Master of Public Health

Master International de Santé Publique

Mobile Health in Developing Countries

A systematic review and meta-analysis

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MPH Master 2

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Acronyms

KAP: knowledge, attitude, practice

MEMS: medication event monitoring system

OR: odds ratio

QOL: Quality of life

RCT: randomise controlled trials

RR: risk ratio

SMDs: standardized mean differences

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ABSTRACT

Background: Due to its low-cost, ease of use and wide-spread availability, mobile phone could be a powerful tool to increase access to health care and to bridge the communication gap between health care providers and patients in developing countries (3, 15, 18-22).

Objectives: The aim of our review is to assess the effectiveness of mobile phone interventions dedicated to patients and general public in improving adherence to treatment, attendance at clinical appointments, related clinical outcomes and health behaviours in developing countries.

Study selection: We searched four electronic databases in April 2014: CENTRAL, PubMed, EMBASE and Global Health Library for published articles and trial registries for registered trials. We included only RCTs and cluster RCTs using mobile phones to improve health behaviour or health status dedicated to patients or general public in developing countries.

Data collection and analysis: Two reviewers independently assessed the eligibility of all articles identified by the search strategy and the retrieved full text articles for inclusion into the review. Data was extracted by one reviewer into a computer-based form. For outcomes with adequate number of studies, we used random-effect models to pool the results. Otherwise, we made narrative synthesis of the findings.

Results: In total, we identified 4943 citations. We selected 35 full text articles, reporting 29 RCTs and 1 cluster RCT involving 22479 participants. Overall mobile phone interventions improved surrogate outcomes such as adherence to treatment, attendance rate and KAP scores in education programs, but there was no strong evidence that it improved patient important outcomes like health behaviour changes and clinical outcomes.

Conclusions: Mobile phones could be a cost-effective tool to improve health and health care in developing countries. Better-designed high-quality studies are needed to evaluate the true effect of mobile phone interventions, especially on patient important outcomes.

Keywords: mobile health; cellular phone; text messaging; reminder systems; appointments; adherence; behaviour change; risk of bias; meta-analysis as topic; systematic review as topic

RÉSUMÉ

Titre: mHealth-santé téléphonie mobile dans les pays en développement: une revue systématique et méta-analyse

Contexte: En raison de son faible coût, la facilité d'utilisation et sa disponibilité, le téléphone mobile pourrait être un outil puissant pour améliorer l'accès aux soins de santé et combler le fossé de communication entre les fournisseurs de soins de santé et les patients dans les pays en développement.

Objectifs: L'objectif de notre étude est d'évaluer l'efficacité des interventions de téléphonie mobile dédiés aux patients et au grand public dans l'amélioration de l'observance du traitement, la participation à des rendez-vous cliniques, liés à des résultats cliniques et les comportements de santé des pays en développement.

Sélection des études: Nous avons cherché quatre bases de données électroniques en Avril 2014: CENTRAL, PUBMED, EMBASE et la Global Health Library, pour des articles publiés. Nous avons cherché des registres d'essais pour les essais enregistrés. Nous avons inclus seulement RCT et cluster RCT à l'aide de téléphones mobiles pour améliorer la santé, le comportement de la santé ou de soins de santé dédié aux patients ou grand public dans les pays en développement.

La collecte de données et analyse: Deux auteurs ont évalué indépendamment l'éligibilité de tous les articles identifiés par la stratégie de recherche et les articles en texte intégral récupérées pour l'inclusion dans l'étude. Les données ont été extraites par un examinateur en une forme informatique. Pour les résultats avec un nombre suffisant d'études, nous avons utilisé le random-effect model afin de mettre en commun les résultats. Sinon, nous avons fait la synthèse narrative des résultats.

Résultats: Au total, nous avons identifié 4943 citations. Nous avons sélectionné 35 articles en texte intégral, les rapports 29 RCT et 1 cluster RCT impliquant 22,479 participants. Globalement, les interventions de téléphonie mobile améliorent des résultats intermédiaires tels que l'adhésion au traitement, le taux de participation et les scores KAP dans les programmes d'éducation, mais il n'y avait aucune preuve solide concernant l'amélioration des résultats importants des patients comme les changements de comportement de santé et les résultats cliniques.

