention

Intervention group participants were asked to download and use the Medisafe® app to help them to manage their medications for 12 weeks. The researchers assisted the participants with downloading the Medisafe® app on their personal smartphone, setting their medication schedule and reminders on the app, and learning how to use the app. Participants were asked to use the app freely outside the healthcare setting and add the research group as a “Medfriend” for their medication-taking patterns to be observed.

Rationale for selecting Medisafe® app

The Medisafe® app a commercial, free to download medication management app available on both the Android and iOS platforms. Its features include medication scheduling, reminders, tracking, data sharing and medication adherence assessments. The medication schedule can be shared with a “Medfriend”, who can help to monitor and encourage better medication-taking behaviour. For the purpose of the research, this feature will only be used by the researcher to track participants' medication-taking patterns. Participants were not called up by the researcher if they missed a dose due to feasibility concerns. A more intrusive intervention may also deter participants from taking part in the study.

The Medisafe® app fulfilled the highest number (19/27, 70.4%) of medication management criteria in the app assessment described in Chapters 4 and 5. This app also fulfilled 6/8 app-HONcode criteria. One criterion—Attribution—was not fulfilled as the medication information in the app were not cited. There was an “NA” response in terms of justifiability as the app did not make any claims.

Another app—Care Zone—also fulfilled as many criteria in the app assessment but was not selected, as the app was created mainly for the U.S. population. Although the app can be downloaded in Singapore, users were encouraged to link their insurance number for free medication refill delivery. This may confuse the Singapore study participants. Another medication management app—Mango Health—had features that were not commonly found in other apps (i.e. drug interaction warning, a reward system for medication adherence), but was not available for the Singapore population.

Therefore, the Medisafe® app was selected based on the app assessment outcomes (detailed in Chapter 5), its applicability (free to download, available on both Android and iOS platforms) to the study, and evidence supporting its effectiveness^{62, 149}. A study which systematically assessed the features and quality of medication adherence apps ranked the Medisafe® app as the best advanced medication reminder app, as it had the highest engagement, functionality, aesthetics, and subjective quality score¹⁴⁹. Figures 6.1(a) – (d) show four screenshots of Medisafe® app features used by participants.

6. Smartphone app for medication adherence: A feasibility trial (Study methods)

Figure 6.1 (a) Screenshot of a participant's visual pillbox

Figure 6.1 (b) Screenshot of a participant's medication list

Figure 6.1 (c) Screenshot of a participant's medication adherence

Figure 6.1 (d) Screenshot of a participant's medication adherence

Participation follow-up

Intervention group participants were reminded via email to complete two intermediate surveys and one final online survey at 4-week intervals during the 12-week follow-up period. Control group participants were instructed to complete only one online survey at the end of the 12-week follow-up period. All follow-up surveys were conducted online via a unique link sent to the participants' email address. Each unique survey link was accessible for a maximum of 14 days or until the participant completed the survey. Calls were made to participants in both groups through their mobile phones to remind them to complete the final survey if no response was received a week after the survey was sent out. Participants were given grocery vouchers upon completion of each online survey. Voucher rewards were consolidated and collected by the participants from the diabetes centre at the end of the study. Feedback was collected from a small number of participants through the online satisfaction survey and while handing out vouchers to participants who completed the online survey(s).

6.3.6 Study outcomes

The primary outcomes were to determine the feasibility, effectiveness and acceptability of using a smartphone app to improve medication adherence in a multi-ethnic T2D Asian population (see Figure 6.2 for the schedule of data collection). Feasibility was determined based on the recruitment/enrolment rate (i.e. the percentage of people who declined participation in the study; the number of patients who consented to the study divided by the total number of clinic sessions). Another measure of feasibility is adherence to trial participation, which was assessed by observing the interaction of the intervention group participants with the app throughout the intervention using the "Medfriend" feature of the app. The research team, as a "Medfriend" of the participant, did not interact with the participant during the follow-up period. Reports on the medication-taking status of participants were generated at the end of the intervention (T3) through the app.

Effectiveness was measured with self-reported barriers to medication adherence, assessed at baseline (T0) and post-study (T3) in both groups with the ASK-12 questionnaire³³¹. The Appraisal of Diabetes Scale (ADS)³³⁴ was administered concurrently with ASK-12 to account for changes (if any) in the self-appraisal of T2D (refer to [Appendix 6](#) for the questionnaires).

Acceptability of app use intervention was determined through the self-reported perceptions, attitudes and satisfaction levels with using the app. Perception towards medication adherence and app usage were assessed at all three time points (T1, T2, T3), while attitude and satisfaction were only assessed post-study (T3). Control group participants were asked for the app that they used to manage their medication(s) (if any) in the past three months to assess the level of contamination in the control arm.

Secondary outcomes were T2D-related health outcomes. Data for assessing secondary outcomes such as anthropometric, blood glucose level, and lipids measurements were extracted from clinical records. The following data were also collected for participant profiling and baseline adjustments: data on medications and history of T2D-related complications from clinical records; socio-demographic data; and responses from a 16-item Diabetes Self-Management Questionnaire (DSMQ)²³⁰ collected at baseline (T0).

6. Smartphone app for medication adherence: A feasibility trial (Study methods)

Figure 6.2 Schedule of outcome measurements

Questionnaire abbreviations

ASK-12: Adherence Starts with Knowledge-12

ADS: Appraisal of Diabetes Scale

DSMQ: Diabetes Self-Management Questionnaire

6.3.7 Sample size

Power considerations are not necessary for a pilot or feasibility trial as the objectives are to test the trial procedures to obtain parameter estimates for a full trial rather than to prove the superiority of the intervention³³⁵. Since a formal assessment of the study efficacy is not required in a trial, rules of thumb are the simplest method to apply to a pilot or feasibility trial³³⁶. As a rule of thumb, a minimum of 12 participants per treatment arm is necessary to assess the objectives of the study in a two-arm trial³³⁶. Teare et al. recommended an overall pilot sample size of 70 to reduce the imprecision around standard deviation estimates³³⁶. Twenty-five to 35 participants per arm are sufficient to account for a dropout rate of about 40% as reported for email and internet response questionnaires³³⁷. An analysis of the sample size for a full trial is presented in [Appendix 7](#).

In summary, a minimum of 12 participants per treatment arm is necessary to assess the objectives of the study in a two-arm trial³³⁶ and 25 participants per arm is sufficient to account for a dropout rate of about 40%³³⁷. Therefore, a minimum of 25 participants per arm was targeted for ten weeks of recruitment.

6.3.8 Randomisation

Block randomisation (blocks of 4) was conducted to ensure a balanced allocation since the final sample size could not be anticipated. Eligible participants were asked to draw a card from a box with two “intervention” and two “control” cards which were reset after all four cards were drawn.

6.3.9 Blinding

The clinical care team was blinded from the study. Participants were only partially blinded as they had to be explained the purpose of before randomisation. The name of the app was only disclosed to participants who were randomised into the intervention group or screened out of the study (if participants request for it).

6.3.10 Data analyses

The intention-to-treat approach was used to analyse the data. Participants who did not complete the final survey due to the lack of post-study data for pre-post comparison were excluded. Intervention group participants who stopped using the app during the study and control group participants who used an app to manage their medications during the study follow-up period were included in the analysis. Scores for the ASK-12, ADS and DSMQ surveys were computed in accordance with the method suggested by the original authors^{230, 331, 334}. Descriptive analyses were used for baseline comparisons; linear regressions, controlled for baseline imbalances, were used to compare the pre-test and post-test change scores. All statistical assumptions were checked to ensure the accuracy of the analyses. Statistical significance was set at $p < 0.05$. SPSS version 22 was used for all statistical analyses²⁹⁹.

6.3.11 Ethics approval

This study was approved by the SingHealth Centralised Institutional Review Board (Reference: 2018/2563) and the Nanyang Technological University Institutional Review Board (Reference: IRB-2018-09-029) in Singapore. Licenses and permission to use published questionnaires were obtained from the original authors and relevant institutions prior to data collection (refer to [Appendix 8](#) for the IRB approval letters).

Chapter 7

Smartphone app for medication adherence: A feasibility trial (Results and Discussion)

Following a description of the study methods in the previous chapter, this chapter continues with the results and discussion. The chapter begins with a description of the recruitment outcome, followed by baseline characteristics and intervention outcomes of participants included in the analysis. I then discuss the results, strengths, limitations and observations of the recruitment before concluding this chapter with recommendations for future research.

7.1 Results

7.1.1 Recruitment

One hundred and seventy-six patients were referred and approached for recruitment over 48 three-hour clinic sessions. Fifteen patients (8.5%) declined to participate in the study, resulting in an enrolment rate of approximately three (161/48) patients per clinic session. The reasons given for rejecting study participation include concerns over the collection of personal data, pressed for time to leave the clinic, and refusal to complete the baseline survey. Of the 161 enrolled participants, 110 were not eligible for randomisation: 82 (50.9%) reported that they were adherent to their medications; 18 (11.2%) were not smartphone astute; seven (4.3%) refused participation, did not have an email address or were not confident with completing the online surveys; two (1.2%) were already using a smartphone app to complement T2D management, and one (0.6%) could not install the app.

Fifty-one (31.7%) participants met the inclusion criteria and were randomised to the intervention (n = 25) or control (n = 26) group. Twenty-two (88.0%) participants from the intervention group and 19 (73.1%) participants from the control group completed the post-intervention survey (see Figure 2). Three intervention group participants (3/22) indicated that they stopped using the app and two control group

participants (2/19) indicated that they had used an app for T2D self-management during the follow-up period (see Figure 7.1 for a diagram of participant flow).

Figure 7.1 Diagram of participant flow

*Participants were considered adherent if they answered “disagree/neutral” to the question “I forget to take my medicines some of the time” or any option within 3 months to the question “Have you taken a medicine more or less often than prescribed?” in the Adherence Starts with Knowledge-12 questionnaire.

**Patients who were not confident of using a new app.

#Three intervention group participants stopped using the app; two control group participants started using an app to manage T2D during the follow-up period.

7.1.2 Randomisation

Table 7.1 shows the baseline characteristics of the patients included in the analysis. Randomisation was successful as there are no statistically significant differences at baseline between groups for socio-demographic, clinical characteristics (e.g. blood test results, T2D-related complications, anthropometric measurements) and baseline questionnaires (e.g. DSMQ, ADS), apart from the number of years with T2D and the pre-test total ASK-12 score. Control group participants lived, on average, seven more years with T2D ($p=0.005$) and had a lower total ASK-12 score (I: 28.6; C: 25.5; $p=0.044$) compared with the intervention group. Higher ASK-12 scores represent higher barriers to medication adherence.

Table 7.1 Baseline characteristics of patients included in the analyses

Socio-demographics	Intervention (n = 22)	Control (n = 19)	p-value	
Age, median (min, max)				
Age	51.5 (22, 69)	52 (28, 67)	0.848 [#]	
Sex, n (%)				
Male	9 (40.9)	11 (57.9)	0.278	
Female	13 (59.1)	8 (42.1)		
Ethnicity, n (%)				
Chinese	10 (45.5)	12 (63.2)	0.257	
Non-Chinese	12 (54.5)	7 (36.8)		
Highest Education, n (%)				
Secondary school and below	11 (50.0%)	6 (31.6%)	0.488	
Junior college/Diploma	4 (18.2%)	5 (26.3%)		
University	7 (31.8%)	8 (42.1%)		
Housing, n (%)				
3-room and below	2 (9.1%)	4 (21.1%)	0.515	
4 and 5-room	12 (54.5%)	10 (52.6%)		
Above 5-room	8 (36.4%)	5 (26.3%)		
Household income, n (%)		(n = 20)	(n = 19)	0.170
<\$4000		6 (30.0%)	9 (47.4%)	
\$4000 - \$6999		4 (20.0%)	6 (31.6%)	
≥\$7000		10 (50.0%)	4 (21.1%)	
Clinical characteristics	Intervention (n = 22)	Control (n = 19)	p-value	
No. of years with Type 2 diabetes, mean (SD)				
Years with Type 2 diabetes	11.1 (7.1)	18.3 (8.4)	0.005 [*]	
No. of different types of medications, median (min, max)				
No. of medications	4 (1, 9)	4 (1, 13)	0.471 [#]	

7. Smartphone app for medication adherence: A feasibility trial (Results and Discussion)

Type of medications, n (%)				
Insulin	7 (31.8)	9 (47.4)	0.309	
Anti-hypertensive medication	11 (50.0)	5 (26.3)	0.121	
Cholesterol lowering medication	8 (36.4)	5 (26.3)	0.491	
Medication intensity, n (%)				
Oral medications only	7 (31.8%)	9 (47.4%)	0.051	
Insulin only	0 (0.0%)	3 (15.8%)		
Oral and insulin	15 (68.2%)	7 (36.8%)		
Anthropometric data, median (min, max)				
BMI	28.7 (20.2, 49.2)	28.3 (21.1, 35.6)	0.657 [#]	
Type 2 diabetes-related complications, n (%)				
Proliferative Diabetic Retinopathy	4 (18.2)	3 (15.8)	1.000 [^]	
Peripheral Vascular Disease	2 (9.1)	3 (15.8)	0.649 [^]	
Chronic Kidney Disease (≥Stage 3)	3 (13.6)	4 (21.1)	0.703 [^]	
History of major cardiovascular events	5 (22.7)	3 (15.8)	0.685 [^]	
Blood glucose level, median (min, max)				
HbA1c (%) (Pre-intervention)	8.2 (5.9, 14.8)	8.5 (6.4, 11.8)	0.574 ^b	
Lipid profile, median (min, max)				
LDL (mmol/L)	2.7 (2.0, 6.6)	2.4 (1.3, 4.3)	0.296 [#]	
HDL (mmol/L)	1.1 (0.9, 1.7)	1.0 (0.7, 2.0)	0.091 [#]	
Total cholesterol (mmol/L)	4.1 (3.2, 8.2)	4.1 (2.5, 6.9)	0.555 [#]	
Baseline questionnaires		Intervention (n = 22)	Control (n = 19)	p-value
Appraisal of Diabetes Scale, mean (SD) ^a				
Total score (baseline)		19.7 (3.7)	19.0 (3.8)	0.565
Diabetes Self-Management Scale score, mean (SD) ^b				
Total score (baseline)		2.0 (0.4)	2.0 (0.3)	0.693
ASK-12 medication adherence barrier survey, mean (SD) ^c				
Total score (baseline)		28.6 (5.2)	25.5 (4.4)	0.044 [*]

*p<0.05

[#]Mann-Whitney U test for continuous variables, median is presented

[^]Fisher's exact test for categorical variables with small sample sizes

^a Scores (Min = 7, Max =35) are summed up (q2 & q6 reverse scored). Lower scores signify more positive appraisal of diabetes.

^b Scale scores are computed (Min = 0, Max = 4) as there are responses that cannot be scored (e.g. "Not part of my treatment"). Items 5, 7, 10, 11, 12, 13, 14, 15, 16 are reverse scored. Scale scores can be computed with Total_Sum(All)/(16-missing). Higher scores signify better diabetes self-management.

^c Scores are summed up with reverse scoring for Inconvenience (q1 - q3) and Behaviour (q8 - q12). Higher scores signify higher barriers to adherence.

7.1.3 Outcomes

The mean ASK-12 (adherence barrier) score decreased in the intervention group but increased in the control group. Higher ASK-12 scores signify higher barriers to medication adherence. After baseline adjustment of “years with T2D” and “baseline ASK-12 score”, the ASK-12 pre-post “change score” is statistically significant ($p=0.01$), with the intervention group having a 4.7 (1.2, 8.2) lower mean score compared with the control group (Table 7.2).

There are no statistically significant mean differences between the groups for baseline adjusted regression in ADS Score, HbA1c, lipids and BMI (Table 7.2). Although the mean HbA1c level increased slightly in both groups, intervention group participants had, on average, 0.5% lower increment compared with the control group.

Table 7.2 Adjusted mean differences between treatment groups

Outcome measure	Intervention		Control		Adjusted mean difference (95% CI) ^c	p-value
	Baseline	Post-study	Baseline	Post-study		
Self-reported questionnaires, mean (SD)						
	(n = 22)	(n = 22)	(n = 19)	(n = 19)		
Adherence Starts with Knowledge-12 score ^a	28.6 (5.2)	27.2 (5.8)	25.5 (4.4)	28.5 (7.0)	-4.73 (-8.26, -1.21)	0.01*
Appraisal of Diabetes scale score ^b	19.7 (3.7)	19.4 (3.5)	19.0 (3.8)	19.4 (4.3) [^]	-0.48 (-1.82, 2.78)	0.425 [#]
Clinical measurements, mean (SD)						
	(n = 22)	(n = 19)	(n = 19)	(n = 15)		
Blood glucose level						
HbA1c (%)	8.7 (2.4)	9.0 (1.6)	8.6 (1.5)	9.4 (2.4)	-0.42 (-1.89, 1.06)	0.567 [#]
	(n = 21)	(n = 17)	(n = 19)	(n = 12)		
Lipids						
LDL (mmol/L)	3.1 (1.2)	3.1 (0.7)	2.7 (1.0)	2.7 (0.8)	0.11 (-0.20, 0.06)	0.746 [#]
HDL (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	-0.09 (-0.56, 0.77)	0.135
Total cholesterol (mmol/L)	4.5 (1.2)	4.6 (0.8)	4.2 (1.0)	4.1 (1.1)	-0.02 (-0.69, 0.72)	0.052 [#]
	(n = 22)	(n = 18)	(n = 19)	(n = 13)		
Anthropometric data						
BMI	29.4 (7.3)	25.2 (12.5)	28.0 (4.0)	27.5 (4.2)	0.02 (-1.13, 1.10)	0.977 [#]

*p<0.05

[#]Normality assumption is violated due to a small number of outliers and small sample sizes per group[^]One missing value, n = 18^a Scores are summed up with reverse scoring for Inconvenience (q1 - q3) and Behavior (q8 - q12). Higher scores signify higher barriers to adherence.^b Scores (Min = 7, Max =35) are summed up (q2 & q6 reverse scored). Lower scores signify more positive appraisal of diabetes.^c Adjusted variables for linear regressions: mean baseline ASK-12 score, Years with T2D, baseline of outcome variable

7.1.4 Adherence to trial participation

Three intervention group participants did not complete the final survey. Of the three participants, two of them had intermittent app usage while the last one did not use the app from the start. Another three participants who completed the final survey indicated that they stopped using the app after a period of two weeks to two months into the study, as they found the app to be either not useful or distracting. Two participants who indicated that they were still using the app at the end of the study did not have their medication-taking status tracked, as they were unfamiliar with app-based medication-logging. The average individual 12-week medication adherence rate tracked by the app was 38.3–100% for the remaining 17 participants. Eight participants had 100% adherence for the first two weeks of the intervention, but this number decreased to four participants by the third week of the intervention.

The medication adherence rates tracked by the app also reflects the app usage patterns of the participant. Despite differences in the app usage patterns between participants, the aggregated weekly medication adherence tracked by the app did not fall below 50% over the 12 weeks (Figure 7.2 (a)). Figures 7.2 (b)–(d) show actual examples of three typical app usage patterns observed from the participants. Medication adherence and health outcomes improved for participant W, who was still non-adherent to the medication but highly adherent to app usage. Participant X had waning app usage as her perception of the app became less positive over time. Medication adherence and health outcomes did not improve for Participant X, as this participant ran out of medication in week 7. Several participants exhibited similar cyclical app usage behaviour to Participant Y, in which medication adherence increases when they receive survey reminders through email. This cyclical pattern was also observed in the aggregated weekly medication adherence tracked by the app.

7. Smartphone app for medication adherence: A feasibility trial (Results and Discussion)

Figure 7.2 (a) Aggregated weekly medication adherence over 12 weeks, extracted from participants' "Medisafe®" reports

Figure 7.2 (b) Weekly medication adherence of a participant who used an app over a period of 12 weeks but was medication non-adherent

7. Smartphone app for medication adherence: A feasibility trial (Results and Discussion)

Figure 7.2 (c) Weekly medication adherence of a participant who had intermittent app usage over a period of 12 weeks

Figure 7.2 (d) Weekly medication adherence of a participant whose app usage was responsive to the research team's prompts over a period of 12 weeks

7.1.5 Acceptability of the medication management smartphone app

Table 7.3 shows the perception, attitude and satisfaction of app use. These surveys measure the acceptability of a smartphone app in supporting medication management in the feasibility trial and were only administered in the intervention group.

Perception of app usage

The perception on app usage was generally positive among respondents, with the majority (>80%) agreeing that the app made them more aware of the importance of medication adherence, more confident in managing their medication, and more adherent to their medication. For 90.9% of respondents, the app was easy to use. However, the use of the app did not reduce medication management stress in 34% of respondents, and 80% of respondents found the reminder notification annoying.

Attitude towards app use

The attitude towards app use was generally positive, with 95.5% of the respondents answering “Yes” when asked if they would recommend the app to another person with the same condition and if they would trust their doctor to recommend an app for them to manage T2D. The majority of respondents (86.4%) indicated that they would continue to use the app after the study.

Satisfaction

General satisfaction was high, with a median score of 8 on a scale of 1 to 10. Participants who stopped using the app rated the app lower on satisfaction. For example, one participant who stopped using the app gave a score of 1/10.

Participant feedback

Two participants expressed their desire to add their spouses as a “Medfriend” but were unable to, as the free version only allowed the addition of one “Medfriend” (i.e. the study team). Other feedback included suggestions to incorporate doctor’s appointment scheduling and other T2D self-management features, simplify the app interface, educate participants on manipulating the settings, and integrate some of the hospital’s services with the app. Although Medisafe® is a third-party app,

patients would prefer the integration of all health services into a one-stop reliable and personalised platform.

Table 7.3 Perception, attitude and satisfaction of app use in the intervention group

Perception on app usage [#]	n (%)
<u>Thinking about the past few days, how far do you agree that the app:</u>	
Made you more aware of your adherence to medication? [Agree] (n = 21)	19 (90.5)
Made you more adherent to your medication? [Agree] (n = 21)	17 (81.0)
Made you more confident in managing your medication? [Agree] (n = 21)	17 (81.0)
Reduces the stress in managing your medication? [Agree] (n = 21)	14 (66.7)
Is easy to use? [Agree] (n = 22)	20 (90.9)
Annoys you when the notification goes off? [Agree/Neutral] (n = 20)	16 (80.0)
Attitude towards app use	n (%)
Would you recommend Medisafe® to another person with the same condition? [Yes]	21 (95.5)
Would you trust your doctor to recommend an app for you to manage your condition? [Yes]	21 (95.5)
Will you continue to use the Medisafe® app after today? [Yes]	19 (86.4)
Satisfaction	Median (Min, Max)
On a scale of 1 to 10, with 10 being very satisfied, how would you rate your experience in using an app for managing your medication?	8 (1, 10)

[#] There is a "Not applicable" option for "Perception on app usage" questions, which caused the denominator, n to differ.

7.2 Discussion

The use of a smartphone app to improve medication adherence in T2D patients managed at a public diabetes specialist outpatient centre in Singapore was feasible as a pilot study. Recruitment was slow, as only 31.7% of participants who consented to the study met the inclusion criteria. The medication non-adherence rate determined by the study (49.1%) falls within the range of rates reported by other studies in Singapore and internationally using a variety of measurement tools^{82, 236}. Significantly lower self-reported barriers to medication adherence were observed in the intervention group compared with the control group, but there was no improvement in the HbA1c level. This result concurs with the findings of a similar U.S. study, which observed improvement in self-reported medication adherence but no change in blood pressure over 12-weeks¹⁵⁴.

The control group had a slightly lower HbA1c level, lower barriers to medication adherence, and a more positive appraisal of T2D at baseline compared with the intervention group. This observation was reversed 12-weeks later when the intervention group had slightly better outcomes in all three measurements. Improvement in barriers to medication adherence in the intervention group is likely attributed to medication-taking reinforcements by the app and monthly email reminders to complete the online surveys. Adherence reinforcements will likely lead to short-term improvement in medication adherence⁷⁷.

The slight increase in HbA1c levels in both groups may be attributed to the follow-up period falling within a few holiday seasons (i.e. Diwali, Christmas, Chinese New Year) where festive feasting in Asian cultures (i.e. Singapore) is likely³³⁸. The social environment exerts a strong influence on the behaviour of people managing chronic diseases⁵⁴. For example, a person with T2D may be tempted or pressured to consume a larger amount of food during festive gatherings²⁷⁷. Participants may also have to consume sweetened drinks offered by their hosts out of courtesy. As mentioned by Vassilev et al., “self-management support requires awareness of and the ability to deal with network relationships”⁵³. These influences from the social environment affect a person’s resolution in maintaining the care regime, which makes the control

of HbA1c challenging³³⁸. A different intervention period may change study outcomes, although it was acknowledged that the degree of medication non-adherence, personal motivation and response to treatment could affect HbA1c levels and add complexity to the interpretation of outcomes.

The Medisafe® app fulfilled at least one criterion in eight of the nine categories important for medication management in Table 4.1. Medication reminders and planning were the main features used by all participants. The app supported caregiver's involvement, but the free version only allowed the participant to have one “Medfriend”, which was used by the researcher to track their medication adherence status (e.g. via the “Medfriend” function, refer to Section 7.2.2 on participant’s feedback).

As discussed in Section 5.2, the use of complementary medicine is common in many cultures, but almost all the assessed apps did not have a cautionary message to warn the users of contraindications. The use of Traditional Chinese Medicine (TCM) is common among Singaporeans with T2D, but none of the participants mentioned the use of TCM during the study. One endocrinologist at the study site shared that they were often unaware of the use of TCM in patients until an adverse event occurs.

The app could track and export up to a year's medication adherence data, but none of the participants exported their adherence report and discussed with their endocrinologist. There were a few reasons why app adherence data from the app were not discussed with the doctor. First, the discussion on medication adherence tracked by the app was unlikely to happen if participants did not deem the app to be useful. Second, healthcare providers often do not discuss medication non-adherence with their patients³³⁹. In a study assessing the content of 350 electronic medical records on medication communication, 42% of the conversations did not end with a conclusion, and only 9% of the conversations included discussions on medication non-adherence. Third, the reason for medication non-adherence extends beyond remembering to take the medication. The social environment in which T2D self-management takes place is important¹⁸⁷. For example, T2D self-care activities may be hindered by work

pressure and the desire for people with T2D to keep their condition confidential at the workplace.

None of the participants who consented to the study expressed concern about data privacy, although they had to provide an email address to register for an account. Only one patient refused to sign the consent form due to concerns about the collection of his personal data. During the app installation, none of the participants requested to read the privacy policy of the app. There was probably higher trust in the use of the Medisafe® app for this study as the participants were referred to the study team from their healthcare providers.

As discussed by Glenn et al., many consumers do not read the online private policies to understand how third-party organisations use the collected data. Many people also mistakenly believe that the presence of a privacy policy means that their personal information will not be shared^{340, 341}. These and other examples (Refer to Section 1.4.3)^{173, 256} suggest that consumers often overlook privacy issues when sharing personal health information on digital platforms.

The above discussions show that despite possessing many comprehensive features (70.4%) important for medication management, app use largely depends on participants' motivation to improve medication adherence and their digital literacy level. The observations and participants' feedback of the study will be discussed in the next two sub-sections.

7.2.1 Observations of the study

Various factors which influenced study feasibility were observed during recruitment, data collection and data analysis.

Importance of physician advocacy

Physician advocacy is important in encouraging the uptake of new health interventions. The majority (>85%) of patients referred by their endocrinologists were willing to provide informed consent and complete the baseline questionnaire.

Most of the intervention group participants also indicated that they would trust their doctor to recommend an app to manage their condition.

Use of electronic data collection tools

The use of digital data collection tools (i.e. REDCap) minimised data entry errors and human resource required for data collection. The follow-up time frame differed for each participant as they were recruited for over ten weeks. REDCap enabled me to pre-set time intervals for emailing participants the online surveys (i.e. counting from the day the participant was recruited), which significantly reduced administrative work for participant follow-up.

Participants' ability to use an app for T2D self- management

The participants' digital literacy and the app's usability influenced adherence to intervention and satisfaction. Many older participants had difficulty adjusting the app settings, which caused the reminders to become a distraction instead.

Health-seeking behaviour of participants

The health-seeking behaviour of participants influenced study outcomes. For example, one motivated participant in the control group started using an app for T2D management during study follow-up and achieved >0.5% HbA1c improvement in 12 weeks. The study piqued some participants' interest in using an app to manage their medication. For example, one participant requested to use the app even though he was screened out of the study.

Two participants who self-reported that they were adherent to their medications were already using an app to self-manage their T2D (including medication adherence) at the point of data collection. Although these participants were screened out of the study, these examples showed that smartphone apps could be useful for T2D self-management.

Reasons for declining participation

Patients declined study participation due to several reasons. One patient was concerned about the collection of personal data despite the reassurances of data confidentiality. Several patients did not wish to be followed-up for 12 weeks. Some

patients were in a rush or were not keen on spending time to complete the survey. For example, Muslim patients with Friday late morning appointments did not have time to complete the recruitment process due to the need to be on time for Friday prayers. Patients who had waited a long time for consultation also may not want to stay to complete the baseline survey. Although it would have been ideal to approach patients while they were waiting for their consultation, I was not able to do so due to stipulations set by the Institutional Review Boards.

7.2.2 Participants' feedback

Unstructured participant feedback was collected during recruitment, data collection and issuance of grocery vouchers. A few participants commented that the questions in the validated questionnaires were not suited to the local context (e.g. the way the questions were phrased); hence, they had difficulty interpreting the questions. Questionnaires with reverse scoring (i.e. DSMQ) garnered much feedback. In general, participants felt that the questions were too repetitive; many had difficulty interpreting the reverse-scored items. The language used in questionnaires needs to be further simplified and re-validated with the local population to ensure accurate interpretation of survey questions.

I asked the participants how they felt about the app while issuing grocery vouchers to them for completing the online surveys. Two participants would have preferred to be able to add their spouses as a “Medfriend” but could not as the free app (i.e. paid features were available) only allowed the addition of one “Medfriend” (i.e. the study team). The interest in this feature only surfaced from the participants' feedback. Therefore, this feature was not assessed in the research. Studies have demonstrated the effectiveness of social support in improving medication adherence in people with T2D^{52, 109, 342, 343}. Gu et al. found that social support (measured by a validated, 14-item scale) was significantly ($p=0.003$) higher in the high medication adherence group compared with the low adherence group⁵². Another Mexican study also found social support to be associated with adherence to diet ($p=0.007$) and medication

($p=0.002$) in people with non-insulin dependent DM¹⁰⁹. Consistent results were also observed in studies on adherence to HIV treatments^{342, 343}.

Other feedback included suggestions to incorporate doctor's appointment scheduling and other T2D self-management features, simplify the app interface, educate participants on manipulating the settings, and integrate some of the hospital's services with the app. Although Medisafe® is a third-party app, patients would prefer the integration of all the health services into a one-stop reliable and personalised platform.

One participant said that she was still using the app but mentioned that she had stopped using the app in the online survey. Online surveys could have removed some degree of social desirability, as participants do not feel pressured to provide positive feedback. Another participant deleted the app a few days after recruitment as she would remember to take her medication after drinking a glass of tea during the day if she forgot to take her medication in the morning. This participant was included in the study as she agreed that she "sometimes forgot to take her medication" (i.e. took the medication in the afternoon instead of morning). An app would not be useful in this case, as the degree of medication non-adherence was not high at baseline.

7.2.3 Study limitations

Limitations of the study are discussed below.

Self-reported medication adherence rates

Self-reported tools are subjective to the patient's self-judgement, recall bias, and social desirability bias; hence, actual medication adherence may not be accurately reflected. I observed patients who over- or under-reported their medication adherence status. There were a few participants who claimed that they took all their medications. When such cases occur, the data collector will prompt the participant: "100% means you did not miss a single pill, which is unlikely. Are you sure you took all your medications? Have you ever taken a pill at night when it is supposed to be taken in

the morning?” After further prompting, some participants revealed their tendency to unintentionally miss a few doses or skip medications which they think may not work. For example, a participant mentioned that he took all his important medications for T2D but skipped his water retention medication without informing his doctor.

A few other participants mentioned that they skipped or stopped taking their medications because they ran out, or because the medications made them felt terrible in the past few months. The inclusion of these participants into the study depended on whether the problems were discussed and resolved with the doctor before recruitment.

Problems with digital literacy

A few participants were screened out of the study due to the lack of an email address for follow-up. Older participants who used their relative’s email address or hardly checked their email inbox were less responsive to the follow-up surveys.

Many older participants who were less technologically astute did not know how to use/had limited knowledge on smartphone app usage. For example, an older participant used the medication reminder feature of the app but did not tap on the “taken” button to log medication-taking. Hence, the study team could not track this participant’s medication-taking status. Similarly, the full medication-taking status of participants who changed smartphones during study follow-up could not be tracked.

Problems with validated questionnaires and literacy

Participants with lower educational levels may have lower English and survey literacy. These participants could not be followed-up unless a caregiver or relative could translate the online surveys for them. This may improve survey interpretation, but the caregiver’s influence may bias responses to the questionnaire.

It is unknown if the participants correctly interpreted the survey questionnaires; as the validated questionnaires were not tested in the local context. There were also questions that some participants could not answer. For example, physical activity may be challenging for participants with leg amputations or participants who have undergone heart by-pass surgery.

Some participants were confused with questions assessing medication adherence. A few participants perceived missing a few medication doses as “reducing” instead of “skipping” their medication.

The question “How many types of medications (e.g. pills, injections, eye drops, etc.) are you currently taking?” was misinterpreted by a few participants as categories of medications. For example, one participant answered “two” for “pills and injections”, but she had a few different kinds of pills to take. This problem was rectified in the survey questionnaire after clarifying with the participant.

Older participants had difficulty answering Likert-scale questions and had to be prompted extensively by the researcher to complete the questionnaire. For example, when the researchers verbally asked (at baseline), “How likely do you think your diabetes will worsen in the next few years?”, a few participants answered “I hope it will not worsen” instead of choosing a Likert scale response.

Problems with the Medisafe® app

Two participants in the intervention group returned for a follow-up with their endocrinologist while the data collection was ongoing. Both had problems with the Medisafe® app; one went overseas and had problems reconfiguring the app to the local time zone; another changed his smartphone and did not know how to reinstall the app on his new phone. These problems were resolved face-to-face with the participants, but problems faced by other participants were not addressed unless they contacted the principal investigator. In addition, there were also several update problems with the “Medfriend” function, which was eventually resolved with Medisafe Inc.

Other limitations

The study may not be generalisable to all people with T2D, as tertiary specialist outpatient clinics are likely to manage more complex cases that cannot be managed in the primary care setting. Eligible patients might be lost to recruitment if their attending endocrinologist forgot to refer them to the study team. Lastly,

contamination may have occurred when control group participants were exposed to the idea of using an app for T2D medication management.

7.2.4 Implications and future work

This study allowed me to better understand the impact of a health app on T2D patients and identify potential problems that could arise before scaling up the study. One registered trial that sought to use a self-developed smartphone app to improve the 6-month medication adherence among T2D patients in Singapore was withdrawn due to poor patient recruitment²⁴⁵. Therefore, I chose to conduct a pilot with a commercial app to evaluate factors that are important in the implementation of a full trial. The recruitment outcome of this study suggests that a fivefold scale-up is needed to achieve full trial power under the same conditions. A scale-up is achievable with the involvement of more physicians, more study sites or a longer recruitment period. Validated questionnaires should also be tested in the local context prior to a full RCT. Future studies should assess factors that could enhance the usability of apps in older adults who are less technologically astute. The app usage behaviour of different patient subgroups and interaction between various T2D app features can also be explored.

7.3 Conclusion

In conclusion, a pilot smartphone app intervention for medication non-adherent T2D patients in a developed Asian setting is feasible, acceptable, improves awareness of medication adherence, and reduces self-reported barriers to medication adherence. Digital literacy, health-seeking behaviour, app usability, and the time period of the intervention are factors that influence feasibility. A full trial with a fivefold study scale-up and a refined study design should be conducted to assess the effectiveness of a smartphone app in improving medication adherence in people with T2D.

Chapter 8

Discussion and concluding remarks

This chapter discusses the main findings and their implications for healthcare providers, patients, app developers, policymakers and researchers. The chapter consists of seven sections. First, I present a summary of the key findings, followed by a discussion of these findings. Second, I discuss the strengths and limitations of the overall methodological approach. Third, I describe the contributions of my research to the field of mHealth. Fourth, I discuss the implications of the findings for the various stakeholders and make recommendations on how to take this field forward. Fifth, I suggest aspects of the research that can be further explored in the future. Finally, I reflect on the influence of the research work on my PhD study and end with concluding remarks.

8.1 Discussion of key findings

8.1.1 Summary of key findings

Study 1: Assessment of DM apps in multiple languages

The key findings from Study 1, which was designed and conducted to assess the (1) number and proportion of DM self-management apps in major languages spoken in ten countries with the largest number of people with DM; and (2) clinical relevance of selected apps in each language are summarised in point form below:

- i. Access to high quality DM self-management apps is unequal across populations. Among the national languages of ten countries with the highest numbers of people with DM (i.e. China, India, USA, Brazil, Russian Federation, Mexico, Indonesia, Egypt, Japan and Pakistan), English and Mandarin apps constitute more than 80% of apps for DM self-management.

- ii. English language apps were the most highly downloaded. Among the top three most downloaded English language apps, all had very comprehensive DM management features, but none had any form of information provision.
- iii. Two of the three most downloaded Mandarin apps had both comprehensive information provision and app features but contained online retail services and health advice from sources that were not cited.

Study 2: Assessment of English language T2D apps (focus on medication management features)

The key findings from Study 2, which aimed to (1) construct a diagram linking good medication management practice with possible app features; (2) systematically assess and characterise the medication management features in T2D self-management apps, and their congruence with best-practice evidence-based criteria; and (3) systematically assess the transparency of information disseminated via these apps against eight criteria adapted from the Health On the Net (HONcode) principles, are summarised in point form below:

- i. Many apps for the self-management of T2D lacked any form of medication management features despite the importance of medication adherence in T2D self-care activity. Our systematic app assessment of T2D self-management apps found that only 43% had medication management features.
- ii. Of the T2D self-management apps with medication management features, a large proportion of the apps lacked features that were useful for enhancing medication adherence and safety, such as the capability to enter allergy-related information and medication-taking instructions, working reminders, information provision, and prompts for the usage of complementary medicine.
- iii. Less than 5% of apps with medication management features provided any form of motivation to the user.

- iv. Approximately three-quarters of the assessed apps did not provide any health information.
- v. Two-thirds of the assessed T2D self-management apps were not transparent in indicating its content source.
- vi. More than half of the assessed apps did not fulfil essential criteria, such as indicating the qualifications of individuals involved in the app development or disclaiming that the app does not replace the healthcare provider's advice.
- vii. Approximately a third of the apps did not have a privacy and confidentiality clause nor indicated any funding source.
- viii. A higher proportion of iOS apps fulfilled more HONcode criteria compared with Android apps, although the differences were not significant.
- ix. Among the assessed Android apps, those with higher downloads ($\geq 100,000$) were more likely to have features that allowed the user to separate medications into "take as needed" sections, document medication-intake, vary dosage input options, set up reminders to refill prescriptions, sync medication-taking schedule with a caregiver's phone, support multiple user profiles, and support data export. These apps were also more likely to have a privacy and confidentiality clause and more likely to discuss their funding sources.

Study 3: Medication adherence feasibility trial

The key findings from Study 3, which aimed to determine the feasibility, acceptability and clinical outcomes of using a smartphone app to improve medication adherence in a multi-ethnic T2D Asian population (Singapore) through a pilot are summarised in point form below:

- i. The feasibility trial showed that the use of a medication management app significantly lowered self-reported barriers to medication adherence in the intervention group compared with the control group but did not improve HbA1c levels.
- ii. Our study suggested various factors which influenced study feasibility: (1) physician advocacy; (2) use of digital data collection tools; (3) participants' digital literacy; (4) the app's usability; and (5) the health-seeking behaviour of participants.
- iii. Our findings suggest that a fivefold scale-up is needed to achieve full trial power under the same conditions, which can be achieved with the involvement of more physicians, more study sites or a longer recruitment period.

8.1.2 Systematic assessment of apps

The systematic app assessment studies provided both a broad and throughout overview of the features of DM self-management apps. High quality-apps were disproportionately distributed across populations. English language apps have more comprehensive DM management features and higher downloads compared with apps in other languages, despite a disproportionately smaller population of native English speakers worldwide. In low resource settings, smartphone users would benefit from using a translated high-quality app rather than a low-quality app.

A few apps claiming to cure or reverse diabetes were discovered during app screening despite the presence of app store review policies. These apps provided herbal or nutritional advice to users without any evidence backing the claims, which may potentially mislead users who are eager to seek a cure for DM or cause those with lower health literacy to act inappropriately.

The global app assessments, however, provided a glimpse of the top three most highly downloaded DM apps available on China's most popular Android app platform at the

point of app assessment. Two of these apps had very comprehensive information provision and app features but also contained online retail services and information sources that were inadequately cited. In addition, the data management and privacy policies of Mandarin apps were not assessed amidst the changing data privacy protection laws regarding Mandarin apps on China's app platforms³⁴⁴.

Subsequent studies focused on English language apps as they were more comprehensive, highly downloaded and widely available on both the Android and iOS platforms. The app assessments did not cover Mandarin apps, although there were approximately 400 Mandarin apps in the Android market. China's ban on Google led to the emergence of many third-party app platforms exclusive to users residing in China. Therefore, collaborations are required to access and assess these apps.

The app assessment findings concurred with other published studies in terms of the lack of essential medication management features. A 2017 study found that only 50% of the highest-rated iOS T2D management apps had medication adherence features¹⁷⁰, while I found that only 43% of T2D management apps had any form of medication management features.

A prior study which systematically reviewed the medication reminder apps available in the Australian app stores found that only a small number of apps have at least half the desired features considered to be essential in a high-quality medication adherence app¹⁴⁹. I did not consolidate the app assessment features available in each app, as the comprehensive assessment criteria covered aspects of medication management of varying importance for different users. Both app assessment studies (mine and Santo et al.'s) identified gaps in the medication management features of apps, but the proportions were different due to differences in app categorisation and nuances in assessment criteria. For example, the study by Santo et al. reported that 54.8% of apps allowed medication history tracking, while my study found that 78.3% of apps allowed medication logging, but only 16.8% of the apps reviewed medication adherence with the user. The other study did not report the length of history tracking; hence, the proportions were not comparable.

Systematic app assessments are resource-intensive amidst a fast-moving app market, but it is currently the most comprehensive way to gain an overview of the app landscape. Therefore, human resources have to be allocated until the automation of app assessment (including downloading and interacting with the app) becomes a possibility.

8.1.3 Effectiveness of apps in T2D self-management

Health or disease management apps are marketed to help consumers to manage their health better. As yet, no apps were recommended by any T2D or medication management guidelines due to immaturity of evidence on the effectiveness of apps. The lack of evidence-based features in apps was assumed to reduce the effectiveness of an app in achieving its intended purpose and improving health outcomes.

Evidence-based features are essential for an app to effectively target disease management, which can potentially improve health outcomes. However, an app that merely conforms to international T2D or medication management guidelines is not sufficient to achieve effectiveness in T2D self-management on a broader scale. The effectiveness of an app in complementing T2D self-management depends on the personal motivation and coping skills of the person with T2D, the social context (social environment and social network) of the person, the app's usability, and its ability to protect the privacy of data and disseminate accurate and high-quality content.

To date, there is only one randomised controlled study assessing an mHealth adherence app as a standalone for medication adherence and blood pressure control¹⁵⁴. The team recruited 411 participants and instructed half the participants to use the Medisafe® app for 12 weeks. While the choice of app and follow-up period of my study was similar to this study, the study design, population, medication adherence questionnaires and clinical outcome measurements of my study were different. Despite the differences in study population, the study outcomes were similar. Self-reported (barriers to) medication adherence improved slightly, but there

was no change in clinical outcomes (HbA1c in my case). The research team of both studies nudged participants to complete actions during the follow-ups (e.g. email survey reminders for my study; submitting periodic blood pressure measurements for Morawski's study), which possibly influenced the improvement in medication adherence. These results suggest that apps may not be an efficient stand-alone tool to improve medication adherence. Incorporating medication management features into disease-specific apps may be more useful towards helping patients to manage all important aspects of the disease. App features that can be integrated with the wider mobile media ecosystem also need to be considered to facilitate app adoption.

Highly motivated individuals will seek ways to effectively self-manage T2D. For individuals who are motivated and technologically astute, an app with evidence-based features will more effectively help them to manage the demands of a lifestyle with T2D more effectively. Physicians' advocacy will also elevate the importance of an app (i.e. for decision support) in helping the patient to self-manage T2D. For example, a patient may feel good about showing his/her physician the metrics tracked by the app as a measure of effort placed on T2D self-management, which in turn helps to build rapport with the physician.

Apps may not be the preferred tool to complement T2D self-management for some people. Older users may struggle with adapting to app use on top of the demands of coping with T2D. Usability and ease of navigation are of particular importance to this group of patients. The utility of the app is diminished if the user is not able to adjust the settings as required, log daily readings appropriately, or interpret data tracked by the app for decision support. Support from younger family members by assisting and engaging older adults in technology use can also facilitate app adoption in older adults.

The transparency, reliability and stability of the app are all important facilitators of app adoption. Data privacy and confidentiality are top concerns of disease management app users, as data breaches in a few apps will erode consumers' trust in these apps. The operational stability of the app is also important as the user may render the app ineffective after experiencing multiple app glitches.

Using an app alone will not tackle all problems associated with poor T2D or poor medication management. For example, medication non-adherence associated with cost, fear of needles, or medication side-effects can only be solved by addressing financial and treatment-related problems. Nevertheless, an app should be safe and evidence-based to benefit people who choose to use an app for the management of all types of DM.

Many digital devices are now linked with apps for more comprehensive disease management. Perhaps platform-agnostic technologies—products that run equally well on various platforms—will provide users with more choices and seamless experiences in personal health management.

8.2 Strengths and limitations

This section discusses the strengths and limitations of the overall methodological approach. The strengths and limitations of each study have been discussed in Chapters 3, 5 and 7.

8.2.1 Systematic app assessments

Assessment of DM apps in multiple languages

This study provided a good overview of the advancements and shortcomings of the global DM app landscape. The study covered app markets beyond the Apple and Google Play app stores. All top downloaded apps were assessed by native speakers to ensure the accuracy of language interpretation.

One limitation of this study is the assumption of population needs based on international guidelines of professional societies. In low resource settings, the demand for DM apps may be low, hence receiving and even lower emphasis on DM app development. The study also did not evaluate popular apps in major languages used in some developed countries, such as German and French, as Germany and

France were not amongst the top ten countries with the highest numbers of people with DM¹⁶. Therefore, a few high-quality apps were possibly excluded from the global assessment.

Assessments of medication management features of T2D apps

This study provided a more thorough evaluation of one aspect of self-management important to T2D care. The method, framework and criteria developed for the assessment of apps can also apply to apps for other chronic diseases or medication management apps. Various stakeholders (discussed in section 8.4) can develop checklists from the framework to assess apps based on needs (e.g. making app recommendations).

The limitations are as follows. While the framework was validated with a range of health professionals in our team, there was a lack of input from international medication management experts, which would further strengthen the validity of the framework. In addition to the assessed transparency and reliability of information dissemination, data management policies (i.e. consent to data collection, storage etc.) should also be assessed as they are vital for the protection of consumer interests.

The app market explorer (<https://42matters.com>) is a convenient and comprehensive database for retrieving app titles. However, the newest apps may not be captured at the point of app retrieval due to possible time lapses between the release of new apps and market explorer updates.

8.2.2 Feasibility trial

There are several advantages of recruiting participants during their routine clinical follow-up. First, the attempt to cover all patients who meet the inclusion criteria reduces selection bias from a self-selected group of patients highly motivated to improve their health. Second, approaching patients after being referred to the study team by their endocrinologist, while they waited for the next station (e.g. payment, collection of medication) was convenient for patients and allowed researchers time

to explain the study. Third, the face-to-face interaction with patients helped the researchers to understand the nuances of the recruitment process and to probe them on their interpretation of medication non-adherence. At the end of data collection, I informally asked the patients about their experience with the Medisafe® app during the face-to-face issuance of vouchers to make better sense of the collected data.

There were several limitations to the study design and data collection. First, one of the requirements by the Institutional Review Boards was that the attending doctor had to make the first contact with the study participants. This arrangement potentially introduced a small degree of selection bias as patients that met the inclusion criteria but were deemed unsuitable by the attending doctor were not referred. Second, patients attending the DM specialist outpatient clinic were referred from primary care and often had conditions that were more complex than cases that can be managed in the primary care setting. The focus of makes it the study less generalisable to all people with T2D in Singapore.

Third, I was not able to monitor the participants' app use behaviour closely as I did not own or develop the app. For example, I could not distinguish between medication non-adherence or a lack of interaction with the app when the patients did not log their readings. Observing the "number of times the user visits the app" would more accurately reflect participants' app use behaviour.

Fourth, self-reported questionnaires can be subjected to social desirability and recall biases. Medication non-adherence is a sensitive issue, and some patients may not wish to disclose this detail to the researcher. Biological testing (i.e. mass spectrometry from urine samples) would be a more objective measure of medication non-adherence, but this is currently not offered as a routine diagnostic test and may change the outcome of recruitment (e.g. patients may reject the intervention due to the inconvenience of providing their urine samples). Although HbA1c is routinely monitored, it is not a good measure of medication adherence as it is collectively influenced by diet, physical activity and other self-care activities.

Fifth, it is less unlikely for improvement in health outcomes to be observed for an intervention eliciting behavioural change in chronic disease management within a short follow-up period (i.e. 12 weeks). Improvement in health outcomes will more likely be observed for patients who adhere strictly to the intervention and are highly non-adherent at baseline. Such cases are rare given the myriad of factors for medication non-adherence and the complexity of management.

Sixth, participants who encounter technical issues will not fully benefit from all the app features. For example, the time zone of the app automatically adjusted when one participant travelled overseas but did not automatically adjust back when the participant returned to Singapore. The reminder alarm became a nuisance as the participant did not know how to adjust the settings. Providing participants with an instruction manual on adjusting the app settings would increase patients' confidence in using the app.

Seventh, the quality of self-reported data was affected by patients with poor questionnaire literacy. Validated questionnaires with Likert scale options were difficult to interpret as many patients could not distinguish the slight differences between the options (e.g. slight vs moderate, large vs extremely large). Many patients also tended to avoid thinking about their health status. Therefore, the responses to the question "How likely do you think your diabetes will worsen?" were often ambiguous or "Not likely". Semi-structured mini interviews would have captured patients' thoughts more accurately in these instances.