Conclusions: Les téléphones mobiles pourraient être un outil rentable pour améliorer la santé et les soins de santé dans les pays en développement. Des Études de haute qualité sont nécessaires pour évaluer le véritable impact des interventions de téléphonie mobile, en particulier sur les résultats importants des patients.

I. INTRODUCTION

1.1. Background

Mobile phone is a portable, powerful and inexpensive communication media that is reaching the most remote corners of the world. According to International Telecommunication Union (ITU), the mobile phone subscription rate has reached 89.4 per 100 inhabitants in developing countries in 2013. The number of mobile phone subscription is over 5.2 billion in developing countries in 2013, more than three times of that in the developed world (1.6 billion)(1). Many countries in Africa and Asia have “leapfrogged” into the mobile era, bypassing land-line telephone that is highly dependent on infrastructure(2).

1.2. Description of the intervention

The use of mobile phones in health system is called mobile health or mHealth(3). Standard mobile phones have three basic functions: Short Message Service (SMS), Multimedia Message Service (MMS) and phone call(4). As a communication media, mobile phones can be used in health system to facilitate communication between health care providers and patients(5), to support healthy lifestyle and behaviour changes(4, 6-10), to improve patient follow-up and medication adherence etc(3, 6, 11-17). In this review, we do not consider interventions using smart-phones or internet-connection because of their limited availability in developing countries.

1.3. How the intervention might work

Due to its low-cost, ease of use and wide-spread availability, mobile phone is a powerful tool to increase access to health care and to bridge the communication gap between health care providers and patients in resource-limited settings(3, 15, 18-22). Mobile phones can be used to remind patients of the medical appointment or date of screening test or improve patient follow-up after the medical consultation(2, 23-27). Text messages can be sent to patients as a daily reminder to improve adherence to treatment(3, 4, 25, 27-29). It can be used as an education tool to dismiss information and raise awareness on health-related issues (4, 30-35).

While the price of mobile phones is dropping dramatically, the penetration rate is surging rapidly(1). Mobile phones have a great potential to play an important role in improving health, health behaviour and health care in developing countries.

1.4. Barriers to effectiveness of the intervention

Although mobile phone has extensive coverage in the developing countries, the reliability of the network and availability of electric access are two factors that limit its use in health

care(3, 18). The high illiteracy rate in many low-income countries can significantly reduce the effectiveness of SMS interventions(3). The content of the SMS can be misinterpreted if it is not adapted to the literacy level of the target population(15, 18, 23, 30). Funding opportunities for mobile phone interventions are rare in developing countries, especially for long-term projects(3, 18).

1.5. Why it is important to do this review

Existing systematic reviews focus on mobile health interventions in a single disease (eg. diabetes or HIV)(11, 12, 26, 31, 36) or a certain field of health care (eg. preventive health care or health care delivery)(4, 14, 15, 32, 37) or a specific type of program (eg. smoking cessation or weight loss)(7, 10, 38). Most of the existing reviews are out of date and used narrative synthesis instead of meta-analysis due to the limited number and heterogeneity of included studies(3, 18, 20, 33). Since a high percentage of the studies are carried out in developed countries, only a few reviews target developing countries(2, 3, 11, 15, 30, 33, 37, 39, 40).

Following the surge of mobile phone penetration rate in the developing countries, the use of mobile phone interventions in health care and public health is rapidly expanding but the evidence base and long-term effect of these interventions remain unclear(1, 3, 23). A detailed up-to-date systematic review on the effectiveness of mobile health interventions in improving health, health behaviour and health care in developing countries is necessary to clarify this question.

II. OBJECTIVES

The aim of our review is to assess the effectiveness of mobile phone interventions dedicated to patients and general public in improving adherence to treatment, attendance at clinical appointments, related clinical outcomes and health behaviours in developing countries.

III. METHODS

3.1. Criteria for considering studies for this review

3.1.1. Types of studies

We included only RCTs and cluster RCTs in this review.