Eighth, it was challenging to define medication adherence for the intervention. The widely validated Morisky Medication Adherence Scale was too costly for a feasibility study, while the Visual Analogue Scale (VAS) was subject to the ceiling effect. Many patients encountered difficulties in approximating the proportion of medication non-adherence. Patients who admitted that they forgot to take their medications sometimes indicated that they took 100% of their medications on the VAS scale. The VAS scale was, therefore, not included in the analysis due to its inaccuracy. Medication non-adherence was determined by an "agree" response to the ASK-12 question "Have you taken your medication more or less often than prescribed?". This

inclusion criterion was insensitive to an 80% cut-off value for medication non-adherence as patients with higher adherence may still feel that they are non-adherent to their medications. Nevertheless, this question provided an opportunity for the patient to receive an intervention to improve their medication adherence and provided the research team sufficient flexibility to recruit patients.

Lastly, research in the health services setting is complex due to difficulty in controlling the environment. Compromises were made to the study design due to the existence of confounding factors. For example, recruitment was affected by the need for a member of the healthcare team to approach the patient first, patients' self-perception of medication adherence, and their willingness to take part in a research study. The effectiveness of the app intervention also depends on whether there are other underlying issues for medication non-adherence. Therefore, a pragmatic approach (i.e. considering the contextual factors that shaped the setting instead of the ideal environment)³⁴⁵ is often used in these studies. Although limitations exist in the study design, the necessary rigour of patient recruitment (described in Sections 6.3.3 and 6.3.4) were still maintained. As medication non-adherence is a multi-factorial problem, the purpose of the feasibility study was to assess if the app can help medication non-adherent patients who were willing to change their behaviour rather than to improve the medication adherence of all patients at the clinic.

8.3 Contributions of the research

By developing app assessment criteria, assessing apps and implementing app use for people with T2D, this thesis contributed to evidence on the capabilities and effectiveness of apps in supporting T2D medication management. To the best of my knowledge, the work presented in this thesis was the first to provide a comprehensive overview of the DM app landscape and highlight the shortcomings of apps (as a tool) in T2D medication management via a series of linked studies.

The methodological innovations discussed in Sections 3.3 and 4.3 demonstrate the significance and novelty of the app assessment research. Unlike other studies that

developed app assessment criteria based on researchers' and healthcare providers' consensus^{112, 149}, the app assessment criteria used in this thesis were developed with reference to evidence-based practices and input from multidisciplinary health professionals. The method of app search was adapted from the principles of conducting systematic reviews. Instead of assessing apps based on the researchers' perception of "high quality" or random internet searches^{61, 112, 149, 170}, the app assessment work described in this thesis employed a systematic search process that covered a broader range of apps.

The global app assessments demonstrated a digital divide in disease management apps between global populations, with far-reaching implications for policymakers. Section 8.4 discusses the recommendations to bridge the digital gap between high and low resource settings. The findings of this study provided a comparative glimpse of DM apps for different populations, which was essential for determining the direction of future research that assess apps outside the English language market.

The in-depth app assessment work in this thesis contributed to the creation of an evidence-based framework for the assessment of medication management apps. Although the study focused on T2D as the context of management, the app assessment criteria are applicable to other chronic disease management apps. This study is also timely and applicable to global agencies seeking to develop or update policies on disease management app regulation. Researchers can build on the evidence generated from this study to include other digital devices for medication management to advance the field. The implications for policy and practice together with the recommendations (Section 8.4) show the significance and importance of this research.

The feasibility study filled a gap by addressing the lack of studies on smartphone apps for medication adherence, particularly in an Asian setting. While previous smartphone app studies mainly focused on Minority World Countries^{153, 154}, this study was focused on a multi-ethnic Asian population in Singapore. Although this is a feasibility study, the method employed had the rigour of a full randomised controlled trial. The findings established a baseline reference for future research and

identified challenges associated with patient recruitment for improvement, which is crucial for the success of future trials.

Instead of inviting participants via email, which may introduce selection bias, the researchers of this study (including myself) had face-to-face contact with patients during recruitment. This interaction allowed a better understanding of the participants' experiences and perceptions of the intervention, which were both rarely discussed in published studies. Problems with questionnaire comprehension and denial/reluctance to envisage the possibility of T2D worsening were unexpected. These observed delicate nuances in participant behaviour demonstrated the novelty and importance of this research for the design of future studies.

8.4 Research implications and recommendations

The research implications and recommendations for healthcare providers, people with T2D, app developers, policymakers and researchers are described below. These recommendations are not standalone actions but often require a collaborative effort among stakeholders to actualise.

8.4.1 Perspective of healthcare providers

The perspectives of healthcare providers are important as they play a vital role in advising and supporting their patients' health management. As patients' health advisers, healthcare providers can recommend apps based on patient needs. The app assessment checklist provides a quick and objective way for healthcare providers to assess, compare and select apps for recommending. Flexibility can also be exercised to tailor the criteria for more personalised care.

Currently, no clinical guideline recommends an app for DM management due to the immaturity of app features and paucity of evidence in influencing positive health outcomes. Healthcare providers should be more involved in co-designing DM apps

due to their familiarity with clinical practice and guidelines. They can also encourage their patients to take part in app intervention studies to advance research in this field.

Digital health technologies should be incorporated into medical education to familiarise younger healthcare professionals with digital health. Incorporating digital technologies in medical education will help future healthcare professionals keep pace with the rapid technological developments in healthcare.

8.4.2 Perspective of people with T2D

People with T2D (and their families) are the targeted users of T2D management apps. However, the extent of T2D self-care or medication adherence is a personal decision influenced by factors beyond app use. App adoption depends on its perceived usefulness, which differs across individuals and populations. For example, younger app users may be interested in apps with more sophisticated functions, while older users may prefer easy to navigate apps with larger screens. Therefore, the personalisation or customisation of apps is important to suit different users.

While the app assessment studies were conducted from the patients' perspective, the recommendations were mostly directed at app developers and policymakers. When improvements in the identified gaps take effect, the overall standard of apps will be raised, and patients will benefit from better quality apps for disease management. Patients can also make more informed choices by being aware of the benefits and shortcomings of these apps.

Although an app may not be useful for everyone, people with T2D should be encouraged to try to use an app or a digital device for self-management (within their capacity) to keep pace with technological developments. More user feedback from the patients' perspective will help app developers to design apps that are closer to users' needs. For patients who are interested in attempting innovative solutions to tackle their health problems, participation in research projects may motivate them to perform a new action to improve their health³⁴⁶.

8.4.3 Perspective of app developers

App developers play a fundamental role in the creation of apps used by their target audience (i.e. people with T2D in this context). App developers are assumed to want to raise the quality of their apps to achieve a high number of downloads and a large user base. Very often, a misalignment exists between the users' needs and the app developer's awareness of these needs. Therefore, app developers should attempt to blend user feedback and research literature to ensure that their apps are evidence-based and meet users' needs.

The app assessments identified gaps in (1) the transparency and reliability of information disseminated by the apps; and (2) the conformance of app features with evidence-based T2D and medication management guidelines. These findings, together with the developed app assessment criteria, can be used as a checklist to cross-check and improve the app development process. Although new regulations are emerging to protect users' interests, app developers should attempt to have their apps certified by established entities to increase user confidence. Collaborations, such as with personnel that possess medical domain expertise, in the app development process and testing the effectiveness of the app will also greatly improve the clinical relevance and applicability of these apps.

The transparency and reliability of information disseminated by the apps are as yet immature to gain users' trust. App developers or app stores could play a more significant role in ensuring the disclosure of the background and information sources of apps. For example, developers with fewer resources should be transparent in declaring the lack of app support, and be upfront about the presence and type of advertisements in the app.

In addition to ensuring user privacy and evidence-based app features, a good app should also possess excellence in usability, user interface, app support and performance reliability, which require substantial investments. App developers could consider cross collaborations to improve the quality of their apps or translate their

app to other languages to cover a more extensive user base. These measures will allow users of lower resource settings to access higher quality apps.

The standard of apps is expected to increase in the future as research continues to emerge. Big app players will need to conform to higher standards to keep their business viable, to the benefit of app users. Therefore, keeping abreast of the latest research findings in the field is essential for app developers.

8.4.4 Perspective of policymakers

Policymakers and regulatory agencies carry the responsibility of safeguarding consumers' health. Unlike medications or medical devices, apps are challenging to regulate due to its proliferation, ubiquity and ambiguity in classification. The FDA currently regulates apps that are classified as medical devices, and exercise enforcement discretion on health apps that pose a low risk to consumers (i.e. apps that facilitate or supplement clinical care by behavioural change or coaching)³⁴⁷. In Europe, apps classified as pieces of software with “medical purpose” (i.e. apps that perform medical tasks) or deemed to pose a risk to patient health (i.e. apps that provide information for decision support, or tools combining medical knowledge with patient-specific physiological parameters) are regulated under the European Union regulatory framework on medical devices³⁴⁸. These regulations, however, only cover app markets in Europe and the United States. Health apps that do not meet regulatory standards may still fall through the regulatory net in other global app markets.

Policymakers must be knowledgeable in interpreting research findings to make well-founded policy decisions. The findings from the app assessments and feasibility trial provide added evidence for policymakers to consider when drafting app-related policies. For example, the medication management framework for apps can be used as a reference when updating medication management guidelines. Understanding the app landscape can also help policymakers to position themselves in the regulatory pathway accurately.

The FDA is considering certifying app companies and institutions instead of individual apps in view of the challenges in regulating the app market. However, not every country will have an app regulatory body. FDA approved apps may also not be available in other markets. Therefore, government agencies in other countries can facilitate app developers in getting their apps certified by a recognised entity to increase user confidence in the app. Lastly, app adoption can be encouraged, with appropriate incentives, by incorporating app use in health services (e.g. appointment booking, bill payment etc.) to familiarise patients with using an app to manage their health.

8.4.5 Perspective of health app researchers

Researchers play a vital role in advancing the field of digital health. Despite the growing literature on the quality and efficacy of apps on disease management, research translation from “bench to bedside” has not kept pace with technological advances in app utilisation. Therefore, researchers should consider ways that can advance the field to reach the level of disruption similar to the use of apps in the banking and e-commerce industries.

Researchers can use or improve on the developed checklist to build or select apps for future intervention studies. The app that is used for intervention should be fit for purpose (i.e. contain evidence-based features) to appropriately assess its effectiveness in disease management.

Collaborative health system level studies are required to bring about large-scale implementations. Incentives can be used to encourage behavioural change, such as in the form of app usage, to support these implementations. Research should be targeted at patients who will more likely benefit from using an app for disease management, aimed at longer study follow-ups, and designed to emulate patients’ daily living to obtain more accurate study outcomes.

8.5 Recommendations for future research

Future research can include populations, aspects of T2D self-management, and app attributes that were not included in the scope of this thesis. After the assessment of the features of English language apps, international collaborations can be established to assess and validate the app assessment criteria in other languages for broader population coverage. For example, Mandarin app assessments alone will cover a fifth of the global population with DM². Creating a universal guideline with context flexibility provides opportunities to reduce global inequality in the evaluation and development of high-quality apps. The app assessment criteria can also be used to evaluate apps for other chronic diseases such as hypertension, mental illness and asthma.

While the medication management app assessment framework was developed with input from a multi-disciplinary team of health professionals, it has yet to be validated by international medication management experts. Contributions from international medication management experts will strengthen the framework, enabling its development to an international standard. This framework can also be expanded to cover other digital devices for chronic disease medication management beyond smartphone apps.

The assessment of the transparency and reliability of health information dissemination in DM apps is at its preliminary stage. It could be further expanded to include accuracy of disclosures, data consent processes and data management policies, especially in non-English language apps.

The medication management feasibility trial helped to identify problems that can be rectified prior to a full trial. First, the questionnaires should be adapted to the local context for better comprehension. Older participants were generally hesitant in responding to questions that required them to predict the prognosis of their condition. Such cultural sensitivities should be considered during the selection of questionnaires.

Second, future studies should consider more convenient and accurate ways to measure medication adherence. Mass spectrometry with urine samples can be used as an objective measure of medication adherence, although it may increase the cost of research and be subjected to additional ethical justification. Triangulation of various methods would also increase the accuracy of measuring medication adherence.

Third, cross-institution collaboration is required to scale up the study as it was challenging to identify medication non-adherent patients who were willing to change their behaviour. It is possible to be less selective about the medication adherence status of participants and instead conduct sub-group analyses from the overall dataset. Healthcare professionals will also need to be involved in utilising data captured by the app for decision support.

Fourth, a longer follow-up period (i.e. a minimum of six months) is required to observe changes in glycated haemoglobin levels (if any). Lastly, more resources should be allocated towards training or supporting patients to facilitate their adjustments to app use. For example, pamphlets, explanatory videos or a support platform can be provided during recruitment and follow-up.

Future research can also explore patient app use behaviour in greater detail, such as observing the period and number of times a participant logs into the app or provide diminishing incentives over time to assess participants' behavioural change over time. However, close behavioural monitoring poses ethical challenges and requires access to back end app data, which most likely means that researchers need to develop or own the app. The app should preferably be co-designed with patients, healthcare providers and researchers to be able to meet the needs of all parties.

Recent studies have moved on to more sophisticated technology classed under the "Internet of Things", which include wireless sensors and wearables such as app linked smartwatches^{68, 349, 350}. Platform agnostic devices (a device which runs equally well across different platforms) will provide patients with a more seamless experience in digital disease management. Future digital health research can consider

evaluating patient experiences and health outcomes with integrated digital technologies. Instead of focusing on individual digital devices, the entire patient care process should be evaluated to determine the value of digital disease health management in improving health outcomes.

8.6 Reflections of the researcher on the research

The PhD journey began with many uncertainties. Having worked as a junior health services researcher prior to the PhD, I was familiar with projects that sought solutions to problems confined within a health service region. In order to broaden my thinking and expand my perspectives in problem-solving, I embarked on the PhD study with an open mind, exploring a topic that I had limited knowledge of at the beginning.

During my PhD study, I encountered unexpected problems that challenged me to think out of the box. I also met people who taught me different approaches to problem-solving. The multi-method approach trained me to consider solutions from different perspectives and focus on finding solutions that could best answer the questions of interest.

Working in a research team diverse in nationalities and capabilities have helped to facilitate global health projects. For example, native speakers were quickly sought for small scale language translations and app assessments. The networks brought in by international colleagues were also valuable in expanding the capabilities of the team.

There were challenging moments in the search for solutions to problems and the execution of projects. More often, the difficulty of an amateur researcher lies in gauging the feasibility of research plans and the level of persistence in problem-solving.

The app assessment project was a resource-intensive project that required team effort to realise. As smartphone app technology is a fast-moving field, quick and robust methods must be devised to keep pace with its developments. Tackling a large and

multi-dimensional problem offers ample opportunities to contribute to the research field, but also means the solution presented is based on investigating just one angle of the problem. Much more work is required to piece the puzzle together.

There were unforeseen circumstances during the data collection of the feasibility trial despite extensive planning. For example, the REDCap data collection platform was suddenly blocked by the university midway through data collection. I was fortunate to have prepared hardcopy versions of the data collection forms, but that created additional inconvenience in the data collection process. The data collectors (including myself) encountered non-accommodating patients when attempting to explain the study to potential participants. These encounters were unsurprising in the health services setting, but also reiterated the challenges in collecting data within the health services setting.

On reflection, there were steps of the research that could have been done differently. For example, I would have sought more expert opinions before embarking on problem-solving. I would also register the trial even though it was meant as a feasibility study to prevent publication bias, and include more endocrinologists in the project for ethical clearance from the start to prevent delays in recruitment. A better data collection period could have been chosen to avoid holidays and festive seasons.

8.7 Concluding remarks

Smartphone apps present a novel and interesting way to complement T2D self-management. The quality, utility, (clinical and data) safety, and user experience of these apps are important factors to app adoption. While a few studies assessed the features of top DM apps, the overall clinical relevance, utility, and user experience of these apps were not well understood to transform care.

The development of evidence-based criteria and systematic app assessments against these criteria provided an overview of the global DM app landscape, helped to identify gaps where the safety and utility of these apps were compromised, and

enabled the selection of a suitable app to assess the feasibility of an app in supporting medication management in people with T2D. The medication management feasibility trial addressed the lack of studies on smartphone apps for medication adherence in an Asian setting.

To increase DM app adoption, governments and app developers should bridge the digital gap between high and low resource settings by fostering more collaborations. Research on app assessments should also be collaborative to include apps beyond the English language. App developers, healthcare providers and policymakers can benefit from more evidence and guidance for decision making. People with DM will also benefit from higher quality apps for medication management support. Although the use of a medication management app did not improve health outcomes in people with T2D, the intervention was acceptable and improved self-reported medication adherence. Future studies can improve from the lessons learnt from this pilot study.

A good app should not only possess essential evidence-based features, but also safeguard data privacy and security, disseminate accurate and high-quality content, be tailored to users' needs, and be easy to use. Moving forward, disease management apps should be co-designed with healthcare providers and patients and checked against evidence-based checklists. Disease management app studies should also be aware of cultural sensitivities and focus on aspects of the app (or a combination of digital support) that have the potential to improve health outcomes.

References

1. World Health Organization. Global report on diabetes. Geneva: World Health Organization; 2016. Available from: <http://www.who.int/diabetes/global-report/en/>.
2. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation; 2017.
3. Herman WH, Zimmet P. Type 2 Diabetes: An Epidemic Requiring Global Attention and Urgent Action. *Diabetes Care* [Internet]. 2012; 35(5):[943 p.]. Available from: <https://doi.org/10.2337/dc12-0298>.
4. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology* [Internet]. 2018; 14(2):[88 p.]. Available from: <https://doi.org/10.1038/nrendo.2017.151>.
5. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus: Geneva: World health organization; 1999 [Available from: https://apps.who.int/iris/bitstream/handle/10665/66040/WHO_NCD_NCS_99.2.pdf?sequence=1&isAllowed=y].
6. Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *The lancet Diabetes & endocrinology* [Internet]. 2018; 6(5):[361-9 pp.]. Available from: [https://doi.org/10.1016/S2213-8587\(18\)30051-2](https://doi.org/10.1016/S2213-8587(18)30051-2).
7. Prato SD, LaSalle J, Matthaei S, Bailey C. Tailoring treatment to the individual in type 2 diabetes practical guidance from the Global Partnership for Effective Diabetes Management. *International journal of clinical practice* [Internet]. 2010; 64(3):[295-304 pp.]. Available from: <https://doi.org/10.1111/j.1742-1241.2009.02227.x>.
8. American Diabetes Association. Standards of medical care in diabetes—2017 abridged for primary care providers. *Clinical Diabetes*. 2017;35(1):5-26.
9. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes* [Internet]. 2008 2008-04-01 00:00:00; 26(2):[77-82 pp.]. Available from: <https://doi.org/10.2337/diaclin.26.2.77>.
10. Home P, Mant J, Diaz J, Turner C. Management of type 2 diabetes: summary of updated NICE guidance. *BMJ* [Internet]. 2008 2008-06-05 22:01:25; 336(7656):[1306-8 pp.]. Available from: <https://doi.org/10.1136/bmj.39560.442095.AD>
11. American Diabetes Association. Screening for type 2 diabetes. *Diabetes care* [Internet]. 2004; 27:[S11 p.]. Available from: <https://doi.org/10.2337/diacare.23.10.1563>.
12. American Diabetes Association. Diabetes Symptoms American Diabetes Association [cited 2019 July 15]. Available from: <http://www.diabetes.org/diabetes-basics/symptoms/>.

13. McAuley KA, Williams SM, Mann JI, Goulding A, Chisholm A, Wilson N, et al. Intensive lifestyle changes are necessary to improve insulin sensitivity: a randomized controlled trial. *Diabetes care* [Internet]. 2002; 25(3):[445-52 pp.]. Available from: <https://doi.org/10.2337/diacare.25.3.445>.
14. Group DPPR. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes care* [Internet]. 2002; 25(12):[2165-71 pp.]. Available from: <https://doi.org/10.2337/diacare.25.12.2165>.
15. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Archives of Internal Medicine* [Internet]. 2007; 167(11):[1145-51 pp.]. Available from: <http://dx.doi.org/10.1001/archinte.167.11.1145>.
16. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4· 4 million participants. *The Lancet* [Internet]. 2016; 387(10027):[1513-30 pp.]. Available from: [https://doi.org/10.1016/S0140-6736\(16\)00618-8](https://doi.org/10.1016/S0140-6736(16)00618-8).
17. Phan TP, Alkema L, Tai ES, Tan KHX, Yang Q, Lim W-Y, et al. Forecasting the burden of type 2 diabetes in Singapore using a demographic epidemiological model of Singapore. *BMJ Open Diabetes Research & Care* [Internet]. 2014; 2(1). Available from: <http://dx.doi.org/10.1136/bmjdr-2013-000012>.
18. Ebrahim S, Kinra S, Bowen L, Andersen E, Ben-Shlomo Y, Lyngdoh T, et al. The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study. *PLoS medicine* [Internet]. 2010; 7(4):[e1000268 p.]. Available from: <https://doi.org/10.1371/journal.pmed.1000268>.
19. Centers for Disease Control Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011 [cited 2019 July 15]. Available from: <https://sunshinepando.com/wp-content/uploads/2015/01/national-diabetes-fact-sheet-2011-Sunshine-Prosthetics-and-Orthotics-Wayne-NJ.pdf>.
20. Hossain P, Kavar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge. *N Engl j med* [Internet]. 2007; 2007(356):[213-5 pp.]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMp068177>.
21. Candib LM. Obesity and diabetes in vulnerable populations: reflection on proximal and distal causes. *The Annals of Family Medicine* [Internet]. 2007; 5(6):[547-56 pp.]. Available from: <http://www.annfammed.org/content/5/6/547.short>.
22. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care* [Internet]. 2018; 41(5):[917 p.]. Available from: <https://doi.org/10.2337/dci18-0007>.
23. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. <http://nice.org.uk/guidance/ng28>: National Institute for Health and Care Excellence; 2015.

24. Png ME, Yoong J, Phan TP, Wee HL. Current and future economic burden of diabetes among working-age adults in Asia: conservative estimates for Singapore from 2010-2050. *BMC Public Health* [Internet]. 2016; 16(1):[1-9 pp.]. Available from: <http://dx.doi.org/10.1186/s12889-016-2827-1>.
25. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *The Lancet* [Internet]. 2009 2009/10/03/; 374(9696):[1196-208 pp.]. Available from: [https://doi.org/10.1016/S0140-6736\(09\)61460-4](https://doi.org/10.1016/S0140-6736(09)61460-4).
26. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice* [Internet]. 2014 2014/02/01/; 103(2):[137-49 pp.]. Available from: <http://www.sciencedirect.com/science/article/pii/S0168822713003859>.
27. Shetty P. Grey matter: ageing in developing countries. *The Lancet* [Internet]. 2012; 379(9823):[1285-7 pp.]. Available from: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(12\)60541-8/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60541-8/fulltext).
28. Kamarul Imran M, Ismail A, Naing L, Wan Mohamad W. Type 2 diabetes mellitus patients with poor glycaemic control have lower quality of life scores as measured by the Short Form-36. *Singapore medical journal* [Internet]. 2010; 51(2):[157 p.]. Available from: <http://smj.sma.org.sg/5102/5102a10.pdf>.
29. Funnell MM, Brown TL, Childs BP, Haas LB, Hosey GM, Jensen B, et al. National Standards for Diabetes Self-Management Education. *Diabetes Care* [Internet]. 2009 2009-01-01 00:00:00; 32(Supplement 1):[S87-S94 pp.]. Available from: <https://doi.org/10.2337/dc09-S087>.
30. Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice* [Internet]. 2010 2010/03/01/; 87(3):[293-301 pp.]. Available from: <https://doi.org/10.1016/j.diabres.2010.01.026>.
31. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. *Diabetes Care* [Internet]. 2018. Available from: <https://doi.org/10.2337/dc17-1962>
32. Graham ID, Harrison MB. Evaluation and adaptation of clinical practice guidelines. *Evidence Based Nursing* [Internet]. 2005; 8(3):[68 p.]. Available from: <http://dx.doi.org/10.1136/ebn.8.3.68>.
33. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *New England Journal of Medicine* [Internet]. 2008; 359(15):[1577-89 pp.]. Available from: <https://www.nejm.org/doi/full/10.1056/nejmoa0806470>.
34. Barnett AH, Krentz A, Strojek K, Sieradzki J, Azizi F, Embong M, et al. The efficacy of self - monitoring of blood glucose in the management of patients with type 2 diabetes treated with a gliclazide modified release - based regimen. A multicentre, randomized, parallel - group, 6 - month evaluation (DINAMIC 1 study). *Diabetes, Obesity and Metabolism* [Internet]. 2008; 10(12):[1239-47 pp.]. Available from: <https://doi.org/10.1111/j.1463-1326.2008.00894.x>.