3.1.2. Types of participants

We only included studies carried out in developing countries, and multi-centre studies with at least one study centre located in developing countries. We included all the participants in the

studies regardless of age, gender and ethnicity. We included studies on all types of diseases and medical conditions carried out in all types of settings include hospitals, primary care clinics, outpatient clinics and communities.

3.1.3. Types of interventions

We included interventions using mobile phones (SMS, MMS, phone call and voice call) to improve health behaviour or health status dedicated to patients or general public. We included all types of interventions regardless of the purpose, duration and delivery methods. We excluded studies targeting only health care providers, such as doctors, nurses and community health workers. We excluded studies in which the participants used land-line telephones, smart-phones, PDAs, computers and internet-based technologies. We also excluded studies using mobile phones as data collection tool, not as part of the intervention. We excluded studies with multi-component interventions, mobile phone as part of it, if there is no proper control group to assess the effect of mobile phone alone.

3.1.4. Types of outcome measures

We included all studies using mobile phone intervention.

3.1.4.1. Primary outcomes

We included all outcomes related to health behaviour or health status.

Surrogate outcomes: (a) adherence to treatment measured by self-report, pill count, MEMS or questionnaires, (b) attendance rate at clinical appointments, (c) Knowledge, Attitude and Practise as assessed by the (KAP) scores in education programs.

Patient important outcomes: (a) behaviour changes related to the intervention and (b) any important clinical outcomes such as viral load in HIV patients.

3.1.4.2. Secondary outcomes

Secondary outcomes include (a) user feedback/evaluation of intervention, including satisfaction level, perceived effectiveness, willingness to continue the program and to recommend it to other people; (b) Adverse effects of the intervention or drawbacks, such as disclosure of disease status, disturbing daily life, technological problems etc; (c) costs of the intervention; (d) health service utilisation following the intervention

3.2. Search methods for identification of studies

We developed the search strategy according to a published Cochrane review on mobile phone messaging for preventive health care. We made necessary modifications to include mobile phone calls and voice calls in the search and used the Cochrane highly-sensitive RCT filter to include all the RCTs.

3.2.1. Electronic searches

One review author (XG) searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE and Global Health Library (an electronic database containing literatures in regional medical indices supported by WHO) in April 2014. There were no restrictions on language or publication date in our search. The search strategies were presented in the Annex I.

3.2.2. Searching other resources

We searched WHO Clinical Trial Search Portal and ClinicalTrials.gov for ongoing trials and unpublished completed trials. We also searched the reference lists of previous systematic reviews on mobile phone interventions and contacted authors of included studies, completed trials and on-going trials to ask whether they knew about any published or unpublished studies.

3.3. Data collection and analysis

3.3.1. Selection of studies

Two reviewers (XG, TF) independently assessed the eligibility of all articles identified by the search strategy. We examined the titles and abstracts to exclude those not relevant to the review and retrieved full text for all the articles that were potentially relevant. When the full text articles not available online or not accessible, we contacted the authors to request for a copy of the article. The same reviewers assess all the full text articles retrieved independently for inclusion into the review. Disagreements were resolved by discussion between the two reviewers and with another reviewer (IB) when necessary. We contacted the authors for further details if there was no sufficient information to make the judgment for inclusion. Excluded studies were listed in the supplementary materials with reason of exclusion.

3.3.2. Data extraction and management

Data was extracted from all included studies using a data extraction template developed for this study. The data extraction form was designed on WEPI 1.0, an online questionnaire design platform developed by EpiConcept. The form was tested with five included studies and modifications were made when necessary. One reviewer (XG) extracted the data for each included study. The following data was extracted into the computer-based form:

General information: Title, author, journal, year of publication, country of authors, country of recruitment, starting and ending dates of study, study setting, funding source.

Participants: Population, age, gender, inclusion and exclusion criteria, disease or medical condition, informed consent and ethical approval.

Interventions: Type of intervention, delivery method, timing, frequency, content, follow up duration

Comparisons: Type of control, number of control groups

Outcomes: Definition of outcomes, measurement methods, timing of assessment, adverse events

Results: Effect measure, number of events and total number of participants randomized in each group (dichotomous outcome), mean and standard deviation in each group or median and inter-quartile range (continuous outcome)

3.3.3. Assessment of risk of bias in included studies

The risk of bias of included studies were assessed using the Cochrane Collaboration's Risk of bias tool for RCTs(41). Below are some specific points we made for the assessment.