35. MacLean C. Patient education: Sharing a passion, sharing resources. *Canadian Family Physician* [Internet]. 2010; 56(7):[721- pp.]. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2922822/>.
36. American Diabetes Association. 4. Lifestyle management: Standards of medical care in diabetes—2018. *Diabetes Care* [Internet]. 2018; 41(Supplement 1):[S38-S50 pp.]. Available from: <https://doi.org/10.2337/dc18-S004>.
37. Rosal MC, Ockene IS, Restrepo A, White MJ, Borg A, Olendzki B, et al. Randomized Trial of a Literacy-Sensitive, Culturally Tailored Diabetes Self-Management Intervention for Low-Income Latinos. *Diabetes Care* [Internet]. 2011. Available from: <https://doi.org/10.2337/dc10-1981>.
38. Deakin TA, McShane CE, Cade JE, Williams R. Group based training for self - management strategies in people with type 2 diabetes mellitus. *Cochrane database of systematic reviews* [Internet]. 2005; (2). Available from: <https://doi.org/10.1002/14651858.CD003417.pub2>.
39. Brunisholz KD, Briot P, Hamilton S, Joy EA, Lomax M, Barton N, et al. Diabetes self-management education improves quality of care and clinical outcomes determined by a diabetes bundle measure. *Journal of multidisciplinary healthcare* [Internet]. 2014; 7:[533 p.]. Available from: <https://doi.org/10.2147/JMDH.S69000>.
40. Cochran J, Conn VS. Meta-analysis of quality of life outcomes following diabetes self-management training. *The Diabetes Educator* [Internet]. 2008; 34(5):[815-23 pp.]. Available from: <http://dx.doi.org/10.1177/0145721708323640>.
41. Yuan C, Lai CWK, Chan LWC, Chow M, Law HKW, Ying M. The effect of diabetes self-management education on body weight, glycemic control, and other metabolic markers in patients with type 2 diabetes mellitus. *Journal of diabetes research* [Internet]. 2014; 2014:[789761- pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25136645>.
42. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management, NICE guideline [NG28] 2015 [updated 2017 May; cited 2019 July 15]. Available from: <https://www.nice.org.uk/guidance/ng28>.
43. American Diabetes Association. 1. Introduction: standards of medical care in diabetes—2018. *Diabetes Care* [Internet]. 2018; 41(Supplement 1):[S1-S2 pp.]. Available from: <https://doi.org/10.2337/dc18-Sint01>.
44. Control D, Group CTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England journal of medicine* [Internet]. 1993; 329(14):[977-86 pp.]. Available from: <https://doi.org/10.1056/NEJM199309303291401>.
45. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2018. *Diabetes Care* [Internet]. 2018; 41(Supplement 1):[S55-S64 pp.]. Available from: <https://doi.org/10.2337/dc18-S006>.

46. Yamaoka K, Tango T. Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. *BMC Medicine* [Internet]. 2012 2012/11/14; 10(1):[138 p.]. Available from: <https://doi.org/10.1186/1741-7015-10-138>.
47. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2018. *Diabetes care* [Internet]. 2018; 41(Supplement 1):[S73-S85 pp.]. Available from: <https://doi.org/10.2337/dc18-S008>.
48. Vassilev I, Rogers A, Sanders C, Kennedy A, Blickem C, Protheroe J, et al. Social networks, social capital and chronic illness self-management: a realist review. *Chronic Illness* [Internet]. 2010 2011/03/01; 7(1):[60-86 pp.]. Available from: <https://doi.org/10.1177/1742395310383338>.
49. Gallant MP. The Influence of Social Support on Chronic Illness Self-Management: A Review and Directions for Research. *Health Education & Behavior* [Internet]. 2003 2003/04/01; 30(2):[170-95 pp.]. Available from: <https://doi.org/10.1177/1090198102251030>.
50. Bandura A. Social cognitive theory of self-regulation. *Organizational Behavior and Human Decision Processes* [Internet]. 1991 1991/12/01; 50(2):[248-87 pp.]. Available from: <http://www.sciencedirect.com/science/article/pii/074959789190022L>.
51. Schiøtz ML, Bøgelund M, Almdal T, Jensen BB, Willaing I. Social support and self-management behaviour among patients with Type 2 diabetes. *Diabetic Medicine* [Internet]. 2012 2012/05/01; 29(5):[654-61 pp.]. Available from: <https://doi.org/10.1111/j.1464-5491.2011.03485.x>.
52. Gu L, Wu S, Zhao S, Zhou H, Zhang S, Gao M, et al. Association of Social Support and Medication Adherence in Chinese Patients with Type 2 Diabetes Mellitus. *Int J Environ Res Public Health* [Internet]. 2017; 14(12):[1522 p.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/29211039>.
53. Vassilev I, Rogers A, Kennedy A, Koetsenruijter J. The influence of social networks on self-management support: a metasynthesis. *BMC public health* [Internet]. 2014; 14:[719- pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25023948>.
54. Morris RL, Kennedy A, Sanders C. Evolving ‘self’-management: exploring the role of social network typologies on individual long-term condition management. *Health Expectations* [Internet]. 2016 2016/10/01; 19(5):[1044-61 pp.]. Available from: <https://doi.org/10.1111/hex.12394>.
55. Raghupathi W, Raghupathi V. Big data analytics in healthcare: promise and potential. *Health Information Science and Systems* [Internet]. 2014; 2(1):[3 p.]. Available from: <https://doi.org/10.1186/2047-2501-2-3>.
56. Ahern DK, Woods SS, Lightowler MC, Finley SW, Houston TK. Promise of and Potential for Patient-Facing Technologies to Enable Meaningful Use. *American Journal of Preventive Medicine* [Internet]. 2011 2011/05/01; 40(5, Supplement 2):[S162-S72 pp.]. Available from: <https://doi.org/10.1016/j.amepre.2011.01.005>.
57. Car J, Huckvale K, Hermens H. Telehealth for long term conditions. *BMJ* [Internet]. 2012; 344:[e4201 p.]. Available from: doi: <https://doi.org/10.1136/bmj.e4201>

58. Chow WL, Jiang J, Cho LW, Foo JP, Fock KM, Chen R. Telehealth for improved glycaemic control in patients with poorly controlled diabetes after acute hospitalization - a preliminary study in Singapore. *Journal Of Telemedicine And Telecare* [Internet]. 2014; 20(6):[317-23 pp.]. Available from: <https://doi.org/10.1177%2F1357633X14544441>.
59. Polisena J, Tran K, Cimon K, Hutton B, McGill S, Palmer K. Home telehealth for diabetes management: a systematic review and meta - analysis. *Diabetes, Obesity and Metabolism* [Internet]. 2009; 11(10):[913-30 pp.]. Available from: <https://doi.org/10.1111/j.1463-1326.2009.01057.x>.
60. Cassimatis M, Kavanagh DJ. Effects of type 2 diabetes behavioural telehealth interventions on glycaemic control and adherence: a systematic review. *Journal of telemedicine and telecare* [Internet]. 2012; 18(8):[447-50 pp.]. Available from: <https://doi.org/10.1258%2Fjtt.2012.gth105>.
61. Tran J, Tran R, White JR. Smartphone-Based Glucose Monitors and Applications in the Management of Diabetes: An Overview of 10 Salient “Apps” and a Novel Smartphone-Connected Blood Glucose Monitor. *Clinical Diabetes* [Internet]. 2012; 30(4):[173-8 pp.]. Available from: <https://doi.org/10.2337/diaclin.30.4.173>.
62. Aitken M, Clancey B, Nass D. The Growing Value of Digital Health: Evidence and Impact on Human Health and the Healthcare System. New Jersey, U.S.: IQVIA Institute for Human Data Science; 2017. Contract No.: PB.0009-1-11.2017.
63. Hou C, Carter B, Hewitt J, Francisa T, Mayor S. Do Mobile Phone Applications Improve Glycemic Control (HbA1c) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials. *Diabetes Care* [Internet]. 2016; 39(11):[2089-95 pp.]. Available from: <https://doi.org/10.2337/dc16-0346>.
64. Klonoff DC, Ahn D, Drincic A. Continuous glucose monitoring: a review of the technology and clinical use. *Diabetes research and clinical practice* [Internet]. 2017; 133:[178-92 pp.]. Available from: <https://doi.org/10.1016/j.diabres.2017.08.005>.
65. Heinemann L, Freckmann G. CGM Versus FGM; or, Continuous Glucose Monitoring Is Not Flash Glucose Monitoring. *Journal of Diabetes Science and Technology* [Internet]. 2015 2015/09/01; 9(5):[947-50 pp.]. Available from: <https://doi.org/10.1177/1932296815603528>.
66. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. *Diabetes Therapy* [Internet]. 2017 2017/02/01; 8(1):[55-73 pp.]. Available from: <https://doi.org/10.1007/s13300-016-0223-6>.
67. Lloyd B, Groat D, Cook CB, Kaufman D, Grando A. iDECIDE: A Mobile Application for Insulin Dosing Using an Evidence Based Equation to Account for Patient Preferences. *Stud Health Technol Inform* [Internet]. 2015; 216:[93-7 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26262017>.
68. Piwek L, Ellis DA, Andrews S, Joinson A. The rise of consumer health wearables: promises and barriers. *PLoS Med* [Internet]. 2016; 13(2):[e1001953 p.]. Available from: <https://doi.org/10.1371/journal.pmed.1001953>.

69. Park C, Le QA. The Effectiveness of Continuous Glucose Monitoring in Patients with Type 2 Diabetes: A Systematic Review of Literature and Meta-analysis. *Diabetes Technology & Therapeutics* [Internet]. 2018 2018/09/01; 20(9):[613-21 pp.]. Available from: <https://doi.org/10.1089/dia.2018.0177>.
70. Lam WY, Fresco P. Medication Adherence Measures: An Overview. *BioMed research international* [Internet]. 2015. Available from: <http://dx.doi.org/10.1155/2015/217047>.
71. Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization, Avenue Appia 20, CH-1211 Geneva 27, Switzerland 2003. Available from: <https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf>.
72. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. *Value in health* [Internet]. 2008; 11(1):[44-7 pp.]. Available from: <https://doi.org/10.1111/j.1524-4733.2007.00213.x>.
73. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes care* [Internet]. 2004; 27(5):[1218-24 pp.]. Available from: <https://doi.org/10.2337/diacare.27.5.1218>.
74. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and drug safety* [Internet]. 2006; 15(8):[565-74 pp.]. Available from: <https://doi.org/10.1002/pds.1230>.
75. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical Therapeutics* [Internet]. 21(6):[1074-90 pp.]. Available from: [http://dx.doi.org/10.1016/S0149-2918\(99\)80026-5](http://dx.doi.org/10.1016/S0149-2918(99)80026-5).
76. Patel P, Gupta P, Burns A, Mohamed AA, Cole R, Lane D, et al. Biochemical Urine Testing of Adherence to Cardiovascular Medications Reveals High Rates of Nonadherence in People Attending Their Annual Review for Type 2 Diabetes. *Diabetes Care* [Internet]. 2019; 42(6):[1132 p.]. Available from: <https://doi.org/10.2337/dc18-1453>.
77. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keenanasseril A, et al. Interventions for enhancing medication adherence. *The Cochrane Library* [Internet]. 2014. Available from: <https://doi.org/10.1002/14651858.CD000011.pub3>.
78. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane database syst Rev* [Internet]. 2008; 2(2). Available from: <https://doi.org/10.1002/14651858.CD000011.pub3>.
79. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. *Diabetic Medicine* [Internet]. 2015; 32(6):[725-37 pp.]. Available from: <https://doi.org/10.1111/dme.12651>.
80. Lehane E, McCarthy G. Intentional and unintentional medication non-adherence: A comprehensive framework for clinical research and practice? A discussion paper. *International Journal of Nursing Studies* [Internet]. 2007 2007/11/01/; 44(8):[1468-77 pp.]. Available from: <https://doi.org/10.1016/j.ijnurstu.2006.07.010>.

81. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Therapeutics and Clinical Risk Management* [Internet]. 2008 02/; 4(1):[269-86 pp.]. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2503662/>.
82. Lin L-K, Sun Y, Heng BH, Chew DEK, Chong P-N. Medication adherence and glycemic control among newly diagnosed diabetes patients. *BMJ Open Diabetes Research and Care* [Internet]. 2017; 5(1):[e000429 p.]. Available from: <http://dx.doi.org/10.1136/bmjdr-2017-000429>.
83. Kini V, Ho PM. Interventions to Improve Medication Adherence: A Review. *Interventions to Improve Medication Adherence*. *JAMA* [Internet]. 2018; 320(23):[2461-73 pp.]. Available from: <https://doi.org/10.1001/jama.2018.19271>.
84. Lam WY, Fresco P. Medication Adherence Measures: An Overview. *BioMed research international* [Internet]. 2015; 2015. Available from: <http://dx.doi.org/10.1155/2015/217047>.
85. Jimmy B, Jose J. Patient Medication Adherence: Measures in Daily Practice. *Oman Medical Journal* [Internet]. 2011; 26(3):[155-9 pp.]. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191684/>.
86. National Institute for Health and Care Excellence (NICE). Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence, Clinical guideline [CG76] 2009 [updated 2009 January 28; cited 2019 July 15]. Available from: <https://www.nice.org.uk/guidance/cg76>.
87. Brown MT, Bussell JK. Medication Adherence: WHO Cares? *Mayo Clinic Proceedings* [Internet]. 2011; 86(4):[304-14 pp.]. Available from: <https://doi.org/10.4065/mcp.2010.0575>.
88. Shrivastava SR, Shrivastava PS, Ramasamy J. Role of self-care in management of diabetes mellitus. *Journal of Diabetes & Metabolic Disorders* [Internet]. 2013; 12(1):[1 p.]. Available from: <https://doi.org/10.1186/2251-6581-12-14>.
89. Bailey CJ, Kodack M. Patient adherence to medication requirements for therapy of type 2 diabetes. *International Journal of Clinical Practice* [Internet]. 2011; 65(3):[314-22 pp.]. Available from: <http://dx.doi.org/10.1111/j.1742-1241.2010.02544.x>.
90. DiBonaventura M, Wintfeld N, Huang J, Goren A. The association between nonadherence and glycated hemoglobin among type 2 diabetes patients using basal insulin analogs. *Patient preference and adherence* [Internet]. 2014; 8:[873-82 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24971002>.
91. Currie CJ, Peyrot M, Morgan CL, Poole CD, Jenkins-Jones S, Rubin RR, et al. The impact of treatment noncompliance on mortality in people with type 2 diabetes. *Diabetes care* [Internet]. 2012; 35(6):[1279-84 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22511257>.
92. Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, et al. Effect of Medication Nonadherence on Hospitalization and Mortality Among Patients With

- Diabetes Mellitus. Archives of Internal Medicine [Internet]. 2006; 166(17):[1836-41 pp.]. Available from: <https://doi.org/10.1001/archinte.166.17.1836>.
93. Khattab M, Khader YS, Al-Khawaldeh A, Ajlouni K. Factors associated with poor glycemic control among patients with type 2 diabetes. Journal of diabetes and its complications [Internet]. 2010; 24(2):[84-9 pp.]. Available from: <https://dx.doi.org/10.1111%2Fjdi.12175>.
 94. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Medical care [Internet]. 2005; 43(6):[521-30 pp.]. Available from: <http://dx.doi.org/10.1097/01.mlr.0000163641.86870.af>.
 95. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. Health affairs [Internet]. 2011; 30(1):[91-9 pp.]. Available from: <https://doi.org/10.1377/hlthaff.2009.1087>.
 96. Haynes R, McDonald HP, Garg AX. Helping patients follow prescribed treatment: Clinical applications. JAMA [Internet]. 2002; 288(22):[2880-3 pp.]. Available from: <http://dx.doi.org/10.1001/jama.288.22.2880>.
 97. Hung C-I. Factors predicting adherence to antidepressant treatment. Current opinion in psychiatry [Internet]. 2014; 27(5):[344-9 pp.]. Available from: <http://dx.doi.org/10.1097/YCO.0000000000000086>.
 98. Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. Cancer treatment reviews [Internet]. 2013; 39(6):[610-21 pp.]. Available from: <https://doi.org/10.1016/j.ctrv.2012.12.014>.
 99. Lehane E, McCarthy G. An examination of the intentional and unintentional aspects of medication non - adherence in patients diagnosed with hypertension. Journal of clinical nursing [Internet]. 2007; 16(4):[698-706 pp.]. Available from: <https://doi.org/10.1111/j.1365-2702.2005.01538.x>.
 100. Wroe AL. Intentional and unintentional nonadherence: a study of decision making. Journal of behavioral medicine [Internet]. 2002; 25(4):[355-72 pp.]. Available from: <https://doi.org/10.1023/A:1015866415552>.
 101. Ruppert TM, Dobbels F, Lewek P, Matyjaszczyk M, Siebens K, De Geest SM. Systematic Review of Clinical Practice Guidelines for the Improvement of Medication Adherence. International journal of behavioral medicine [Internet]. 2015; 22(6):[699-708 pp.]. Available from: <https://10.1007/s12529-015-9479-x>.
 102. Ingersoll K, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. Journal of Behavioral Medicine [Internet]. 2008 2008/06/01; 31(3):[213-24 pp.]. Available from: <http://dx.doi.org/10.1007/s10865-007-9147-y>.
 103. Srivastava K, Arora A, Kataria A, Cappelleri JC, Sadosky A, Peterson AM. Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-

- analysis. Patient preference and adherence [Internet]. 2013; 7:[419-34 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23737662>.
104. Mann DM, Ponieman D, Leventhal H, Halm EA. Predictors of adherence to diabetes medications: the role of disease and medication beliefs. *Journal of behavioral medicine* [Internet]. 2009; 32(3):[278-84 pp.]. Available from: <https://doi.org/10.1007/s10865-009-9202-y>.
 105. Schmittiel JA, Uratsu CS, Karter AJ, Heisler M, Subramanian U, Mangione CM, et al. Why don't diabetes patients achieve recommended risk factor targets? Poor adherence versus lack of treatment intensification. *Journal of general internal medicine* [Internet]. 2008; 23(5):[588-94 pp.]. Available from: <https://doi.org/10.1007/s11606-008-0554-8>.
 106. Davis RE, Jacklin R, Sevdalis N, Vincent CA. Patient involvement in patient safety: what factors influence patient participation and engagement? *Health expectations* [Internet]. 2007; 10(3):[259-67 pp.]. Available from: <https://doi.org/10.1111/j.1369-7625.2007.00450.x>.
 107. Coulter A, Ellins J. Effectiveness of strategies for informing, educating, and involving patients. *BMJ* [Internet]. 2007; 335(7609):[24-7 pp.]. Available from: <https://doi.org/10.1136/bmj.39246.581169.80>.
 108. Aikens JE, Bingham R, Piette JD. Patient-Provider Communication and Self-care Behavior Among Type 2 Diabetes Patients. *The Diabetes Educator* [Internet]. 2005 2005/09/01; 31(5):[681-90 pp.]. Available from: <https://doi.org/10.1177/0145721705280829>.
 109. Garay-Sevilla ME, Nava LE, Malacara JM, Huerta R, de León JD, Mena A, et al. Adherence to treatment and social support in patients with non-insulin dependent diabetes mellitus. *Journal of Diabetes and its Complications*. 1995;9(2):81-6.
 110. King DK, Glasgow RE, Toobert DJ, Strycker LA, Estabrooks PA, Osuna D, et al. Self-efficacy, problem solving, and social-environmental support are associated with diabetes self-management behaviors. *Diabetes care*. 2010;33(4):751-3.
 111. Magrin ME, D'Addario M, Greco A, Miglioretti M, Sarini M, Scignaro M, et al. Social support and adherence to treatment in hypertensive patients: a meta-analysis. *Annals of Behavioral Medicine*. 2015;49(3):307-18.
 112. Dayer L, Heldenbrand S, Anderson P, Gubbins PO, Martin BC. Smartphone medication adherence apps: potential benefits to patients and providers. *Journal of the American Pharmacists Association* [Internet]. 2013; 53(2):[172-81 pp.]. Available from: <http://dx.doi.org/10.1331/JAPhA.2013.12202>.
 113. Zweig M, Shen J, Jug L. Healthcare consumers in a digital transition: Rock Health; 2017 [10th September 2018]. Available from: <https://rockhealth.com/reports/healthcare-consumers-in-a-digital-transition/>.
 114. Adams A, Shankar M, Tecco H. 50 things we now know about digital health consumers: Rock Health; 2016 [10th September 2018]. Available from: <https://rockhealth.com/reports/digital-health-consumer-adoption-2016/>.

115. Kay M, Santos J, Takane M. mHealth: new horizons for health through mobile technologies: second global survey on eHealth. World Health Organization 2011 [cited 2019 July 17]. Available from: <https://apps.who.int/iris/handle/10665/44607>.
116. Hasvold PE, Wootton R. Use of telephone and SMS reminders to improve attendance at hospital appointments: a systematic review. *Journal of telemedicine and telecare* [Internet]. 2011; 17(7):[358-64 pp.]. Available from: <https://10.1258/jtt.2011.110707>.
117. Anderson AE, Kerr WT, Thames A, Li T, Xiao J, Cohen MS. Electronic health record phenotyping improves detection and screening of type 2 diabetes in the general United States population: A cross-sectional, unselected, retrospective study. *Journal of Biomedical Informatics*.60:162-8.
118. Jahns R-G. Currently, only 1.2% of diabetics that have a smartphone use a diabetes app. Until 2018 the share will rise to 7.8% globally: Research 2 Guidance; 2017 [Available from: <https://research2guidance.com/currently-only-12-of-diabetics-that-have-a-smartphone-use-a-diabetes-app-until-2018-the-share-will-rise-to-78-globally/>].
119. Car J, Tan WS, Huang Z, Sloot P, Franklin BD. eHealth in the future of medications management: personalisation, monitoring and adherence. *BMC Medicine* [Internet]. 2017 2017/04/05; 15(1):[73 p.]. Available from: <https://doi.org/10.1186/s12916-017-0838-0>.
120. Kitsiou S, Paré G, Jaana M, Gerber B. Effectiveness of mHealth interventions for patients with diabetes: An overview of systematic reviews. *PloS one* [Internet]. 2017; 12(3):[e0173160 p.]. Available from: <https://doi.org/10.1371/journal.pone.0173160>.
121. Veazie S, Winchell K, Gilbert J, Paynter R, Ivlev I, Eden KB, et al. Rapid Evidence Review of Mobile Applications for Self-management of Diabetes. *Journal of General Internal Medicine* [Internet]. 2018 2018/07/01; 33(7):[1167-76 pp.]. Available from: <https://doi.org/10.1007/s11606-018-4410-1>.
122. Bonoto BC, de Araújo VE, Godói IP, de Lemos LLP, Godman B, Bennie M, et al. Efficacy of Mobile Apps to Support the Care of Patients With Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *JMIR mHealth and uHealth* [Internet]. 2017; 5(3):[e4 p.]. Available from: <https://mhealth.jmir.org/2017/3/e4/>.
123. Conway N, Campbell I, Forbes P, Cunningham S, Wake D. mHealth applications for diabetes: User preference and implications for app development. *Health Informatics Journal* [Internet]. 2015 2016/12/01; 22(4):[1111-20 pp.]. Available from: <https://doi.org/10.1177/1460458215616265>.
124. Terry NP. Information technology's failure to disrupt health care. *Nev LJ* [Internet]. 2012; 13:[722 p.]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2118653.
125. Goh G, Tan NC, Malhotra R, Padmanabhan U, Barbier S, Allen Jr JC, et al. Short-term trajectories of use of a caloric-monitoring mobile phone app among patients with type 2 diabetes mellitus in a primary care setting. *Journal of medical Internet research* [Internet]. 2015; 17(2). Available from: <https://www.jmir.org/2015/2/e33/>.

126. Payne HE, Lister C, West JH, Bernhardt JM. Behavioral Functionality of Mobile Apps in Health Interventions: A Systematic Review of the Literature. *JMIR mHealth and uHealth* [Internet]. 2015; 3(1):[e20 p.]. Available from: <https://mhealth.jmir.org/2015/1/e20/>.
127. Free C, Phillips G, Galli L, Watson L, Felix L, Edwards P, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. *PLoS med* [Internet]. 2013; 10(1):[e1001362 p.]. Available from: <https://doi.org/10.1371/journal.pmed.1001362>.
128. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* [Internet]. 2012 12/15/; 380(9859):[2224-60 pp.]. Available from: [http://dx.doi.org/10.1016/S0140-6736\(12\)61766-8](http://dx.doi.org/10.1016/S0140-6736(12)61766-8).
129. Miller AS, Cafazzo JA, Seto E. A game plan: Gamification design principles in mHealth applications for chronic disease management. *Health Informatics Journal* [Internet]. 2014 2016/06/01; 22(2):[184-93 pp.]. Available from: <https://doi.org/10.1177/1460458214537511>.
130. Canhoto AI, Arp S. Exploring the factors that support adoption and sustained use of health and fitness wearables. *Journal of Marketing Management* [Internet]. 2017; 33(1-2):[32-60 pp.]. Available from: <https://doi.org/10.1080/0267257X.2016.1234505>.
131. Cafazzo JA, Casselman M, Hamming N, Katzman DK, Palmert MR. Design of an mHealth app for the self-management of adolescent type 1 diabetes: a pilot study. *Journal of medical Internet research* [Internet]. 2012; 14(3):[e70 p.]. Available from: <https://mhealth.jmir.org/2017/6/e82/>.
132. Wargny M, Kleinebreil L, Diop SN, Ndour-Mbaye M, Ba M, Balkau B, et al. SMS-based intervention in type 2 diabetes: clinical trial in Senegal. *BMJ Innovations* [Internet]. 2018; 4(3):[142 p.]. Available from: <http://dx.doi.org/10.1136/bmjinnov-2018-000278>.
133. Shariful Islam SM, Niessen LW, Ferrari U, Ali L, Seissler J, Lechner A. Effects of Mobile Phone SMS to Improve Glycemic Control Among Patients With Type 2 Diabetes in Bangladesh: A Prospective, Parallel-Group, Randomized Controlled Trial. *Diabetes Care* [Internet]. 2015; 38(8):[e112 p.]. Available from: <https://doi.org/10.2337/dc15-0505>.
134. Van Olmen J, Kegels G, Korachais C, de Man J, Van Acker K, Kalobu JC, et al. The effect of text message support on diabetes self-management in developing countries – A randomised trial. *Journal of Clinical & Translational Endocrinology* [Internet]. 2017; 7:[33-41 pp.]. Available from: <https://doi.org/10.1016/j.jcte.2016.12.005>.
135. Dobson R, Whittaker R, Pfaeffli Dale L, Maddison R. The effectiveness of text message-based self-management interventions for poorly-controlled diabetes: A systematic review. *DIGITAL HEALTH* [Internet]. 2017 2017/01/01; 3:[2055207617740315 p.]. Available from: <https://doi.org/10.1177/2055207617740315>.

136. American Diabetes Association. 7. Diabetes Technology: Standards of Medical Care in Diabetes—2019. *Diabetes Care* [Internet]. 2019; 42(Supplement 1):[S71-S80 pp.]. Available from: http://care.diabetesjournals.org/content/42/Supplement_1/S71.abstract.
137. Hall AK, Cole-Lewis H, Bernhardt JM. Mobile text messaging for health: a systematic review of reviews. *Annual review of public health* [Internet]. 2015; 36:[393 p.]. Available from: <https://doi.org/10.1146/annurev-publhealth-031914-122855>.
138. Firth J, Torous J. Smartphone apps for schizophrenia: a systematic review. *JMIR mHealth and uHealth* [Internet]. 2015; 3(4):[e102 p.]. Available from: <https://mhealth.jmir.org/2015/4/e102/>.
139. Park LG, Howie-Esquivel J, Dracup K. A quantitative systematic review of the efficacy of mobile phone interventions to improve medication adherence. *Journal of Advanced Nursing* [Internet]. 2014; 70(9):[1932-53 pp.]. Available from: <https://doi.org/10.1111/jan.12400>.
140. DeKoekkoek T, Given B, Given CW, Ridenour K, Schueller M, Spoelstra SL. mHealth SMS text messaging interventions and to promote medication adherence: an integrative review. *Journal of Clinical Nursing* [Internet]. 2015; 24(19-20):[2722-35 pp.]. Available from: <http://dx.doi.org/10.1111/jocn.12918>.
141. Thakkar J, Kurup R, Laba T-L, Santo K, Thiagalingam A, Rodgers A, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. *JAMA internal medicine* [Internet]. 2016; 176(3):[340-9 pp.]. Available from: <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2484905>.
142. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, De Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS (London, England)* [Internet]. 2011; 25(6):[825 p.]. Available from: <https://dx.doi.org/10.1097%2FQAD.0b013e32834380c1>.
143. Vervloet M, van Dijk L, Santen-Reestman J, van Vlijmen B, van Wingerden P, Bouvy ML, et al. SMS reminders improve adherence to oral medication in type 2 diabetes patients who are real time electronically monitored. *International Journal of Medical Informatics* [Internet]. 2012; 81(9):[594-604 pp.]. Available from: <https://doi.org/10.1016/j.ijmedinf.2012.05.005>.
144. Vervloet M, Linn AJ, van Weert JC, De Bakker DH, Bouvy ML, Van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. *Journal of the American Medical Informatics Association* [Internet]. 2012; 19(5):[696-704 pp.]. Available from: <https://doi.org/10.1136/amiajnl-2011-000748>.
145. Munro S, Lewin S, Swart T, Volmink J. A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? *BMC public health* [Internet]. 2007; 7(1):[104 p.]. Available from: <https://doi.org/10.1186/1471-2458-7-104>.
146. Wald DS, Butt S, Bestwick JP. One-way versus two-way text messaging on improving medication adherence: meta-analysis of randomized trials. *The American journal*

- of medicine [Internet]. 2015; 128(10):[1139. e1-. e5 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26087045>.
147. Choudhry NK, Krumme AA, Ercole PM, et al. Effect of reminder devices on medication adherence: The remind randomized clinical trial. *JAMA Internal Medicine* [Internet]. 2017; 177(5):[624-31 pp.]. Available from: <http://dx.doi.org/10.1001/jamainternmed.2016.9627>.
 148. Ahmed I, Ahmad NS, Ali S, Ali S, George A, Danish HS, et al. Medication Adherence Apps: Review and Content Analysis. *JMIR mHealth and uHealth* [Internet]. 2018; 6(3). Available from: <https://mhealth.jmir.org/2018/3/e62/>.
 149. Santo K, Richtering SS, Chalmers J, Thiagalingam A, Chow CK, Redfern J. Mobile Phone Apps to Improve Medication Adherence: A Systematic Stepwise Process to Identify High-Quality Apps. *JMIR mHealth and uHealth* [Internet]. 2016; 4(4):[e132 p.]. Available from: <https://mhealth.jmir.org/2016/4/e132/>.
 150. Geuens J, Swinnen TW, Westhovens R, de Vlam K, Geurts L, Vanden Abeele V. A Review of Persuasive Principles in Mobile Apps for Chronic Arthritis Patients: Opportunities for Improvement. *JMIR Mhealth Uhealth* [Internet]. 2016 2016/10/13; 4(4):[e118 p.]. Available from: <http://mhealth.jmir.org/2016/4/e118/>.
 151. Morrissey EC, Corbett TK, Walsh JC, Molloy GJ. Behavior Change Techniques in Apps for Medication Adherence: A Content Analysis. *American Journal of Preventive Medicine* [Internet]. 2016; 50(5):[e143-e6 pp.]. Available from: <https://doi.org/10.1016/j.amepre.2015.09.034>.
 152. Santo K, Chow CK, Thiagalingam A, Rogers K, Chalmers J, Redfern J. MEDication reminder APPs to improve medication adherence in Coronary Heart Disease (MedApp-CHD) Study: a randomised controlled trial protocol. *BMJ Open* [Internet]. 2017; 7(10). Available from: <http://dx.doi.org/10.1136/bmjopen-2017-017540>.
 153. Mira JJ, Navarro I, Botella F, Borrás F, Nuño-Solinís R, Orozco D, et al. A Spanish Pillbox App for Elderly Patients Taking Multiple Medications: Randomized Controlled Trial. *J Med Internet Res* [Internet]. 2014; 16(4):[e99 p.]. Available from: <https://www.jmir.org/2014/4/e99/>.
 154. Morawski K, Ghazinouri R, Krumme A, et al. Association of a smartphone application with medication adherence and blood pressure control: The medisafe-bp randomized clinical trial. *JAMA Internal Medicine* [Internet]. 2018; 178(6):[802-9 pp.]. Available from: <http://dx.doi.org/10.1001/jamainternmed.2018.0447>.
 155. Anglada-Martínez H, Martin-Conde M, Rovira-Illamola M, Sotoca-Momblona JM, Sequeira E, Aragunde V, et al. Feasibility and Preliminary Outcomes of a Web and Smartphone-Based Medication Self-Management Platform for Chronically Ill Patients. *Journal of medical systems* [Internet]. 2016; 40(4):[1-14 pp.]. Available from: <https://doi.org/10.1007/s10916-016-0456-y>.
 156. Research2Guidance. mHealth App Developer Economics: How mHealth app publishers are monetizing their apps. Berlin, Germany; 2016.

157. A Smartphone Application to Improve Medication Adherence Among People With Type 2 Diabetes Mellitus in Singapore [13/05/19]. Available from: <https://ClinicalTrials.gov/show/NCT02105597>.
158. Jafari J, Moonaghi H, Ahmady S, Zary N, Masiello I. Readiness of diabetics to use the internet and mobile services: the case of a large city in a middle-income country. *J Community Med Health Educ* [Internet]. 2015; 5(380):[2161-0711.1000380 pp.]. Available from: https://www.researchgate.net/profile/Nabil_Zary/publication/287984628_Readiness_of_Diabetics_to_Use_the_Internet_and_Mobile_Services_The_Case_of_a_Large_City_in_a_Middle-income_Country/links/567af9ca08ae197583812c56.pdf.
159. Wyatt JC. How can clinicians, specialty societies and others evaluate and improve the quality of apps for patient use? *BMC Medicine* [Internet]. 2018 2018/12/03; 16(1):[225 p.]. Available from: <https://doi.org/10.1186/s12916-018-1211-7>.
160. Hoppe C, Cade J, Carter M. An evaluation of diabetes targeted apps for Android smartphone in relation to behaviour change techniques. *Journal of Human Nutrition and Dietetics* [Internet]. 2016. Available from: <https://doi.org/10.1111/jhn.12424>.
161. Lithgow K, Edwards A, Rabi D. Smartphone App Use for Diabetes Management: Evaluating Patient Perspectives. *JMIR Diabetes* [Internet]. 2017; 2(1):[e2 p.]. Available from: <http://doi.org/10.2196/diabetes.6643>.
162. Fu H, McMahon SK, Gross CR, Adam TJ, Wyman JF. Usability and clinical efficacy of diabetes mobile applications for adults with type 2 diabetes: A systematic review. *Diabetes Research and Clinical Practice*. 2017;131:70-81.
163. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile app rating scale: a new tool for assessing the quality of health mobile apps. *JMIR mHealth and uHealth* [Internet]. 2015; 3(1). Available from: <https://mhealth.jmir.org/2015/1/e27/>.
164. Garabedian LF, Ross-Degnan D, Wharam JF. Mobile phone and smartphone technologies for diabetes care and self-management. *Current diabetes reports* [Internet]. 2015; 15(12):[1-9 pp.]. Available from: <https://doi.org/10.1007/s11892-015-0680-8>.
165. Marcano Belisario JS, Huckvale K, Greenfield G, Car J, Gunn LH. Smartphone and tablet self management apps for asthma. *Cochrane Database of Systematic Reviews* [Internet]. 2013; (11). Available from: <http://dx.doi.org/10.1002/14651858.CD010013.pub2>.
166. Jahns R-G. Top 14 diabetes app publishers capture 65% market share of the diabetes app market Research 2 Guidance2019 [1 Jan 2020]. Available from: <https://research2guidance.com/top-14-diabetes-app-publishers-capture-65-market-share-of-the-diabetes-app-market-2/>.
167. Huang Z, Soljak M, Boehm BO, Car J. Clinical relevance of smartphone apps for diabetes management: A global overview. *Diabetes/Metabolism Research and Reviews* [Internet]. 2018. Available from: <https://doi.org/10.1002/dmrr.2990>.

168. van Velsen L, Beaujean DJ, van Gemert-Pijnen JE. Why mobile health app overload drives us crazy, and how to restore the sanity. *BMC Medical Informatics and Decision Making* [Internet]. 2013; 13(1):[1-5 pp.]. Available from: <http://dx.doi.org/10.1186/1472-6947-13-23>.
169. Wu G, Ngo V-V. Do Free Smartphone Apps Have Features of the Diabetes Self-Management Education/Support Guidelines? *Diabetes* [Internet]. 2018; 67(Supplement 1). Available from: <https://doi.org/10.2337/db18-678-P>.
170. Martinez M, Park SB, Maison I, Mody V, Soh LS, Parihar HS. iOS Appstore-Based Phone Apps for Diabetes Management: Potential for Use in Medication Adherence. *JMIR Diabetes* [Internet]. 2017 2017/07/11; 2(2):[e12 p.]. Available from: <http://diabetes.jmir.org/2017/2/e12/>.
171. Chavez S, Fedele D, Guo Y, Bernier A, Smith M, Warnick J, et al. Mobile Apps for the Management of Diabetes. *Diabetes Care* [Internet]. 2017. Available from: <https://doi.org/10.2337/dc17-0853>.
172. AURORA S. SingHealth data breach a timely reminder of how we can beef up cyber defence with AI: Today; 2018 [updated 2nd August cited 2018 December 4]. Available from: <https://www.todayonline.com/commentary/singhealth-data-breach-timely-reminder-how-we-can-beef-cyber-defence-ai>.
173. Huckvale K, Prieto JT, Tilney M, Benghozi P-J, Car J. Unaddressed privacy risks in accredited health and wellness apps: a cross-sectional systematic assessment. *BMC Medicine* [Internet]. 2015; 13:[214 p.]. Available from: <https://doi.org/10.1186/s12916-015-0444-y>.
174. Mendiola MF, Kalnicki M, Lindenauer S. Valuable features in mobile health apps for patients and consumers: content analysis of apps and user ratings. *JMIR mHealth and uHealth* [Internet]. 2015; 3(2). Available from: <https://mhealth.jmir.org/2015/2/e40/>.
175. Hamel MB, Cortez NG, Cohen IG, Kesselheim AS. FDA regulation of mobile health technologies. *New England Journal of Medicine* [Internet]. 2014; 371(4):[372-9 pp.]. Available from: <https://doi.org/10.1056/nejmhle1403384>.
176. Eng DS, Lee JM. The Promise and Peril of Mobile Health Applications for Diabetes and Endocrinology. *Pediatric Diabetes* [Internet]. 2013; 14(4):[231-8 pp.]. Available from: <http://dx.doi.org/10.1111/pedi.12034>.
177. Powell AC, Landman AB, Bates DW. IN search of a few good apps. *JAMA* [Internet]. 2014; 311(18):[1851-2 pp.]. Available from: <http://dx.doi.org/10.1001/jama.2014.2564>.
178. BinDhim NF, Trevena L. There's an App for That: A Guide for Healthcare Practitioners and Researchers on Smartphone Technology. *Online journal of public health informatics* [Internet]. 2015; 7(2). Available from: <https://doi.org/10.5210/ojphi.v7i2.5522>.
179. Huckvale K, Adomaviciute S, Leow M, Car J. Smartphone apps for calculating insulin dose: a systematic assessment. *BMC medicine* [Internet]. 2015; 13(1):[106 p.]. Available from: <https://doi.org/10.1186/s12916-015-0314-7>.

180. Torous J, Roberts LW. Needed innovation in digital health and smartphone applications for mental health: transparency and trust. *JAMA psychiatry* [Internet]. 2017; 74(5):[437-8 pp.]. Available from: <https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2616170>.
181. Bates DW, Landman A, Levine DM. Health Apps and Health Policy: What Is Needed? Health Apps and Health Policy. *JAMA* [Internet]. 2018; 320(19):[1975-6 pp.]. Available from: <https://doi.org/10.1001/jama.2018.14378>.
182. Wicks P, Chiauzzi E. 'Trust but verify'—five approaches to ensure safe medical apps. *BMC medicine* [Internet]. 2015; 13(1):[205 p.]. Available from: <https://doi.org/10.1186/s12916-015-0451-z>.
183. Sunyaev A, Dehling T, Taylor PL, Mandl KD. Availability and quality of mobile health app privacy policies. *Journal of the American Medical Informatics Association* [Internet]. 2014; 22(e1):[e28-e33 pp.]. Available from: <https://doi.org/10.1136/amiajnl-2013-002605>.
184. Ghaddar SF, Valerio MA, Garcia CM, Hansen L. Adolescent Health Literacy: The Importance of Credible Sources for Online Health Information. *Journal of School Health* [Internet]. 2012 2012/01/01; 82(1):[28-36 pp.]. Available from: <https://doi.org/10.1111/j.1746-1561.2011.00664.x>.
185. Nicholas J, Boydell K, Christensen H. mHealth in psychiatry: time for methodological change. *Evidence-based mental health* [Internet]. 2016; 19(2):[33 p.]. Available from: <http://dx.doi.org/10.1136/eb-2015-102278>.
186. Coiera EW. Lessons from the NHS National Programme for IT. *Medical Journal of Australia* [Internet]. 2007; 186(1):[3 p.]. Available from: <https://www.mja.com.au/journal/2007/186/1/lessons-nhs-national-programme-it>.
187. King DK, Glasgow RE, Toobert DJ, Strycker LA, Estabrooks PA, Osuna D, et al. Self-efficacy, problem solving, and social-environmental support are associated with diabetes self-management behaviors. *Diabetes care* [Internet]. 2010; 33(4):[751-3 pp.].
188. Lederman NG, Lederman JS. What Is A Theoretical Framework? A Practical Answer. *Journal of Science Teacher Education* [Internet]. 2015 2015/11/01; 26(7):[593-7 pp.]. Available from: <https://doi.org/10.1007/s10972-015-9443-2>.
189. Alderson P. The importance of theories in health care. *BMJ (Clinical research ed)* [Internet]. 1998; 317(7164):[1007-10 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/9765175>.
190. Kim J, Park H-A. Development of a Health Information Technology Acceptance Model Using Consumers' Health Behavior Intention. *J Med Internet Res* [Internet]. 2012 2012/10/01; 14(5):[e133 p.]. Available from: <http://www.jmir.org/2012/5/e133/>.
191. Wirth W, Von Pape T, Karnowski V. An Integrative Model of Mobile Phone Appropriation. *Journal of Computer-Mediated Communication* [Internet]. 2008 2008/04/01; 13(3):[593-617 pp.]. Available from: <https://doi.org/10.1111/j.1083-6101.2008.00412.x>.

192. Venkatesh V, Morris MG, Davis GB, Davis FD. User Acceptance of Information Technology: Toward a Unified View. *MIS Quarterly* [Internet]. 2003 [cited Full publication date: Sep., 2003; 27(3):[425-78 pp.]. Available from: www.jstor.org/stable/30036540.
193. Ward R. The application of technology acceptance and diffusion of innovation models in healthcare informatics. *Health Policy and Technology*. 2013;2(4):222-8.
194. Hardeman W, Johnston M, Johnston D, Bonetti D, Wareham N, Kinmonth AL. Application of the Theory of Planned Behaviour in Behaviour Change Interventions: A Systematic Review. *Psychology & Health* [Internet]. 2002 2002/01/01; 17(2):[123-58 pp.]. Available from: <https://doi.org/10.1080/08870440290013644a>.
195. Rosenstock IM. Historical Origins of the Health Belief Model. *Health Education Monographs* [Internet]. 1974 1974/12/01; 2(4):[328-35 pp.]. Available from: <https://doi.org/10.1177/109019817400200403>.
196. Bloom Cercone KA, Hart LK. The Relationship Between the Health Belief Model and Compliance of Persons with Diabetes Mellitus. *Diabetes Care* [Internet]. 1980; 3(5):[594 p.]. Available from: <http://care.diabetesjournals.org/content/3/5/594.abstract>.
197. Becker MH, Janz NK. The Health Belief Model Applied to Understanding Diabetes Regimen Compliance. *The Diabetes Educator* [Internet]. 1985 1985/03/01; 11(1):[41-7 pp.]. Available from: <https://doi.org/10.1177/014572178501100108>.
198. Harvey JN, Lawson VL. The importance of health belief models in determining self-care behaviour in diabetes. *Diabetic Medicine* [Internet]. 2009 2009/01/01; 26(1):[5-13 pp.]. Available from: <https://doi.org/10.1111/j.1464-5491.2008.02628.x>.
199. Brownlee-Duffeck M, Peterson L, Simonds JF, Goldstein D, Kilo C, Hoette S. The role of health beliefs in the regimen adherence and metabolic control of adolescents and adults with diabetes mellitus. *Journal of Consulting and Clinical Psychology* [Internet]. 1987; 55(2):[139-44 pp.].
200. Plotnikoff RC, Lippke S, Courneya K, Birkett N, Sigal R. Physical activity and diabetes: An application of the theory of planned behaviour to explain physical activity for Type 1 and Type 2 diabetes in an adult population sample. *Psychology & Health* [Internet]. 2010 2010/01/01; 25(1):[7-23 pp.]. Available from: <https://doi.org/10.1080/08870440802160984>.
201. Davies CA, Mummery WK, Steele RM. The relationship between personality, theory of planned behaviour and physical activity in individuals with type II diabetes. *British Journal of Sports Medicine* [Internet]. 2010; 44(13):[979 p.]. Available from: <http://bjsm.bmj.com/content/44/13/979.abstract>.
202. Blue CL. Does the Theory of Planned Behavior Identify Diabetes-Related Cognitions for Intention to Be Physically Active and Eat a Healthy Diet? *Public Health Nursing*. 2007;24(2):141-50.
203. Rahimi B, Nadri H, Afshar HL, Timpka T. A systematic review of the technology acceptance model in health informatics. *Applied clinical informatics* [Internet]. 2018;

- 9(03):[604-34 pp.]. Available from:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6094026/>.
204. Portz JD, Bayliss EA, Bull S, Boxer RS, Bekelman DB, Gleason K, et al. Using the Technology Acceptance Model to Explore User Experience, Intent to Use, and Use Behavior of a Patient Portal Among Older Adults With Multiple Chronic Conditions: Descriptive Qualitative Study. *J Med Internet Res* [Internet]. 2019 2019/04/08; 21(4):[e11604 p.]. Available from: <https://www.jmir.org/2019/4/e11604/>.
205. Holden RJ, Karsh B-T. The Technology Acceptance Model: Its past and its future in health care. *Journal of Biomedical Informatics* [Internet]. 2010 2010/02/01; 43(1):[159-72 pp.]. Available from:
<http://www.sciencedirect.com/science/article/pii/S1532046409000963>.
206. Rossmann C, Riesmeyer C, Brew-Sam N, Karnowski V, Joeckel S, Chib A, et al. Appropriation of Mobile Health for Diabetes Self-Management: Lessons From Two Qualitative Studies. *JMIR Diabetes* [Internet]. 2019 2019/03/29; 4(1):[e10271 p.]. Available from: <http://diabetes.jmir.org/2019/1/e10271/>.
207. Braithwaite J, Churrua K, Long JC, Ellis LA, Herkes J. When complexity science meets implementation science: a theoretical and empirical analysis of systems change. *BMC Medicine* [Internet]. 2018 2018/04/30; 16(1):[63 p.]. Available from:
<https://doi.org/10.1186/s12916-018-1057-z>.
208. Singh K, Drouin K, Newmark LP, Lee J, Faxvaag A, Rozenblum R, et al. Many Mobile Health Apps Target High-Need, High-Cost Populations, But Gaps Remain. *Health Affairs* [Internet]. 2016; 35(12):[2310-8 pp.]. Available from:
<https://doi.org/10.1377/hlthaff.2016.0578>.
209. Shen C, Wang PM, Chu TWJ, Wan A, Viswanath K, Chan CSS, et al. Health App Possession Among Smartphone or Tablet Owners in Hong Kong: Population-Based Survey. *JMIR Mhealth Uhealth* [Internet]. 2017 06/05; 5(6):[e77 p.]. Available from:
<http://mhealth.jmir.org/2017/6/e77/>.
210. Berger R. Now I see it, now I don't: Researcher's position and reflexivity in qualitative research. *Qualitative research* [Internet]. 2015; 15(2):[219-34 pp.]. Available from: <https://doi.org/10.1177%2F1468794112468475>.
211. Xu K, Soucat A, Kutzin J, Brindley C, Dale E, deMaele NV, et al. New perspectives on global health spending for universal health coverage. Geneva: World Health Organization; 2018.
212. World Health Organization. The world health report 2000: health systems: improving performance: World Health Organization; 2000. Available from:
<https://www.who.int/whr/2000/en/>.
213. Italy's Struggling Economy Has World's Healthiest People [press release]. <https://www.bloomberg.com/news/articles/>: Bloomberg, 2017 March 20.
214. Prime Minister's office strategy group, Singapore department of statistics, Ministry of home affairs, Immigration and checkpoints authority, Ministry of Manpower. Population

- in brief 2018 2018 [Available from: <https://www.strategygroup.gov.sg/docs/default-source/default-document-library/population-in-brief-2018.pdf>].
215. Department of statistics Singapore. Death and Life Expectancy 2018 [cited 2019 August 17]. Available from: <https://www.singstat.gov.sg/find-data/search-by-theme/population/death-and-life-expectancy/latest-data>.
 216. Lee CE, Satkunanantham K. Singapore's Health Care System: What 50 Years Have Achieved. Singapore: World Scientific Publishing Co. Pte. Ltd.; 2015. 392 p.
 217. Lim J. Myth of Magic-The Singapore Healthcare System. Singapore: Select Publishing; 2013. 330 p.
 218. Poon CH. Public healthcare sector to be reorganised into 3 integrated clusters, new polyclinic group to be formed The Straits Times 2017 [updated 18th January 2017]. Available from: <https://www.straitstimes.com/singapore/health/public-healthcare-sector-to-be-reorganised-into-3-integrated-clusters-new>.
 219. Ng JY. Ageing society contributes to hospital bed crunch: Gan: Today; 2014 [27 December 2019]. Available from: <https://www.todayonline.com/singapore/ageing-society-contributes-hospital-bed-crunch-gan>.
 220. Chan A, Malhotra R, Manap NB, Ting YY, Visaria A, Cheng GH-L, et al. Transitions in Health, Employment, Social Engagement And Intergenerational Transfers In Singapore Study (THE SIGNS Study) – I: Descriptive Statistics and Analysis of Key Aspects of Successful Ageing. Singapore: Centre for Ageing Research and Education, Duke-NUS Medical School; 2018.
 221. Ministry Of Finance. Injecting More Into Singapore's Healthcare As We Age 2018 [27 December 2019]. Available from: <https://www.mof.gov.sg/singapore-budget/curated-budget-reads/injecting-more-into-singapore-s-healthcare-as-we-age>.
 222. Lim J. Myth of Magic-The Singapore Healthcare Syatem. Singapore: Select Publishing; 2013. 330 p.
 223. Lim M-K. Shifting the burden of health care finance: a case study of public-private partnership in Singapore. Health Policy. 2004;69(1):83-92.
 224. Loh Y. Public disclosure of healthcare performance information and its application to the Singapore context. ANNALS-Academy of Medicine Singapore. 2003;32(5):676-84.
 225. Prime Minister's office Strategy group. Projection of foreign manpower demand for healthcare sector construction workers and foreign domestic workers 2019 [28 December 2019]. Available from: <https://www.strategygroup.gov.sg/images/Press%20Release%20images/PDFs/projection-of-foreign-manpower-demand-for-healthcare-sector-construction-workers-and-foreign-domestic-workers.pdf>.
 226. Henderson JC, Ng A. Responding to crisis: Severe acute respiratory syndrome (SARS) and hotels in Singapore. International Journal of Tourism Research [Internet]. 2004; 6(6):[411-9 pp.]. Available from: <https://doi.org/10.1002/jtr.505>.