Since the intervention required overt participation, blinding of participants was difficult. We considered participants were blinded if they were "not made aware whether other patients would be messaged or not". We considered self-reported adherence to treatment, KAP scores, quality of life scores, user evaluation of the intervention as subjective outcomes and the participants were the outcome assessors, not the interviewers or researchers. We considered attendance rate, mortality rate, uptake of vaccine, and cost of intervention as objective outcomes that were not subject to risk of bias even though the outcome assessors were not blinded.

3.3.4. Measures of treatment effect

We used intention-to-treat methods to analyze the results. All the participants randomized were included in the final analysis irrespective of the subsequent events. For dichotomous outcomes, we used risk ratio (RR) and 95% confidence interval as effect measures. Odds

ratio was not used because the prevalence of event was high. We used the number of participants in each group after randomization as the denominators in the analysis. Missing data were considered as non-events. For continuous outcomes, we used standardized mean differences (SMDs) and 95% confidence interval to evaluate the effect size.

3.3.5. Unit of analysis issues

For cluster RCT, we took into consideration of the similarity within clusters. We contacted the authors for the ICC if not reported and used ICC and mean cluster size to calculate the effective sample size. For studies with multiple intervention groups, we selected the groups relevant to the review and combined them into one group to create a single pair-wise comparison with the control group.

3.3.6. Assessment of heterogeneity

We assessed the clinical heterogeneity among the included studies. When it is appropriate to conduct meta-analysis, statistical heterogeneity was assessed using I^2 statistics (Higgins 2003). An I^2 value of 0% to 40% represent no important heterogeneity, 40%-60% moderate heterogeneity, 60%-90% substantial heterogeneity and >90% considerable heterogeneity.

3.3.7. Assessment of reporting biases

We used funnel plot to assess the reporting bias of the studies when there was sufficient number of studies in the analysis.

3.3.8. Data synthesis

For the outcomes with adequate number of studies, we used random-effect models to pool the results. For those did not have sufficient number of studies, we made narrative synthesis.

3.3.9. Subgroup analysis and investigation of heterogeneity

We conducted subgroup analysis of included studies according to type of intervention, geographic location and medical conditions when there were sufficient number of studies in the analysis.

3.3.10. Sensitivity analysis

We performed sensitivity analysis according to the risk of bias of included studies. Studies with high or unclear risk of bias of allocation concealment were excluded from the analysis to

test the robustness of the result. Another sensitivity analysis excluding studies with high or unclear risk of attrition bias was performed as well.

IV. RESULTS

4.1. Description of studies

4.1.1. Results of the search

In total, we identified 4943 citations from the four databases. The selection process was shown in the flow chart (Figure 1).