227. Goh K-T, Cutter J, Heng B-H, Ma S, Koh BK, Kwok C, et al. Epidemiology and control of SARS in Singapore. ANNALS-ACADEMY OF MEDICINE SINGAPORE [Internet]. 2006; 35(5):[301 p.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/16829997>.
228. Ministry of Home Affairs - Immigration & Checkpoints Authority. Number of Passengers cleared at the checkpoints [Arrival and Departure] <https://data.gov.sg/dataset/number-of-passengers-cleared-at-the-checkpoints-arrival-and-departure2018> [cited 2019 June 9]. Available from: <https://data.gov.sg/dataset/number-of-passengers-cleared-at-the-checkpoints-arrival-and-departure>.
229. Epidemiology & Disease Control Division MoH, Singapore. National Health Survey 2010. Singapore: Ministry of Health; 2011 [cited 2019 August 17]. Available from: https://www.moh.gov.sg/content/dam/moh_web/Publications/Reports/2011/NHS2010%20-%20low%20res.pdf.
230. Schmitt A, Gahr A, Hermanns N, Kulzer B, Huber J, Haak T. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. Health and Quality of Life Outcomes [Internet]. 2013 2013/08/13; 11(1):[138 p.]. Available from: <https://doi.org/10.1186/1477-7525-11-138>.
231. Ali MK, Bullard K, Imperatore G, Barker L, Gregg EW. Characteristics associated with poor glycemic control among adults with self-reported diagnosed diabetes—National Health and Nutrition Examination Survey, United States, 2007–2010. MMWR Morb Mortal Wkly Rep [Internet]. 2012; 61(2):[32-7 pp.]. Available from: <https://www.scienceopen.com/document?vid=7d4c5dd7-8306-40d5-ad80-a914badb20df>.
232. NATIONAL POPULATION HEALTH SURVEY 2016/17 <https://www.moh.gov.sg2018> [cited 2018 October 9]. Available from: <https://www.moh.gov.sg/resources-statistics/reports/national-population-health-survey-2016-17>.
233. Ang Y, Yap CW, Saxena N, Lin L-K, Heng BH. Diabetes-related lower extremity amputations in Singapore. Proceedings of Singapore Healthcare [Internet]. 2017; 26(2):[76-80 pp.]. Available from: <https://doi.org/10.1177%2F2010105816663521>.
234. OECD. Major lower extremity amputation in adults with diabetes, 2012 and 2017 (or nearest year) Paris: OECD Publishing; 2019 [26 December 2019]. Available from: <https://doi.org/10.1787/77b55d01-en>.
235. Ang Y, Yap CW, Saxena N, Lin L-K, Heng BH. Diabetes-related lower extremity amputations in Singapore. Proceedings of Singapore Healthcare [Internet]. 2016 2017/06/01; 26(2):[76-80 pp.]. Available from: <https://doi.org/10.1177/2010105816663521>.
236. Lee CS, Tan JHM, Sankari U, Koh YLE, Tan NC. Assessing oral medication adherence among patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study. BMJ open [Internet]. 2017; 7(9):[e016317 p.]. Available from: <http://dx.doi.org/10.1136/bmjopen-2017-016317>.

237. Government declares war on diabetes [press release]. <https://www.todayonline.com/singapore/i-am-declaring-war-diabetes-gan2016>.
238. National Day Rally 2017 [press release]. <https://www.pmo.gov.sg/national-day-rally-2017>.
239. Ministry of Health. WAR ON DIABETES 2018 [20th October 2018]. Available from: <https://www.moh.gov.sg/wodcj>.
240. Stepping up the war on diabetes [press release]. <https://www.straitstimes.com/politics/stepping-up-the-war-on-diabetes>; Straits Times, 2018 March 8.
241. Prime Minister's office. Smart Nation 2016 [updated 8th June 2016; cited 2018 December 3]. Available from: <https://www.pmo.gov.sg/Smartnation>.
242. Smart Nation and Digital Government Office. Transforming Singapore Through Technology 2018 [cited 2018 December 3]. Available from: <https://www.smartnation.sg/>.
243. Lee Kuan Yew School of Public Policy. Singapore's Smart Nation Initiative – A Policy and Organisational Perspective. https://lkyspp.nus.edu.sg/docs/default-source/case-studies/singapores_smart_nation_initiative; National University of Singapore; 2017.
244. Koh GC-H, Yen SC, Tay A, Cheong A, Ng YS, De Silva DA, et al. Singapore Tele-technology Aided Rehabilitation in Stroke (STARS) trial: protocol of a randomized clinical trial on tele-rehabilitation for stroke patients. BMC neurology [Internet]. 2015; 15(1):[161 p.]. Available from: <https://doi.org/10.1186/s12883-015-0420-3>.
245. Chong P-N, Tang WE. Transforming primary care—the way forward with the TEAMS2 approach. Family practice [Internet]. 2018. Available from: <https://doi.org/10.1093/fampra/cmy074>.
246. Chan WX, Lin W, Wong RCC. Transitional Care to Reduce Heart Failure Readmission Rates in South East Asia. Cardiac failure review [Internet]. 2016; 2(2):[85-9 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28785458>.
247. Smart Nation and Digital Government Office. HealthHub 2018 [cited 2018 December 4]. Available from: <https://www.smartnation.sg/what-is-smart-nation/initiatives/Health/healthhub>.
248. Ministry of Health Singapore. Healthy 365 app [updated 2018; cited 2018 December 4]. Available from: <https://www.healthhub.sg/apps/25/healthy365>.
249. LOW A. Singapore has the highest smartphone adoption rate in the world 2014 [cited 2018 December 6]. Available from: <https://www.cnet.com/news/singapore-has-the-highest-smartphone-adoption-in-the-world/>.
250. Singapore business review. 4.83 million Singaporeans are now online 2018 [cited 2018 December 6]. 18th May 2019:[Available from: <https://sbr.com.sg/information-technology/news/483-million-singaporeans-are-now-online>.

251. Infocomm Media Development Authority. Mobile Penetration Rate 18th November 2018 [updated 2018 November 18; cited 2018 December 4]. Available from: <https://www.imda.gov.sg/industry-development/facts-and-figures/telecommunications#1x>.
252. 2G mobile network to shut down from April 1: IMDA reminds users to switch to 3G or 4G [press release]. <https://www.straitstimes.com/tech/2g-mobile-network-to-shut-down-from-april-1-imda-reminds-users-to-switch-to-3g-or-4g>: The Straits Times 2017 March 27.
253. 100,000 mobile subscribers still on 2G despite start of the network's shutdown [press release]. <https://www.channelnewsasia.com/news/singapore/100-000-mobile-subscribers-still-on-2g-despite-start-of-the-netw-8708772>: Channel News Asia, 2017 April 2.
254. Arnhold M, Quade M, Kirch W. Mobile Applications for Diabetics: A Systematic Review and Expert-Based Usability Evaluation Considering the Special Requirements of Diabetes Patients Age 50 Years or Older. J Med Internet Res [Internet]. 2014 2014/04/09; 16(4):[e104 p.]. Available from: <http://www.jmir.org/2014/4/e104/>.
255. Burki TK. Mobile apps and metabolic health. The Lancet Diabetes & Endocrinology [Internet]. 2017; 5(1):[17 p.]. Available from: [https://doi.org/10.1016/S2213-8587\(16\)30083-3](https://doi.org/10.1016/S2213-8587(16)30083-3).
256. Huckvale K, Torous J, Larsen ME. Assessment of the Data Sharing and Privacy Practices of Smartphone Apps for Depression and Smoking Cessation. JAMA Network Open [Internet]. 2019; 2(4):[e192542-e pp.]. Available from: <https://doi.org/10.1001/jamanetworkopen.2019.2542>.
257. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ [Internet]. 2008; 337:[a1655 p.]. Available from: <https://doi.org/10.1136/bmj.a1655>.
258. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care [Internet]. 2012 January 1, 2012; 35(Supplement 1):[S64-S71 pp.]. Available from: <https://doi.org/10.2337/dc12-s064>.
259. eVos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Murray C, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet [Internet]. 2016; 386(9995):[57 p.]. Available from: [http://dx.doi.org/10.1016/S0140-6736\(15\)60692-4](http://dx.doi.org/10.1016/S0140-6736(15)60692-4).
260. Statista. Number of smartphone users worldwide from 2014 to 2020 (in billions) 2016 [Available from: <https://www.statista.com/statistics/330695/number-of-smartphone-users-worldwide/>].
261. IQVIA. The Growing Value of Digital Health: Evidence and Impact on Human Health and the Healthcare System. New Jersey, U.S.; 2017 7th November 2017. Contract No.: PB.0009-1-11.2017.

262. Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Training; 2017. Available from: <http://training.cochrane.org/handbook>.
263. Whiting DR, Guariguata L, Weil C, Shaw J. IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Research and Clinical Practice* [Internet]. 2011; 94(3):[311-21 pp.]. Available from: <http://dx.doi.org/10.1016/j.diabres.2011.10.029>.
264. Craig RT. Generalization of Scott's index of intercoder agreement. *Public Opinion Quarterly* [Internet]. 1981; 45(2):[260-4 pp.]. Available from: <https://doi.org/10.1086/268657>.
265. McHugh ML. Interrater reliability: the kappa statistic. *Biochemia medica* [Internet]. 2012; 22(3):[276-82 pp.]. Available from: <http://dx.doi.org/10.11613/BM.2012.031>.
266. Steefel L, Estrada RP. Empowering Patients for Self-Care through Internet Use. *Journal of Nursing Practice Applications & Reviews of Research* [Internet]. 2013. Available from: <https://pdfs.semanticscholar.org/a217/c3266802a4ef26551c5171557cb4071d0398.pdf>.
267. Weiner JP. Doctor-patient communication in the e-health era. *Israel Journal of Health Policy Research* [Internet]. 2012 2012/08/28; 1(1):[33 p.]. Available from: <https://doi.org/10.1186/2045-4015-1-33>.
268. US Food and Drug Administration. Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff. Washington DC2015.
269. Juliet Bauer RM. NHS England [Internet]: NHS. 2017. [cited 2017]. Available from: <https://www.england.nhs.uk/blog/apps-library-is-advance-for-a-digital-nhs/>.
270. Hart JT. The inverse care law. *The Lancet* [Internet]. 1971; 297(7696):[405-12 pp.]. Available from: [https://doi.org/10.1016/S0140-6736\(71\)92410-X](https://doi.org/10.1016/S0140-6736(71)92410-X).
271. Scheibe M, Reichelt J, Bellmann M, Kirch W. Acceptance factors of mobile apps for diabetes by patients aged 50 or older: a qualitative study. *Medicine* 20 [Internet]. 2015; 4(1). Available from: <https://www.medicine20.com/2015/1/e1/>.
272. Sun J, Guo Y, Wang X, Zeng Q. mHealth For Aging China: Opportunities and Challenges. *Aging and Disease* [Internet]. 2016; 7(1):[53-67 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723234/>.
273. Mesko B, Györfy Z, Kollár J. Digital Literacy in the Medical Curriculum: A Course With Social Media Tools and Gamification. *JMIR Medical Education* [Internet]. 2015 2015/10/01; 1(2):[e6 p.]. Available from: <https://doi.org/10.2196/mededu.4411>.
274. Robin BR, McNeil SG, Cook DA, Agarwal KL, Singhal GR. Preparing for the Changing Role of Instructional Technologies in Medical Education. *Academic Medicine* [Internet]. 2011; 86(4):[435-9 pp.]. Available from: https://journals.lww.com/academicmedicine/Fulltext/2011/04000/Preparing_for_the_Changing_Role_of_Instructional.11.aspx.

275. Osterberg L, Blaschke T. Adherence to medication. *New England Journal of Medicine* [Internet]. 2005; 353(5):[487-97 pp.]. Available from: <http://dx.doi.org/10.1056/NEJMra050100>.
276. Furniss D, Barber N, Lyons I, Eliasson L, Blandford A. Unintentional non-adherence: can a spoon full of resilience help the medicine go down? *BMJ Quality & Safety* [Internet]. 2014 24 December 2019; 23(2):[95 p.]. Available from: <http://qualitysafety.bmj.com/content/23/2/95.abstract>.
277. Boulos MNK, Brewer AC, Karimkhani C, Buller DB, Dellavalle RP. Mobile medical and health apps: state of the art, concerns, regulatory control and certification. *Online journal of public health informatics* [Internet]. 2014; 5(3):[229- pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24683442>.
278. IMS Institute for Healthcare Informatics. Patient Adoption of mHealth: Use, Evidence and Remaining Barriers to Mainstream Acceptance 2015 [updated 2015 September; cited 2018 December 5]. Available from: http://www.imshealth.com/files/web/IMSH%20Institute/Reports/Patient%20Adoption%20of%20mHealth/IIHI_Patient_Adoption_of_mHealth.pdf.
279. Lum E, Jimenez G, Huang Z, Thai L, Semwal M, Boehm BO, et al. Decision Support and Alerts of Apps for Self-management of Blood Glucose for Type 2 Diabetes. *JAMA* [Internet]. 2019; 321(15):[1530-2 pp.]. Available from: <https://doi.org/10.1001/jama.2019.1644>.
280. Jimenez G, Lum E, Car J. Examination of diabetes management apps recommended from a Google search: Dr Google, which app should I use? *JMIR mHealth and uHealth* [Internet]. 2018. Available from: <https://mhealth.jmir.org/2019/1/e11848/>.
281. U.S. Food & Drug Administration. *Mobile Medical Applications* Silver Spring, MD: U.S. Food & Drug Administration; 2018 [cited 2019 July 5]. Available from: <https://www.fda.gov/medicaldevices/digitalhealth/mobilemedicalapplications/default.htm#>.
282. Huckvale K, Car M, Morrison C, Car J. Apps for asthma self-management: a systematic assessment of content and tools. *BMC medicine* [Internet]. 2012 PMC4391129; 10(1):[1 p.]. Available from: <https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-10-144>.
283. Chen J, Cade JE, Allman-Farinelli M. The most popular smartphone apps for weight loss: a quality assessment. *JMIR mHealth and uHealth* [Internet]. 2015; 3(4):[e104 p.]. Available from: <https://mhealth.jmir.org/2015/4/e104/>.
284. Martinengo L, Van Galen L, Lum E, Kowalski M, Subramaniam M, Car J. Suicide prevention and depression apps' suicide risk assessment and management: a systematic assessment of adherence to clinical guidelines. *BMC Medicine* [Internet]. 2019 2019/12/19; 17(1):[231 p.]. Available from: <https://doi.org/10.1186/s12916-019-1461-z>.
285. Zhang Y, Sun Y, Xie B. Quality of health information for consumers on the web: A systematic review of indicators, criteria, tools, and evaluation results. *Journal of the Association for Information Science and Technology* [Internet]. 2015 2015/10/01; 66(10):[2071-84 pp.]. Available from: <https://doi.org/10.1002/asi.23311>.

286. Lee K, Hoti K, Hughes JD, Emmerton LM. Interventions to Assist Health Consumers to Find Reliable Online Health Information: A Comprehensive Review. PLOS ONE [Internet]. 2014; 9(4):[e94186 p.]. Available from: <https://doi.org/10.1371/journal.pone.0094186>.
287. Team HON. HONcode certification: Health On the Net; 1995 [updated April 2019; cited 2019 June 19]. Available from: <https://www.hon.ch/en/certification.html#principles>.
288. National Institute for Health and Care Excellence (NICE). Medicines Optimisation: The Safe and Effective Use of Medicines to Enable the Best Possible Outcomes, NICE guideline [NG5] 2015 [updated 2018 September 17; cited 2019 July 15]. Available from: <https://www.nice.org.uk/guidance/ng5>.
289. Nunes V, Neilson J, O'flynn N, Calvert N, Kuntze S, Smithson H, et al. Clinical guidelines and evidence review for medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence 2009. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK55440/>.
290. Usherwood T. Encouraging adherence to long-term medication. Australian prescriber [Internet]. 2017; 40(4):[147 p.]. Available from: <https://doi.org/10.18773/austprescr.2017.050>.
291. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Annals of internal medicine [Internet]. 2012; 157(11):[785-95 pp.]. Available from: <https://annals.org/aim/fullarticle/1357338/interventions-improve-adherence-self-administered-medications-chronic-diseases-united-states>.
292. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock S, Wines RC, et al. Closing the quality gap: revisiting the state of the science (vol. 4: medication adherence interventions: comparative effectiveness)2012. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK114350/>.
293. Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation 2013 [cited 2019 March 25]. Available from: https://www.kingsfund.org.uk/sites/default/files/field/publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf.
294. Bosworth HB, Zullig LL, Mendys P, Ho M, Trygstad T, Granger C, et al. Health Information Technology: Meaningful Use and Next Steps to Improving Electronic Facilitation of Medication Adherence. JMIR Med Inform [Internet]. 2016; 4(1):[e9 p.]. Available from: <https://medinform.jmir.org/2016/1/e9/>.
295. Australian Pharmaceutical Advisory Council. Guiding principles for medication management in the community. Canberra: Commonwealth of Australia [Internet]. 2006. Available from: [https://www1.health.gov.au/internet/main/Publishing.nsf/650f3eec0dfb990fca25692100069854/eea5b39aa0a63f18ca257bf0001dae08/\\$FILE/Guiding-principles-for-medication-management-in-the-community.pdf](https://www1.health.gov.au/internet/main/Publishing.nsf/650f3eec0dfb990fca25692100069854/eea5b39aa0a63f18ca257bf0001dae08/$FILE/Guiding-principles-for-medication-management-in-the-community.pdf).

296. Stowasser DA, Allinson YM, O'Leary M. Understanding the Medicines Management Pathway. *Journal of Pharmacy Practice and Research* [Internet]. 2004 2004/12/01; 34(4):[293-6 pp.]. Available from: <https://doi.org/10.1002/jppr2004344293>.
297. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* [Internet]. 2015 January 01; 4(1):[1 p.]. Available from: <https://doi.org/10.1186/2046-4053-4-1>.
298. Aromataris E, Pearson A. The Systematic Review: An Overview. *AJN The American Journal of Nursing* [Internet]. 2014; 114(3):[53-8 pp.]. Available from: <http://dx.doi.org/10.1097/01.NAJ.0000444496.24228.2c>.
299. IBM Corp. IBM SPSS Statistics for Windows. 22.0 ed. Armonk, NY: IBM Corp; 2013.
300. Michael Soljak, Elaine Lum, Zhilian Huang, Geronimo Jiminez, Li Li, Ming Keat Sng, et al. Developing a global assessment framework for health apps targeted at elderly users with Type 2 Diabetes Mellitus. [Conference poster]. In press 2018.
301. Heldenbrand S, Martin BC, Gubbins PO, Hadden K, Renna C, Shilling R, et al. Assessment of medication adherence app features, functionality, and health literacy level and the creation of a searchable Web-based adherence app resource for health care professionals and patients. 2016 2016/05/01/. In: *Journal of the American Pharmacists Association* [Internet]. [293-302]. Available from: <http://www.sciencedirect.com/science/article/pii/S1544319115000631>.
302. Covington MB. Traditional Chinese Medicine in the Treatment of Diabetes. *Diabetes Spectrum* [Internet]. 2001; 14(3):[154 p.]. Available from: <https://doi.org/10.2337/diaspect.14.3.154>.
303. Trivedi RB, Bryson CL, Udris E, Au DH. The Influence of Informal Caregivers on Adherence in COPD Patients. *Annals of Behavioral Medicine* [Internet]. 2012; 44(1):[66-72 pp.]. Available from: <https://doi.org/10.1007/s12160-012-9355-8>.
304. Francis S-A, Smith F, Gray N, Denham M. Partnerships between older people and their carers in the management of medication. *International Journal of Older People Nursing* [Internet]. 2006 2006/12/01; 1(4):[201-7 pp.]. Available from: <https://doi.org/10.1111/j.1748-3743.2006.00032.x>.
305. Becker S, Kribben A, Meister S, Diamantidis CJ, Unger N, Mitchell A. User profiles of a smartphone application to support drug adherence—experiences from the iNephro project. *PloS one* [Internet]. 2013; 8(10):[e78547 p.]. Available from: <https://doi.org/10.1371/journal.pone.0078547>.
306. Sarbacker GB, Urteaga EM. Adherence to insulin therapy. *Diabetes Spectrum* [Internet]. 2016; 29(3):[166-70 pp.]. Available from: <https://doi.org/10.2337/diaspect.29.3.166>.
307. Davies M, Gagliardino JJ, Gray L, Khunti K, Mohan V, Hughes R. Real - world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes

- mellitus: a systematic review. *Diabetic Medicine* [Internet]. 2013; 30(5):[512-24 pp.]. Available from: <https://doi.org/10.1111/dme.12128>.
308. van Galen LS, Xu X, Koh MJA, Thng S, Car J. Eczema apps conformance with clinical guidelines: a systematic assessment of functions, tools and content. *British Journal of Dermatology* [Internet]. 2019 2019/06/09; n/a(n/a). Available from: <https://doi.org/10.1111/bjd.18152>.
309. Vladeck DC. Truth and consequences: The perils of half-truths and unsubstantiated health claims for dietary supplements. *Journal of Public Policy & Marketing* [Internet]. 2000; 19(1):[132-8 pp.]. Available from: <https://www.jstor.org/stable/30000493>.
310. Store AA. App Store Review Guidelines 2019 [25 December 2019]. Available from: <https://developer.apple.com/app-store/review/guidelines/>.
311. S S. Google tweaks its policy with aim to improve ‘app quality’ in Play Store 2019 [25 December 2019]. Available from: <https://www.digitalinformationworld.com/2019/04/google-android-policy-improve-app-quality-in-play-store.html#>.
312. Middelweerd A, Mollee JS, van der Wal CN, Brug J, Te Velde SJ. Apps to promote physical activity among adults: a review and content analysis. *International journal of behavioral nutrition and physical activity* [Internet]. 2014; 11(1):[97 p.]. Available from: <https://ijbnpa.biomedcentral.com/articles/10.1186/s12966-014-0097-9>.
313. Bondaronek P, Alkhalidi G, Slee A, Hamilton FL, Murray E. Quality of publicly available physical activity apps: review and content analysis. *JMIR mHealth and uHealth* [Internet]. 2018; 6(3):[e53 p.]. Available from: <https://mhealth.jmir.org/2018/3/e53/>.
314. Health On the Net. mHONcode: The new certification of health mobile applications. 2019 [cited 2019 June 25]. Available from: <https://www.hon.ch/en/certification/app-certification-en.html>.
315. Huckvale K, Morrison C, Ouyang J, Ghaghda A, Car J. The evolution of mobile apps for asthma: an updated systematic assessment of content and tools. *BMC medicine* [Internet]. 2015; 13(1):[58 p.]. Available from: <https://doi.org/10.1186/s12916-015-0303-x>.
316. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. *Journal of multidisciplinary healthcare* [Internet]. 2016; 9:[211-7 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/27217764>.
317. Harrington CN, Wilcox L, Connelly K, Rogers W, Sanford J, editors. *Designing Health and Fitness Apps with Older Adults: Examining the Value of Experience-Based Co-Design*. Proceedings of the 12th EAI International Conference on Pervasive Computing Technologies for Healthcare; 2018: ACM.
318. Revenäs Å, Opava CH, Martin C, Demmelmaier I, Keller C, Åsenlöf P. Development of a web-based and mobile app to support physical activity in individuals with rheumatoid arthritis: results from the second step of a co-design process. *JMIR research protocols* [Internet]. 2015; 4(1):[e22 p.]. Available from: <https://www.researchprotocols.org/2015/1/e22/>.