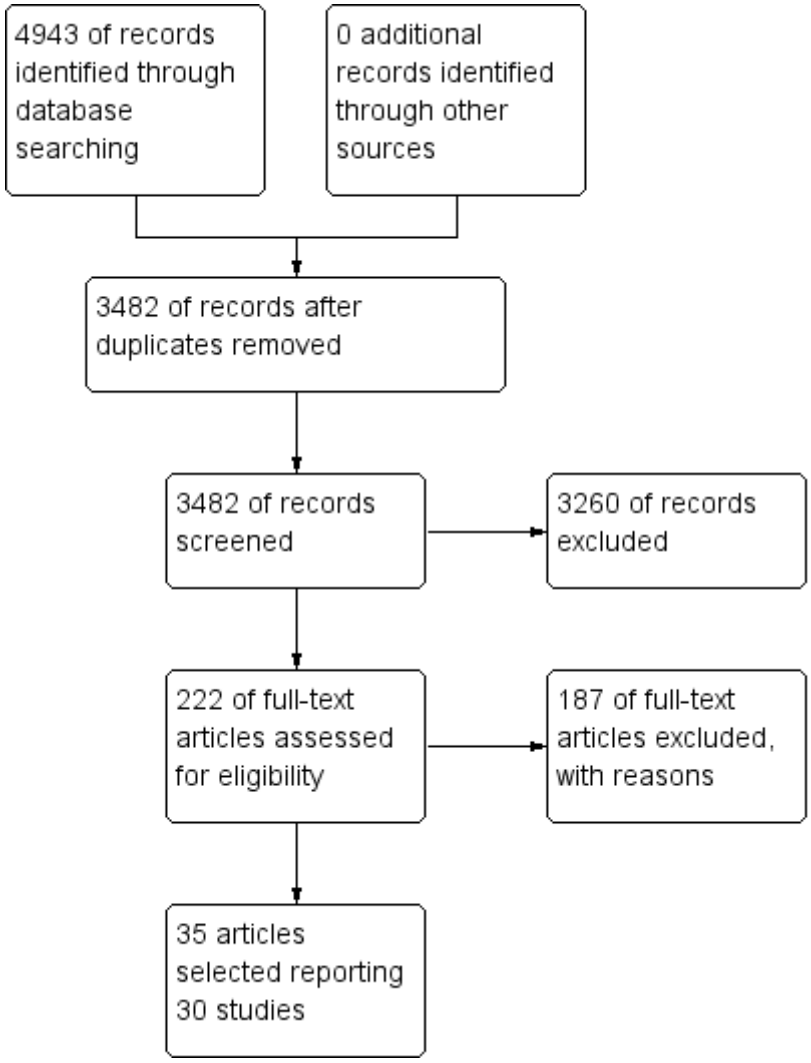

Figure 1. Flow chart of study selection

We contacted the authors of the posters, conference proceedings and presentations to ask whether the study is completed and published or not, and also the country of recruitment for participants if it was not reported in the abstract. Among them, 9 trials were completed but

not published yet. They were included in the list of on-going studies. 1 article was published online at the time of review and was included in list of included studies. The others did not meet the inclusion criteria of the review mainly because the participants were not recruited in developing countries.

Overall, 35 full text articles were included reporting 29 RCTs and 1 cluster RCT on mobile health in developing countries, involving 22479 participants. The details of the included and excluded studies were presented in the Characteristics of included studies and Characteristics of excluded studies in the supplementary materials.

4.1.2.1. Participants

The studies were conducted in various developing countries: 8 in China (including 2 in Taiwan), 5 in Malaysia, 4 in India, 3 in Kenya, 2 in South African, 2 in Iran and one each in Argentina, Brazil, Cameroon, Nigeria, Tanzania and Turkey. There was no multi-centre studies with at least one study centre located in developing countries. The studies were on various disease conditions: 7 studies on HIV, 3 studies on type 2 diabetes, 2 on dental health and 1 each on allergic rhinitis, epilepsy, H1N1, malaria, tuberculosis, acute coronary syndrome, cataract, cervical cancer, chronic disease, iodine deficiency, medial abortion, Down syndrome screening and smoking cessation.

The target groups in the studies were mainly adults, 15 for both men and women, 7 for women only, 2 for men only and 5 did not specifying age limits. Only one study targeted pre-school children and their mothers (Sharma 2011).

Number of participants randomised in the studies ranged from 29 to 3178, with a median of 258. 10 studies were set in hospitals, 7 in primary care clinics, 5 in community, 2 in outpatient clinics and 5 in other settings such as health care centres and pharmacies.

28 studies had ethical approval. Mehran 2012 did not report on ethical approval status, 1 study (Chai 2013) did not ask for ethical approval. All studies got informed consent from the participants, either written or oral.

4.1.2.2. Intervention

23 studies had only one intervention group using SMS. 4 studies (Abdul 2013, Chen 2008, Leong 2006, Liew 2009) had two intervention groups, one using SMS another using phone calls. Huang 2013a had two intervention groups both using phone call reminders. Two studies had 4 intervention groups to compare the effect of SMS reminders with different

frequency and content. The 4 groups in Pop-Eleches 2011 were daily short SMS, daily long SMS, weekly short SMS and weekly long SMS. The 4 groups in Tolly 2012 were all SMS reminders but at different frequency (once every 3 days or once every 10 days) and content (informational or motivational).