319. Woods L, Cummings E, Duff J, Walker K. Design thinking for mHealth application co-design to support heart failure self-management. *Stud Health Technol Inform.* 2412017. p. 97-102.
320. Slegers K, Wilkinson A, Hendriks N, editors. Active collaboration in healthcare design: participatory design to develop a dementia care app. *CHI'13 Extended Abstracts on Human Factors in Computing Systems*; 2013: ACM.
321. Mayberry LS, Osborn CY. Family support, medication adherence, and glycemic control among adults with type 2 diabetes. *Diabetes care* [Internet]. 2012; 35(6):[1239-45 pp.]. Available from: <https://doi.org/10.2337/dc11-2103>.
322. Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *The American journal of medicine* [Internet]. 2010; 123(3):[S3-S11 pp.]. Available from: <https://doi.org/10.1016/j.amjmed.2009.12.004>.
323. Rubens M, Saxena A, Ramamoorthy V, Khera R, Hong J, Veledar E, et al. Trends in Diabetes-Related Preventable Hospitalizations in the U.S., 2005–2014. *Diabetes Care* [Internet]. 2018; 41(5):[e72 p.]. Available from: <https://doi.org/10.2337/dc17-1942>.
324. Cahn A, Akirov A, Raz I. Digital health technology and diabetes management. *Journal of diabetes* [Internet]. 2017. Available from: <https://doi.org/10.1111/1753-0407.12606>.
325. Monroe VD. Testing a smartphone application intervention to improve medication adherence in African American female clinic patients with unstable high blood pressure: A two-group randomized control trial: Texas Women's University; 2018.
326. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Barriers to diabetes management: patient and provider factors. *Diabetes research and clinical practice* [Internet]. 2011; 93(1):[1-9 pp.]. Available from: <https://doi.org/10.1016/j.diabres.2011.02.002>.
327. International Diabetes Federation. *IDF Clinical Practice Recommendations for Managing Type 2 Diabetes in Primary Care* Brussels, Belgium Author; 2017 [Available from: <https://www.idf.org/e-library/guidelines/128-idf-clinical-practice-recommendations-for-managing-type-2-diabetes-in-primary-care.html>].
328. Bahia K. State of Mobile Internet Connectivity 2018 GSM Association [updated August 2018; cited 2019 May 6]. Available from: <https://www.gsma.com/mobilefordevelopment/wp-content/uploads/2018/09/State-of-Mobile-Internet-Connectivity-2018.pdf>.
329. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Pilot and feasibility studies* [Internet]. 2016; 2(1):[64 p.]. Available from: <https://doi.org/10.1136/bmj.i5239>.
330. Agarwal S, LeFevre AE, Lee J, L'Engle K, Mehl G, Sinha C, et al. Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist. *BMJ* [Internet]. 2016; 352:[i1174 p.]. Available from: <https://doi.org/10.1136/bmj.i1174>

331. Matza LS, Park J, Coyne KS, Skinner EP, Malley KG, Wolever RQ. Derivation and validation of the ASK-12 adherence barrier survey. *Annals of Pharmacotherapy* [Internet]. 2009; 43(10):[1621-30 pp.]. Available from: <https://doi.org/10.1345/aph.1M174>.
332. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics* [Internet]. 2009 2009/04/01/; 42(2):[377-81 pp.]. Available from: <http://www.sciencedirect.com/science/article/pii/S1532046408001226>.
333. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics* [Internet]. 2019 2019/07/01/; 95:[103208 p.]. Available from: <http://www.sciencedirect.com/science/article/pii/S1532046419301261>.
334. Carey MP, Jorgensen RS, Weinstock RS, Sprafkin RP, Lantinga LJ, Carnrike C, et al. Reliability and validity of the appraisal of diabetes scale. *Journal of behavioral medicine* [Internet]. 1991; 14(1):[43-50 pp.]. Available from: <https://doi.org/10.1007/BF00844767>.
335. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology* [Internet]. 2010 2010/01/06; 10(1):[1 p.]. Available from: <https://doi.org/10.1186/1471-2288-10-1>.
336. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Statistical Methods in Medical Research* [Internet]. 2016; 25(3):[1057-73 pp.]. Available from: <https://doi.org/10.1177/0962280215588241>.
337. Fincham JE. Response rates and responsiveness for surveys, standards, and the Journal. *American journal of pharmaceutical education* [Internet]. 2008; 72(2):[43 p.]. Available from: <https://doi.org/10.5688/aj720243>.
338. Hawkins RC. Circannual variation in glycohemoglobin in Singapore. *Clinica Chimica Acta* [Internet]. 2010; 411(1-2):[18-21 pp.]. Available from: <https://doi.org/10.1016/j.cca.2009.09.031>.
339. Huizinga MM, Bleich SN, Beach MC, Clark JM, Cooper LA. Disparity in Physician Perception of Patients' Adherence to Medications by Obesity Status. *Obesity* [Internet]. 2010 2010/10/01; 18(10):[1932-7 pp.]. Available from: <https://doi.org/10.1038/oby.2010.35>.
340. Glenn T, Monteith S. Privacy in the Digital World: Medical and Health Data Outside of HIPAA Protections. *Current Psychiatry Reports* [Internet]. 2014 2014/09/14; 16(11):[494 p.]. Available from: <https://doi.org/10.1007/s11920-014-0494-4>.
341. Turow J, Hoofnagle CJ, Mulligan DK, Good N. The federal trade commission and consumer privacy in the coming decade. *ISJLP* [Internet]. 2007; 3:[723 p.]. Available from: <http://scholarship.law.berkeley.edu/cgi/viewcontent.cgi?article=1934&context=facpubs>.
342. Birbeck GL, Chomba E, Kvalsund M, Bradbury R, Mang'ombe C, Malama K, et al. Antiretroviral adherence in rural Zambia: the first year of treatment availability. *The*

- American journal of tropical medicine and hygiene [Internet]. 2009; 80(4):[669-74 pp.]. Available from: <https://www.ajtmh.org/content/journals/10.4269/ajtmh.2009.80.669>.
343. Nakigozi G, Makumbi FE, Bwanika JB, Atuyambe L, Reynolds SJ, Kigozi G, et al. Impact of Patient-Selected Care Buddies on Adherence to HIV Care, Disease Progression, and Conduct of Daily Life Among Pre-antiretroviral HIV-Infected Patients in Rakai, Uganda: A Randomized Controlled Trial. *J Acquir Immune Defic Syndr* [Internet]. 2015; 70(1):[75-82 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26039929>.
344. Chalk W. Commentary: China's great leap forward in data protection: Channel News Asia; 2019 [Available from: <https://www.channelnewsasia.com/news/commentary/china-great-leap-forward-in-data-protection-11429624>].
345. Long KM, McDermott F, Meadows GN. Being pragmatic about healthcare complexity: our experiences applying complexity theory and pragmatism to health services research. *BMC Medicine* [Internet]. 2018 2018/06/20; 16(1):[94 p.]. Available from: <https://doi.org/10.1186/s12916-018-1087-6>.
346. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Effective clinical practice: ECP* [Internet]. 2001; 4(6):[256-62 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11769298>.
347. Shuren J, Patel B, Gottlieb S. FDA Regulation of Mobile Medical Apps. *JAMA* [Internet]. 2018 Jul 24; 320(4):[337-8 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/29971339>.
348. European Commission. GUIDELINES ON THE QUALIFICATION AND CLASSIFICATION OF STAND ALONE SOFTWARE USED IN HEALTHCARE WITHIN THE REGULATORY FRAMEWORK OF MEDICAL DEVICES. 2016 July 2016. Report No.: MEDDEV 2.1/6
349. Gubbi J, Buyya R, Marusic S, Palaniswami M. Internet of Things (IoT): A vision, architectural elements, and future directions. *Future Generation Computer Systems* [Internet]. 2013; 29(7):[1645-60 pp.]. Available from: <https://doi.org/10.1016/j.future.2013.01.010>.
350. Årsand E, Muzny M, Bradway M, Muzik J, Hartvigsen G. Performance of the first combined smartwatch and smartphone diabetes diary application study. *Journal of diabetes science and technology* [Internet]. 2015; 9(3):[556-63 pp.]. Available from: <https://doi.org/10.1177/1932296814567708>.
351. Department of statistics Singapore. Population Trends 2018: Ministry of Trade and industry; [updated September 2018; cited 2018 December 4]. Available from: <https://www.singstat.gov.sg/publications/population-trends>.
352. Statista. Singapore: Average age of the population from 1950 to 2050 (median age in years) 2015 [29th September 2018]. Available from: <https://www.statista.com/statistics/378424/average-age-of-the-population-in-singapore/>.

353. Gorsky M. The British National Health Service 1948–2008: a review of the historiography. *Social History of Medicine* [Internet]. 2008; 21(3):[437-60 pp.]. Available from: <https://doi.org/10.1093/shm/hkn064>.
354. Hsiao WC. Medical savings accounts: lessons from Singapore. *Health affairs* [Internet]. 1995; 14(2):[260-6 pp.]. Available from: <https://doi.org/10.1377/hlthaff.14.2.260>.
355. Lai WL. Paying for healthcare. *Singapore's Health Care System: What 50 Years Have Achieved*: World Scientific; 2016. p. 75-94.
356. Lim M-K. Values and health care: The Confucian dimension in health care reform. *Journal of Medicine and Philosophy* [Internet]. 2012; 37(6):[545-55 pp.]. Available from: <https://doi.org/10.1093/jmp/jhs048>.
357. Health Mo. What is Medishield Life 2018 [cited 2019 August 7]. Available from: <https://www.moh.gov.sg/medishield-life/medishield-life-faqs>.
358. Lim J. Sustainable health care financing: the Singapore experience. *Global Policy* [Internet]. 2017; 8:[103-9 pp.]. Available from: <https://doi.org/10.1111/1758-5899.12247>.
359. Phua KH. *Privatization & Restructuring of Health Services in Singapore*: Marshall Cavendish Corporation; 1991.
360. Khalik S. Changes to system are a healthy move *The Straits Times*: The Straits Times; 2017 [Available from: <https://www.singhealth.com.sg/TomorrowsMed/Article/Pages/Changes-to-system-are-a-healthy-move.aspx>].

Appendices

Appendix 1 Additional information on Singapore's health system

A1.1 Population demographics

Population demographics have changed drastically since post-World War II. The total fertility rate has declined from 3.07 births per woman in 1970 to 1.83 in 1990 and 1.16 in 2017, which is well below the replacement rate³⁵¹. While fertility rates have declined, the post -World War II baby boomers have aged and transited to the above 65 age group. The median age has also increased tremendously from 18.1 years in 1965 at Singapore's independence to 41.7 years today^{214, 352}. A surge in the cases of long-term illnesses, usually developed later in life, is expected as the population ages. The notion of the family as the first line of support for healthcare needs and reliance on children for old age security can no longer hold as family structures change with the changing demographics. The healthcare system must also adapt to the changing population demographics to meet changing needs.

A1.2 Political philosophy of Singapore's health system

The way healthcare is financed and delivered rests largely on the political philosophy of the elite ruling party during the period of nation building²¹⁷. Political ideologies were largely guided by pragmatism, which borrows ideas across various political spectrums. When NHS was founded in 1948, Singapore was still a British colony. NHS was created with the ideal that healthcare should meet the needs of everyone, be free at the point of delivery, and based on clinical aid rather than the ability to pay³⁵³. Singapore chose to turn away from that healthcare model at that time when the idea of welfarism was popular in Europe. The move away from a welfare state was influenced by the then first prime minister, Mr Lee Kwan Yew, based on his personal experiences of the challenges faced by a welfare state in the 1960s and 1970s²¹⁷.

A cradle-to-grave welfare system was not acceptable by the government. A welfare state was believed to lead to moral hazards and eroded work ethics. The individual would maximise his benefits from the system rather than taking responsibility for his personal health, which can inflict a high cost on the government. Subsidies that are given out will be difficult to withhold without political implications. However, high economic growth can never be guaranteed given the uncertainty and Singapore's vulnerability. High healthcare spending will expose the economy to greater uncertainty without guaranteed good health outcomes. Therefore, it was better to err on the side of caution and provide state assistance in smaller amounts^{216, 353}.

The ruling leaders of Singapore have always believed in market-driven efficiency. While preferring to allow the market to guide efficiency, a completely free market that rewarded only winners is unacceptable. The government has to intervene to prevent cherry-picking from private insurers and ensure the provision of sufficient assistance to individuals faced with financial difficulties when seeking health aid. Therefore, it was determined that the state has the responsibility to make decisions and be the overall orchestrator for the good of Singapore²¹⁷. This power enables the government to transfer some responsibilities to individuals to keep fit and healthy. The orientation towards a strong government and maintaining a strong financial position greatly influenced the way the health system is shaped in Singapore.

A1.3 Costs and access to healthcare

Healthcare financing ties closely with Singapore's political philosophy. Public health services remained free of charge, but the government started charging for outpatient and inpatient services to prevent abuse of the health system²¹⁶. Co-payments were introduced in the 1960s to ensure responsible use of resources. Patients had to pay 50 cents for each visit to the outpatient dispensary and one dollar per day for a stay in the subsidised ward²¹⁶. Hardship cases were exempted from payment.

One challenge afflicting many healthcare systems relates to ensuring good quality and affordable healthcare sustainable to the country. The 3M framework: Medisave,

MediShield and Medifund, was rolled out successively in 1984, 1990 and 1993 to ensure affordability of care. Universal health care is achieved through a multi-payer approach where a single healthcare episode is covered by multiple schemes^{216, 354}. **Medisave** constitutes a component of the compulsory savings scheme for all working Singapore citizens and permanent residents. The savings from Medisave can be used to offset hospitalisation and selected outpatient treatment bills to reduce out-of-pocket payments of the patient and his family. **MediShield** is a form of co-insurance that complements Medisave by covering larger subsidised hospital and outpatient treatment bills. MediShield premiums can be paid for by Medisave funds. **Medifund** is used to safeguard patients who cannot afford their bills. Assistance will be given to needy patients after a thorough assessment by medical social workers³⁵⁵.

The quality of healthcare services has increased with the push for efficiency and innovation. As the differences between the quality of subsidised and private services started to narrow, more people who could afford private services were opting for subsidised services. The increase in demand for subsidised services has caused overcrowding in public hospitals. To ensure a fairer distribution of resources, means testing was implemented to control the amount of subsidy that a person can get when he/she chooses a ward. For example, a person with higher socioeconomic status would receive a 65% subsidy at a C class ward instead of the 80% subsidy that was previously available to all³⁵⁶.

Many changes were implemented to adapt to the ageing population. Medisave coverage was expanded to include more outpatient claims for chronic diseases, and MediShield Life was rolled out to include all citizens (the opt-out option was available previously) from birth till death (up to 90 years of age previously)^{355, 357}. Episodic cash vouchers were given out to all citizens to cope with the rising healthcare costs. The pioneer generation package was also introduced to cover the medical needs of the elderly (born before 1949) who did not have enough time to amass sufficient savings in their Medisave account³⁵⁸. With the changing demographics, long-term care has to be considered for the long duration of the disease and longevity of the population

A1.4 Development of the regional health system (RHS)

A sound health system is essential to achieve good population outcomes. The demand for better health services increased with economic progression and rising expectations in the late 1970s. Private sector costs were unregulated, and its services were catered to patients who were privately insured or could pay more²¹⁷. Many healthcare professionals were attracted to the private sector due to the higher salaries, and there was a need to retain talent through competitive wages as the public sector was the training ground for healthcare professionals. The corporatisation of public hospitals in 1984 was a bold move to increase its efficiency and competitiveness³⁵⁹. This gave the hospital some leeway in deciding its administration and management, which was a success as decentralisation from the ministry led to more informed decision making, improved service levels, and better efficiency²¹⁷.

The corporatisation of hospitals drove greater competition and efficiency, but also drove up costs. Competition for talent between healthcare institutions caused the salaries of doctors to rise, and new services were introduced even if the demands were not met²¹⁷. In addition, Singapore's healthcare model had always been reactive to episodic events, which were primarily managed by tertiary care hospitals²¹⁶. The lack of continuity of care made long-term chronic disease management challenging. Patients sometimes had to see multiple providers for the same condition due to fragmentation in care²¹⁶. Episodic healthcare was not sustainable, given the increase in chronic disease cases. There was a need for better-coordinated care.

In the year 2000, the government restructured healthcare to provide vertically integrated care. Restructuring allowed public healthcare institutions to create a balance between competition and cooperation. Polyclinics, specialist centres and hospitals were grouped into two clusters—National Healthcare Group (NHG) and SingHealth. The Integrated Health Information System (IHIS) was later set up in 2008 to digitise Singapore's health system. IHIS currently serves all restructured hospitals, polyclinics, national speciality centres in Singapore, the Ministry of Health and the Agency of Integrated Care. Collaborations with the inclusion of private GPs and community hospitals were needed for better chronic disease management.

Therefore, in 2012, the two clusters were further broken down into six regional health clusters, as the two clusters were geographically too dispersed to deal with the many stakeholders.

The public and private sector were better integrated with the formation of the RHSs, but healthcare became increasingly fragmented with many health clusters in a small country. The problem of fragmentation will worsen with the addition of two more hospitals and five more polyclinics, built to manage the growing demand for health services³⁶⁰. In 2017, the government re-clustered the six RHSs into three clusters²¹⁸. Each cluster has an academic medical centre linked with a medical school to facilitate teaching and research. The clusters share the speciality centres as Singapore is not big enough to have multiple centres for the same condition. The current three RHS clusters are SingHealth, NHG and NUHS.

A1.5 Increased emphasis on primary care

The government has built more tertiary hospitals, community hospitals and polyclinics in recent years to cope with the increased demand for health services. Although it is necessary to expand the bed and service capacity to cope with population growth, the building of more institutions is not a sustainable long-term solution as it is costly and the training of manpower required to fill these new institutions takes time. Family physicians should care for seniors with

The Primary Care Masterplan was launched in 2011 to ease the increasing burden of chronic disease and to relief polyclinics. Private GPs were provided with more support to help patients manage long-term chronic diseases. Community Health Centres were built to support solo GPs with ancillary services such as counselling diabetic screening services for people with T2D. The family medicine clinic (FMC) model was also piloted to promote collaborative effort between the public and private sector. Each FMC is run by a group of GPs and has its own pharmacy and laboratory to support chronic disease management²¹⁶.

With the expansion of GP services, the Community Health Assistance Scheme (CHAS) was introduced to subsidise means-tested patients for primary care to relieve

the load from polyclinics³⁵⁸. The scope of family medicine practice was expanded from polyclinics and GPs to tertiary and community hospitals. Family Medicine was also recognised as a speciality to attract more talent to this field.

In addition to the restructuring of healthcare services in Singapore, the Ministry of Health launched the Healthy Living Master Plan to make healthy living the default choice for Singaporeans by 2020, as it is everyone's responsibility to live well and healthily.

Appendix 2 Pre-review app publication checklist

This sections covers the selected pre-review app publication checklist of Apple and Google Play app stores relevant to the manuscript “Medication management apps for diabetes: A systematic assessment of the transparency and reliability of health information dissemination”

A2.1 Apple app store

The pre-review checklist serves as a guidance for developers who wish to publish apps on the Apple app store and can be found at: <https://developer.apple.com/app-store/review/guidelines/>. Apps do not have to meet all criteria to be published on the app store. The checklist covers the following categories:

1. Safety

(Includes: Objectionable Content, User Generated Content, Kids Category, Physical Harm, Developer Information and Data Security).

Checklist items intended to safeguard health and safety include:

- Rejection of prank apps with false information and features
- Requiring disclosure on the validation of methodology to support accuracy claims relating to health measurements
- Requiring the user to check with a doctor in addition to using the app and before making medical decisions
- Rejection of medical apps that are not from an approved entity or did not pass regulatory clearance (Including drug dose calculators)
- Rejection of apps that encourage consumption of tobacco and vape products, illegal drugs, or excessive amounts of alcohol, or that encourages minors to consume any of these substances
- Requiring apps to have valid contact information
- Requiring apps to implement appropriate security measures to ensure proper handling of user information collected and prevent its unauthorized use, disclosure, or access by third parties

2. Business

(Includes: In-app purchases, Subscriptions, Hardware-Specific Content, Goods and Services Outside of the App, Apple Pay, Advertising)

Checklist items intended to safeguard consumers’ interest in health apps include:

- Disallowing the creation of an interface for displaying third-party apps, extensions, or plug-ins similar to the App Store or as a general-interest collection
- Disallowing artificial manipulation of a user’s visibility, status, or rank on other services unless permitted by that service’s Terms and Conditions

- Disallowing coercing users to rate the app, review the app, download other apps, or perform other similar actions in order to access functionality, content, or use of the app
- Requiring to display all information used to target advertisements (ads) to users without requiring the user to leave the app. Interstitial ads or ads that interrupt or block the user experience must clearly indicate that they are an ad, must not manipulate or trick users into clicking the ad, and must provide easily accessible and visible close/skip buttons large enough for people to easily dismiss the ad

3. Design

(Includes: Copycats, Minimum Functionality, Spam, Extensions, Apple Sites and Services, Alternate App Icons, HTML5 Games, Bots, etc.)

Checklist item intended to safeguard consumers' interest in health apps include:

- Discouraging the creation of multiple bundle IDs of the same app and piling on to a category that is already saturated

4. Legal

(Includes: Privacy, Intellectual Property, Gaming, Gambling, and Lotteries, VPN Apps, Mobile Device Management, Developer Code of Conduct)

Checklist items intended to safeguard consumers' privacy in health apps include:

- Requiring all apps to link their privacy policy in the App Store and within the app in an easily accessible manner
- Requiring apps to clearly and explicitly identify the type of data to be collected, method of data collection, purpose of data usage
- Disallowing apps to use or disclose to third parties data gathered in the health, fitness, and medical research context for advertising, marketing, or other use-based data mining purposes other than improving health management, for the purpose of health research (with permissions) or a direct benefit to that user (such as a reduced insurance premium). App developers must disclose the specific health data that will be collected from the device
- Requiring apps conducting health-related human subject research to obtain appropriate consent from participants and research to secure and provide proof of approval from an independent ethics review board
- Requiring apps to disclose any third parties the app wishes to share data with and how a user can revoke consent and/or request deletion of their data
- Asking for permission to collect user data even if the data is considered to be anonymous and providing an easily accessible and understandable way to withdraw consent

- Disallowing developers to use information from Contacts, Photos, or other APIs that access user data to build a contact database for personal use or for sale/distribution to third parties

*The app **Performance** checklist categories not listed in this document include: App Completeness, Beta Testing, Accurate Metadata, Hardware Compatibility, and Software Requirements

A2.2 Google Play Store

The pre-review checklist serves as a guidance for developers who wish to publish apps on the Google Play store and can be found at: https://play.google.com/about/developer-content-policy/#!?modal_active=none.

Apps do not have to meet all criteria to be published on the app store.

The checklist covers the following categories:

1. Restricted content

(Includes: Child Endangerment, Inappropriate Content, Financial instruments, Gambling, Illegal activities, User Generated Content, Unapproved Substances)

Checklist items intended to safeguard health and safety include:

- Disallowing apps that promote illegal activities such as the sale and purchase of illegal drugs or prescription drugs without prescription, encouraging the use or sale of drugs, alcohol, or tobacco by minors or providing instructions for growing or manufacturing illegal drugs
- Prohibiting the sales of prohibited pharmaceuticals and supplements. The list of products monitored by google can be found here: www.legitscript.com
- Prohibiting the publication of apps with false or misleading health claims, including claims implying that a product is as effective as prescription drugs or controlled substances
- Prohibiting the sales of non-government approved products that are marketed to be safe or effective for use in preventing, curing, or treating a particular disease or ailment. Products that have been subject to any government or regulatory action or warning are also prohibited
- Prohibiting the sales of products containing human chorionic gonadotropin (hCG) in relation to weight loss or weight control, or when promoted in conjunction with anabolic steroids

2. Impersonation and Intellectual property

(Includes: Impersonation, Intellectual Property)

Checklist item intended to safeguard impersonation and intellectual property include:

- Developers are not allowed to falsely suggest an affiliation with another entity

3. Privacy, security and deception

(Includes: User Data, Permissions, Device and Network Abuse, Malicious Behaviour, Deceptive Behaviour, Misrepresentation)

Checklist items intended to safeguard consumers' privacy and security include:

- Requiring developer to be transparent in data handling (by posting a privacy policy) by disclosing the collection, use, and sharing of the data, and limiting the use of the data to the purposes disclosed, and the consent provided by the user. In cases where users may not expect that their personal or sensitive user data will be required to provide or improve the features of the app, these disclosures must be within the app as a separate clause
- Limiting the collection and use of sensitive data such as personally identifiable information, financial and payment information, authentication information, phonebook, contacts SMS and call related data, microphone and camera sensor data, and sensitive device or usage data
- By handling all personal or sensitive user data securely, including transmitting it using modern cryptography
- Requiring the developer to request permissions to access data and use the data only for purposes that the user has consented to. Apps must be actively registered as the default SMS, Phone, or Assistant handler before prompting users to accept any of the above permissions and must immediately stop the use of the permission when it is no longer the default handler
- Disallowing developers to sell collected data or use alternative methods (including other permissions, APIs, or third-party sources) to derive data attributed to the above permissions
- Disallowing apps to contain false or misleading information or claims, including in the description, title, icon, and screenshots. For example, Apps that feature medical or health-related functionalities that are misleading or potentially harmful
- Requiring developers to present the consent dialog in a clear and unambiguous way (e.g. Affirmative user action to accept)

4. Monetization and Ads

(Includes: Payments, Subscriptions and Cancellations, Ads, Ad Network Certification)

Checklist items intended to safeguard consumers' interests include:

- Disallowing apps that contain deceptive or disruptive ads
- Disallowing ads that simulate or impersonate the user interface of any app, notification, or warning elements of an operating system

- Prohibiting coercing the user to click an ad or submit personal information for advertising purposes before they can fully use an app
- Ensuring that the ads within the app does not interfere with the operation of the device, and is easily dismissible without penalty
- Ensuring that the ads shown within the app is appropriate for the intended audience, even if the content is compliant with Google Play's policies

5. Store listings and promotions

(Includes: App Promotion, Metadata, User Ratings, Reviews and Installs, Content Ratings)

Checklist items intended to safeguard consumers' interests include:

- Disallowing apps that directly or indirectly engage in or benefit from promotion practices that are deceptive or harmful to users or the developer ecosystem, such as using deceptive ads on websites, apps, or other properties, including notifications that are similar to system notifications and alerts, promotion or installation tactics that redirect users to Google Play or download apps without informed user action, and unsolicited promotion via SMS services
- Disallowing developers to manipulate the placement of any apps in Google Play by inflating product ratings, review, or install counts by illegitimate means, such as fraudulent or incentivized installs, reviews and ratings

6. Spam and Minimum Functionality

(Includes: Spam, Minimum Functionality)

Checklist item intended to safeguard impersonation and intellectual property include:

- Developers are not allowed to publish apps that spam users or Google Play, such as apps that send users unsolicited messages or apps that are repetitive or low-quality

*Other checklist categories not listed in this document include: Other Programs, Designing Apps for Children and Families, Ads and Monetization, Policy coverage, Enforcement Process, Managing and Reporting Policy, Violations, Updates, and Other Resources.

Appendix 3 Smartphones and operating systems for app assessments

Supplementary material 1

Table A3: List of smartphones and their operating systems used for app assessment

Phone model	Original Operating system	Operating system version*
iPhone 5c	iOS	iOS 10.3.3
iPhone 6	iOS 8.0	iOS 11.1
iPhone7	iOS 10.0.1	iOS 11.1
Samsung Galaxy A5	Android 6.0.1 "Marshmallow"	Android 7.0 (Nougat)
Samsung Galaxy A7	Android 6.0.1 "Marshmallow"	Android 7.0 (Nougat)
Samsung J7 Pro	Android 7.0 (Nougat)	Android 7.0 (Nougat)
Samsung Galaxy Note 4	Android 4.4.4 "KitKat"	Android 6.0.1 "Marshmallow"
OnePlus 3T	OxygenOS	OxygenOS

*Listed above are the phones and OS versions used for our app assessment. The earliest OS version at the start of the app assessment exercise was listed; minor OS version updates may occur during the few months of app assessment but did not affect the apps.

Appendix 4 Checklists for smartphone app feasibility trial

A4.1 Consort 2010 checklist for pilot or feasibility trial reporting

Table A4.1 Consort 2010 checklist of information to include when reporting a pilot or feasibility trial

Section/ Topic	Item No.	Checklist item	Yes/ No/ N.A.
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	Y
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	Y
	2b	Specific objectives or research questions for the pilot trial	Y
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	Y
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N.A.
Participants	4a	Eligibility criteria for participants	Y
	4b	Settings and locations where the data were collected	Y
	4c	How participants were identified and consented	Y
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Y
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	Y
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N.A.
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	
Sample size	7a	Rationale for numbers in the pilot trial	Y
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Y
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Y
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	Y
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Y

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Y
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Y
	11b	If relevant, description of the similarity of interventions	N.A.
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	Y
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	Y
	13b	For each group, losses and exclusions after randomisation, together with reasons	Y
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Y
	14b	Why the pilot trial ended or was stopped	N.A.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Y
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Y
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Y
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Y
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N.A.
	19a	If relevant, other important unintended consequences	N.A.
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	Y
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	Y
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	Y
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	Y
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	N.A.
Protocol	24	Where the pilot trial protocol can be accessed, if available	N.A.
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Y
	26	Ethical approval or approval by research review committee, confirmed with reference number	Y

Reference: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot and feasibility studies. 2016;2(1):64.

A4.2 Authors' checklist of mERA guidelines

Table A4.2 Authors' checklist of the study with the assessment of mHealth evidence reporting and assessment (mERA) guidelines

Criteria	Item no	Notes	Comments from authors
Infrastructure (population level)	1	Clearly presents the availability of infrastructure to support technology operations in the study location. This refers to physical infrastructure such as electricity, access to power, connectivity etc. in the local context. Reporting X% network coverage rate in the country is insufficient if the study is not being conducted at the country level	The smartphone penetration rate of Singapore was presented in the Methods section to show Singapore as a relevant study setting for digital health studies.
Technology platform	2	Describes and provides justification for the technology architecture. This includes a description of software and hardware and details of any modifications made to publicly available software	The digital data collection platform – REDCap and the commercial app-Medisafe® was described in the Methods section.
Interoperability /Health information systems (HIS) context	3	Describes how mHealth intervention can integrate into existing health information systems. Refers to whether the potential of technical and structural integration into existing HIS or programme has been described irrespective of whether such integration has been achieved by the existing system	This criterion is relevant but premature for a pilot study assessing the feasibility of introducing an app to support medication management.
Intervention delivery	4	The delivery of the mHealth intervention is clearly described. This should include frequency of mobile communication, mode of delivery of intervention (that is, SMS, face to face, interactive voice response), timing and duration over which delivery occurred	Intervention delivery was described in the methods section.
Intervention content	5	Details of the content of the intervention are described. Source and any modifications of the intervention content is described	Intervention content was described in the methods section; the recruitment process was tailored to the local context; there were no modifications to the app or questionnaires.
Usability testing	6	Describe formative research and/or content and/or usability testing with target group(s) clearly identified, as appropriate	This study constitutes formative research.
User feedback	7	Describes user feedback about the intervention or user satisfaction with the intervention. User feedback could include user opinions about content or user interface, their perceptions about usability, access, connectivity, etc	User satisfaction was assessed as one of the study outcomes and reported in the manuscript.
Access of individual participants	8	Mentions barriers or facilitators to the adoption of the intervention among study participants. Relates to individual-level structural, economic and social barriers or facilitators to access such as affordability, and other factors that may limit a user's ability to adopt the intervention	Barriers and facilitators to the intervention were described in the discussion section.
Cost assessment	9	Presents basic costs assessment of the mHealth intervention from varying perspectives. This criterion broadly refers to the reporting of some cost considerations for the mHealth intervention in lieu of a full economic analysis. If a formal economic evaluation has been undertaken, it should be	Costs were not assessed in this feasibility study. Apart from the costs of data collectors, vouchers (token of appreciation for participants) and app subscription (for

		mentioned with appropriate references. Separate reporting criterion is available to guide economic reporting	researchers), we worked with existing infrastructure within the healthcare institute.
Adoption inputs/ programme entry	10	Describes how people are informed about the programme including training, if relevant. Includes description of promotional activities and/or training required to implement the mHealth solution among the user population of interest	It was described in the methods section that participants were referred by their doctor to the study.
Limitations for delivery at scale	11	Clearly presents mHealth solution limitations for delivery at scale	Limitations of the study were discussed in the discussion section.
Contextual adaptability	12	Describes the adaptation, or not, of the solution to a different language, different population or context. Any tailoring or modification of the intervention that resulted from pilot testing/usability assessment is described	The recruitment process was tailored to the local context, but the app and surveys were not as this is a feasibility study to assess the acceptability of introducing an app to patients.
Replicability	13	Detailed intervention to support replicability. Clearly presents the source code/screenshots/ flowcharts of the algorithms or examples of messages to support replicability of the mHealth solution in another setting	A commercial app and digital data collection platform which was easily accessible was used. Flowcharts were presented in the methods and results section to explain the recruitment process.
Data security	14	Describes the data security procedures/ confidentiality protocols	The study content was checked and approved by two Institutional Review Boards, which covered data security and confidentiality protocols prior to commencement.
Compliance with national guidelines or regulatory statutes	15	Mechanism used to assure that content or other guidance/information provided by the intervention is in alignment with existing national/regulatory guidelines and is described	The study content was checked and approved by two Institutional Review Boards prior to commencement.
Fidelity of the intervention	16	Was the intervention delivered as planned? Describe the strategies employed to assess the fidelity of the intervention. This may include assessment of participant engagement, use of backend data to track message delivery and other technological challenges in the delivery of the intervention	Adherence to the study, including usage of the app was described in the results section.

Reference: Agarwal S, LeFevre AE, Lee J, L'Engle K, Mehl G, Sinha C, et al. Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist. BMJ. 2016;352:i1174.

Appendix 5 Feasibility trial recruitment pamphlet

**Changi
General Hospital**
SingHealth

**LEE KONG CHAN
SCHOOL OF
MEDICINE**

Help us to improve your diabetes care!

Who can participate?	<ul style="list-style-type: none"> • Type 2 diabetes • Aged between 21 to 75 • Uses a smartphone app daily (Other conditions apply)
What does the study involve?	<ul style="list-style-type: none"> • You will need to answer a few online questionnaires on how you feel about and manage your diabetes. • You may be asked to use an app for 3 months
What you need to know	<ul style="list-style-type: none"> • Your usual care will not be affected • Your information will be kept confidential
Eligible participants will receive participant incentive (NTUC voucher)	
If you are interested to participate and would like to know more about this research study, please inform your doctor.	

Appendix 6 Feasibility trial questionnaires

A6.1 ASK-12 questionnaire

Research ID: _____

Adherence starts with knowledge - 12 (ASK-12) questionnaire

You will be asked to rate 12 statements on your medication taking behaviour. To complete this survey, please mark the response that best reflect your current medication taking status

INCONVENIENCE/FORGETFULNESS

		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Q1	I forget to take my medicines some of the time					
Q2	I run out of my medicines because I don't get refills on time					
Q3	Taking medicines more than once a day is inconvenient					

TREATMENT BELIEFS

		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Q4	I feel confident that each one of my medicines will help me					
Q5	I know if I am reaching my health goals					
Q6	I have someone whom I can call with questions about my medicines					
Q7	My doctor/nurse and I work together to make decisions					

BEHAVIOUR

		In the last week	In the last month	In the last 3 months	More than 3 months ago	Never
Q8	Have you taken a medicine more or less often than prescribed?					
Q9	Have you skipped or stop taking a medicine because you didn't think it was working?					
Q10	Have you skipped or stop taking a medicine because it made you feel bad?					
Q11	Have you skipped, stopped, not refilled, or taken less medicine because of the cost?					
Q12	Have you not had medicine with you when it was time to take it?					

©GlaxoSmithKline

A6.2 Appraisal of diabetes scale

Research ID: _____

Appraisal of Diabetes Scale (ADS)

People differ in their thoughts and feelings about having diabetes. We would like to know how you feel about having diabetes. Therefore, please mark the answer to each question which is closest to the way you feel. Please give your honest feelings - we are interested in how you feel, not what your doctor or family may think.

1. How upsetting is having diabetes for you?

1	2	3	4	5
Not at all	Slightly upsetting	Moderately upsetting	Very upsetting	Extremely upsetting
2. How much control over your diabetes do you have?

1	2	3	4	5
None at all	Slight amount	Moderate amount	Large amount	Total amount
3. How much uncertainty do you currently experience in your life as a result of being diabetic?

1	2	3	4	5
None at all	Slight amount	Moderate amount	Large amount	Extremely large amount
4. How likely is your diabetes to worsen over the next several years? (Try to give an estimate based on your personal feeling rather than based on a rational judgement.)

1	2	3	4	5
Not likely at all	Slightly likely	Moderately likely	Very likely	Extremely likely
5. Do you believe that achieving good diabetic control is due to your efforts as compared to factors which are beyond your control?

1	2	3	4	5
Totally because of me	Mostly because of me	Partly because of me and partly because of other factors	Mostly because of other factors	Totally because of other factors
6. How effective are you in coping with your diabetes?

1	2	3	4	5
Not at all	Slightly effective	Moderately effective	Very effective	Extremely effective
7. To what degree does your diabetes get in the way of your developing life goals?

1	2	3	4	5
Not at all	Slight amount	Moderate amount	Large amount	Extremely large amount

©Michael P. Carey, Professor, Behavioral and Social Sciences (Public Health), Brown University

A6.3 Diabetes Self-Management Questionnaire (DSMQ)

Changi
General Hospital
SingHealth

Diabetes Self-Management Questionnaire (DSMQ)

The following statements describe self-care activities related to your diabetes. Thinking about your self-care over the last 8 weeks , please specify the extent to which each statement applies to you.	applies to me very much	applies to me to a considerable degree	applies to me to some degree	does not apply to me
1. I check my blood sugar levels with care and attention. ☐ Blood sugar measurement is not required as a part of my treatment.	☐ 3	☐ 2	☐ 1	☐ 0
2. The food I choose to eat makes it easy to achieve optimal blood sugar levels.	☐ 3	☐ 2	☐ 1	☐ 0
3. I keep all doctors' appointments recommended for my diabetes treatment.	☐ 3	☐ 2	☐ 1	☐ 0
4. I take my diabetes medication (e. g. insulin, tablets) as prescribed. ☐ Diabetes medication/insulin is not required as a part of my treatment.	☐ 3	☐ 2	☐ 1	☐ 0
5. Occasionally I eat lots of sweets or other foods rich in carbohydrates.	☐ 3	☐ 2	☐ 1	☐ 0
6. I record my blood sugar levels regularly (or analyse the value chart with my blood glucose meter). ☐ Blood sugar measurement is not required as a part of my treatment.	☐ 3	☐ 2	☐ 1	☐ 0
7. I tend to avoid diabetes-related doctors' appointments.	☐ 3	☐ 2	☐ 1	☐ 0
8. I do regular physical activity to achieve optimal blood sugar levels.	☐ 3	☐ 2	☐ 1	☐ 0
9. I strictly follow the dietary recommendations given by my doctor or diabetes specialist.	☐ 3	☐ 2	☐ 1	☐ 0
10. I do not check my blood sugar levels frequently enough as would be required for achieving good blood glucose control. ☐ Blood sugar measurement is not required as a part of my treatment.	☐ 3	☐ 2	☐ 1	☐ 0
11. I avoid physical activity, although it would improve my diabetes.	☐ 3	☐ 2	☐ 1	☐ 0
12. I tend to forget to take or skip my diabetes medication (e. g. insulin, tablets). ☐ Diabetes medication/insulin is not required as a part of my treatment.	☐ 3	☐ 2	☐ 1	☐ 0
13. Sometimes I have real 'food binges' (not triggered by hypoglycaemia).	☐ 3	☐ 2	☐ 1	☐ 0
14. Regarding my diabetes care, I should see my medical practitioner(s) more often.	☐ 3	☐ 2	☐ 1	☐ 0
15. I tend to skip planned physical activity.	☐ 3	☐ 2	☐ 1	☐ 0
16. My diabetes self-care is poor.	☐ 3	☐ 2	☐ 1	☐ 0

© Dr Andreas Schmitt, Research Institute of the Diabetes Academy Mergentheim, Germany, 2012

A6.4 Intermediate survey (Intervention group only)

Research ID: _____

You will be asked to rate your level of agreement on a few statements regarding your use of the medicines management app. Please mark the response that most reflect your preference level.

1a) Are you still using the app?

☐ Yes
 ☐ No

1b) When was the last time you log into the app? (e.g. logged a medication taken or skipped/looked at the medication report)

☐ Today/Yesterday
 ☐ 3 - 5 days ago
 ☐ A week ago
 ☐ More than a week ago

2) Thinking of the past few days, how far did you agree that the app:

a) Made you more aware of your adherence to medication?

☐ Strongly agree
 ☐ Agree
 ☐ Neutral
 ☐ Disagree
 ☐ Strongly disagree

b) Made you more adherent to your medication?

☐ Strongly agree
 ☐ Agree
 ☐ Neutral
 ☐ Disagree
 ☐ Strongly disagree

c) Made you more confident in managing your medication?

☐ Strongly agree
 ☐ Agree
 ☐ Neutral
 ☐ Disagree
 ☐ Strongly disagree

d) Reduces the stress of managing your medication

☐ Strongly agree
 ☐ Agree
 ☐ Neutral
 ☐ Disagree
 ☐ Strongly disagree

e) Is easy to use

☐ Strongly agree
 ☐ Agree
 ☐ Neutral
 ☐ Disagree
 ☐ Strongly disagree

f) Annoys you when the notification goes off?

☐ Strongly agree
 ☐ Agree
 ☐ Neutral
 ☐ Disagree
 ☐ Strongly disagree

A6.5 Intervention group final survey

Finally...

Page 1 of 1

- 1) On a scale of 1 to 10, with 10 being very satisfied, how would you rate your experience in using an app for managing your medication?
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

- 2) Would you recommend Medisafe to another person with the same condition?
☐ Yes ☐ No

- 3) Would you trust your doctor to recommend an app to manage your condition?
☐ Yes ☐ No

- 4) Will you continue to use the Medisafe app after today?
☐ Yes ☐ No

- 5) Was the length of the study
☐ Too short ☐ Just nice ☐ Too long

- 6) How do you think the app can be improved?

A6.6 Control group final survey

Finally...Page 1 of 1

Did you use any apps to manage your medications in the past three months?

☐ Yes
☐ No

If yes, what app did you use? _____

Appendix 7 Sample size estimation for a full trial

The sample size calculations for comparing two continuous means were based on 80% power, 5% significance and a two-sided test. A pre-test post-test control study design was used for sample size estimation. Usually, a pilot trial is required to find the variance or standard deviation to the sample for better estimation.

Medication adherence as outcome

Two-sided test

Mean difference	3%	5%	7%	10%	12%
Standard deviation	15	15	15	15	15
Sample size per arm	883	221	99	44	30

Variance estimation: The standard deviation reported in other studies are about 12 – 14%¹⁴⁴. Hence, a 15% deviation is used as an estimation. The average baseline medication adherence estimation is approximately 74% while medication adherence is defined to be >90% for the instruments that tend to achieve ceiling effects¹³⁹. Medication adherence may improve or worsen, so a two-sided estimation is used in this case.

One-sided test

Mean difference	3%	5%	7%	10%	12%
Standard deviation	15	15	15	15	15
Sample size per arm	696	174	78	35	23

Due to over-estimation at baseline, there is a risk of a ceiling effect, so a 5% difference in improvement between groups should be estimated to be more conservative. Therefore, a crude estimate would be to assume a sample size of 221 should a full trial be conducted. However, an improvement in medication adherence does not necessarily lead to better health outcomes, which should be considered.

HbA1c as outcome

The sample size required to detect a 0.62% reduction in HbA1c⁶³ with 80% power at a 5% significance is 151 per group, assuming equal group ratio. The effect size was estimated as a short term(<6months) improvement from a meta-analysis of studies looking at mobile phone applications to improve glycaemic control (HbA1c) in the Self-management of T2D. The sample size was computed from a mean HbA1c of 8.688% $\pm$ 1.915%, of 6177 patients recruited for a T2D lifestyle intervention managed by Changi General Hospital.

Appendix 8 Institutional Research Board approval letters

A8.1 SingHealth CIRB approval letter

SingHealth
Defining Tomorrow's Medicine

Tel: (65) 6225 0488
Fax: (65) 6557 2138
 Singapore Health Services Pte Ltd
 31 Third Hospital Avenue
 #03-03 Bowyer Block C
 Singapore 168753
www.singhealth.com.sg
 UEN No. 200002698Z

CIRB Ref: **2018/2563**

4 September 2018

Dr Tan Eberta Jun Hui
 Department of Endocrinology
 Changi General Hospital

Dear Dr Tan

SINGHEALTH CENTRALISED INSTITUTIONAL REVIEW BOARD (CIRB) APPROVAL

Protocol Title: Smartphone apps for medication adherence in people with type 2 diabetes: A feasibility trial

We are pleased to inform you that the SingHealth CIRB C has approved the above research project to be conducted in Changi General Hospital.

The documents reviewed are:

- 1) CIRB Application Form dated 1 Sep 2018
- 2) Protocol: Version 2
- 3) Participant Information Sheet and Consent Form
- 4) Recruitment Pamphlet
- 5) Features of Medisafe
- 6) Adherence Starts with Knowledge - 12 (ASK-12) Questionnaire
- 7) Diabetes Self-Management Questionnaire (DSMQ)
- 8) The Summary of Diabetes Self-Care Activities (SDSCA)
- 9) Visual Analogue Scale
- 10) Process Indicator Questionnaire
- 11) Intervention Satisfaction Survey
- 12) Control Group Final Questions
- 13) Appraisal of Diabetes Scale
- 14) Visual Explanation of Data Collection on Redcap
- 15) Sociodemographic Questionnaire

The SingHealth CIRB operates in accordance with the ICH Guideline for Good Clinical Practice, and with the applicable regulatory requirement(s).

The approval period is from **4 September 2018 to 14 August 2019**. The reference number for this study is CIRB Ref: 2018/2563. Please use this reference number for all future correspondence.

PATIENTS. AT THE HEART OF ALL WE DO.®

SingHealth Duke-NUS Academic Medical Centre
 Singapore General Hospital • Changi General Hospital • Sengkang General Hospital • KK Women's and Children's Hospital
 National Cancer Centre Singapore • National Dental Centre Singapore • National Heart Centre Singapore
 National Neuroscience Institute • Singapore National Eye Centre • SingHealth Community Hospitals • SingHealth Polyclinics

CIRB Ref: 2018/2563

The following are to be observed upon SingHealth CIRB Approval:

1. No participant should be admitted to the trial before the Health Sciences Authority notification/ authorisation/ approval has been obtained (for studies involving therapeutic or medicinal products).
2. The Principal Investigator should ensure that this study is conducted in compliance with the ICH Guideline for Good Clinical Practice, the ethical guidelines of which are applicable to all studies to be carried out, and to ensure that the study is carried out in accordance to the guidelines and the submitted protocol. The Principal Investigator should meet with the study team regularly to assess the progress of the study, and be familiar and comply with all applicable research policies in the Institution.
3. No deviation from, or changes of, the protocol should be initiated without prior written SingHealth CIRB approval of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involve(s) only logistical or administrative aspects of the trial (e.g. change of monitor(s), telephone number(s)).
4. Only the approved Participant Information Sheet and Consent Form should be used. It must be signed by each participant prior to enrolling in the study and initiation of any protocol procedures. Two copies of the Informed Consent Form should be signed and dated. Each participant or the participant's legal representative should be given a copy of the signed consent form. The remaining copy should be kept by the PI / medical record.
5. The Principal Investigator should report promptly to the SingHealth CIRB of:
 - i. Deviations from, or changes to the protocol including those made to eliminate immediate hazards to the trial subjects.
 - ii. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial.
 - iii. All serious adverse events (SAEs) and adverse drug reaction (ADRs) that are both serious and unexpected.
 - iv. New information that may affect adversely the safety of the subjects or the conduct of the trial.
 - v. Completion of the study.
6. Study Status Report should be submitted to the SingHealth CIRB for the following:
 - i. Study renewal: the Study Renewal Report is to be submitted at least two months prior to the expiry of the approval period. A valid SingHealth CIRB renewal is essential, as any research performed outside of an approved time frame is not legal, and thus not covered by the hospital's research insurance in case of unexpected adverse reactions.
 - ii. Study completion, withdrawal or termination: the Study Closure Report is to be submitted within 30 days after completion of the study. When the study is withdrawn or terminated by the Institution, PI or the sponsor, the PI should submit the Study Closure Report within 7 days.

Yours sincerely,

Dr J Raghuram
Chairman
SingHealth Centralised Institutional Review Board C

A8.2 NTU IRB approval letter

IRB-2018-09-029

9 January 2019

Associate Professor Josip Car
Lee Kong Chian School of Medicine

NTU INSTITUTIONAL REVIEW BOARD APPROVAL

Project Title: Smartphone apps to improve adherence in patients with type 2 diabetes: A feasibility trial

I refer to your application for ethics approval with respect to the above project.

The Board has considered your application and noted from your application that your research involves collecting behavioral data from participants through questionnaire and survey.

You have also confirmed that informed consent will be obtained from the participants and you have guaranteed the confidentiality of your participants' biodata obtained from them.

The documents reviewed are:

- a) NTU IRB application form dated **28 September 2018**
- b) Participant information sheet and consent form: version 1 dated **28 September 2018**
- c) Data collection form: version 1 dated **28 September 2018**

The Board is therefore satisfied with the bioethical consideration for the project and approves the ethics application under **Expedited** review. The approval period is from **9 January 2019 to 8 January 2020**. The NTU IRB reference number for this study is **IRB-2018-09-029**. Please use this reference number for all future correspondence.

The following protocol and compliances are to be observed upon NTU IRB approval

1. Any research involving subjects less than 21 years old would require IRB approved written Parental Consent and consent from the participant before any research protocols can be administered unless waiver of consent is given by IRB. Minimal risk refers to an anticipated level of harm and discomfort that is no greater than that ordinarily encountered in daily life, or during the performance of routine educational, physical, or psychological examination.
2. Only the approved Participants Information Sheet and Consent Form should be used. It must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject should be given a copy of the signed consent form.
3. Consent forms are important documents therefore they should be stored in the strictest arrangement. Loss of consent form would result in disciplinary action.
4. No deviation from, or changes of, the protocol should be initiated without prior written NTU IRB approval of an appropriate amendment.
5. The Principal Investigator should report promptly to NTU IRB regarding:

Research Integrity and Ethics Office, NTU Institutional Review Board

62 Nanyang Drive, Block N1.2-B1-02A, Singapore 637459, T: (65) 6592-2495, www.ntu.edu.sg

- a. Deviation from, or changes to the protocol.
 - b. Changes increasing the risk to the subjects and/or affecting significantly the conduct of the trial
 - c. All serious adverse events (SAEs) which are both serious and unexpected.
 - d. New information that may affect adversely the safety of the subjects of the conduct of the trial.
 - e. Completion of the study.
6. Continuing Review Request/ Notice of Study completion form should be submitted to NTU IRB for the following:
- a. Annual review: Status of the study should be reported to the NTU IRB at least annually using the Continuing Review Request/ Notice of Study completion form.
 - b. Study completion or termination: Continuing Review Request/ Notice of Study completion form is to be submitted within 4 to 6 weeks of study completion or termination.
7. All Principal Investigators should comply with existing legislation that would have an impact on the domain of their research.
8. Advertisements/ Notices for recruitment of subjects must meet the following requirements:
- a. Advertisements must clearly state that volunteers are being recruited to participate in an NTU research project with proper research title and NTU logo.
 - b. Name and contact details of Principal Investigator (usually a faculty member), and NTU-IRB contact details (Tel: 6592 2495; Email: IRB@ntu.edu.sg) should be provided.
 - c. The NTU-IRB project reference number should be stated.
 - d. Advertisements should include eligibility criteria.
 - e. Advertisements recruiting Minors must explicitly state that parental consent is required for participation (unless NTU-IRB has granted approval for a waiver of parental consent).
- Advertisements/ Notices should NOT contain the following:
- a. State or imply a certainty of favourable outcome or other benefits beyond what is outlined in the informed consent form and the application/protocol.
 - b. Make claims, either explicitly or implicitly, that a procedure or intervention is safe or effective or superior to other standard procedures or interventions.
 - c. Use catchy words like "free" or "exciting."
 - d. Advertisements may state that participants will be paid, but should not emphasize the payment or the amount to be paid (e.g. by such means of larger or bold type)

Lionel

Professor Lionel Lee
Chair, NTU Institutional Review Board
encl.

Research Integrity and Ethics Office, NTU Institutional Review Board

62 Nanyang Drive, Block N1.2-B1-02A, Singapore 637459, T: (65) 6592-2495, www.ntu.edu.sg