Frequency

10 studies sent daily SMS reminders, 3 of them (Khonsari 2014, Pop-Eleches 2011, Wang 2014) for improving adherence to treatment, 1 (Odeny 2012) as attendance reminder, 6 (Chai 2013, Lua 2013, Lv 2012, Mehran 2012, Sharma 2011, Ybarra 2012) for education and behavioural changes. 2 studies (Lester 2010, Mbuagbaw 2012) sent weekly SMS reminders as adherence reminders. 6 studies sent SMS reminders one time only, Modrek 2014 for adherence, Chen 2008, Leong 2006 and Liew 2009 for attendance, Abdul 2013 and Cheng 2008 for promoting testing. The other studies had various frequencies, ranging from several times a day to once every two weeks. Details can be found in the Characteristics of included studies.

Timing

Timing of intervention varied greatly. For studies on adherence to treatment, the reminders were sent mostly at a fixed time of the day or before medication administration. For studies on clinical attendance, reminders were sent 24-48 hours prior to the appointment. For studies on education and behavioural changes, timing depended on content of the program.

Delivery

14 studies delivered reminders by automated computer system, 9 were delivered by researchers, 3 by nurses and 7 did not specify.

Duration

22 studies specified the duration of intervention, which ranged from 4 days to 1 year. 6 studies had equal or less than 30 days follow up, 13 had between 1 to 6 months and 3 had between 6 to 12 months. Studies on attendance did not specify the follow up duration because it depended on the patients' appointment. Studies on adherence had wide range of follow up time, causing substantial heterogeneity in the results.

4.1.2.3. Comparison

Type of control

28 studies compared intervention with no reminder or standard care. For studies on education, we considered traditional education methods such as brochures, printed materials as standard care. In Abdul 2013 the control group was usual recall by letter. In Chai 2013, the intervention targeted H1N1 and the control group was attention control receiving tobacco-cessation messages.

Number of control groups

28 studies had only one control group. Huang 2013a conducted two separate RCT using the same methods, one on antiretroviral treatment-naive patient, one on treatment experienced patients, thus there was 1 control group for each trial. Lv 2012 had one SMS intervention group and two control groups, one no reminder and one traditional methods. We chose the SMS vs no reminder to include in the review.

4.1.2.4. Outcomes

Attendance rate at the clinical appointment

8 studies reported attendance rate at the clinical appointment as the primary outcome. 3 studies had two intervention groups, one receiving SMS reminder, and another receiving phone call reminder. The other 5 studies only had SMS reminder group.

Adherence to treatment

12 studies measured adherence to treatment. 11 studies were SMS intervention and only Huang 2013a was phone call intervention. 9 studies used self-reported adherence as the primary outcome. In addition to self-reported adherence, Costa 2011 reported adherence measured by pill counting and MEMS, Mbuagbaw 2012 measured self report no missed dose and pharmacy refill data. Pop-Eleches 2011 reported adherence measured by MEMS only. In Iribarren 2013, adherence rate was not reported due to missing data in the control group.

KAP scores in education programs

5 studies reported KAP scores as the primary outcome to evaluate the impact of education programs delivered by SMS. All the studies used questionnaires on knowledge, attitude and practise related to the target disease or health condition to assess the participants before and after the intervention.

Behaviour changes

5 studies reported behaviour changes: sustained abstinence from smoking in Ybarra 2012, early resumption of sexual activity after male circumcision in Odeny 2012, uptake of pap smear in Abdul 2013 uptake of H1N1 vaccine in Chai 2013 and testing for HIV in Tolly 2012. See Table 1.

Clinical outcomes

6 studies using mobile phone as adherence reminder reported clinical outcomes: severity of allergic arthritis in Wang 2014, CD4 count and weight change in Huang 2013a, weight, BMI and opportunistic infections in Mbuagbaw 2012, HbA1c and lipid profile in Shetty 2011, TB status in Iribarren 2013, and heart functional status in Khonsari 2014. 2 studies (Mbuagbaw 2012, Khonsari 2014) reported mortality rate. See Table 2.

5 studies using mobile phone to deliver education or behaviour change programs reported clinical outcomes: incidence of type 2 diabetes in Ramachandra 2013, severity of asthma in Lv 2012, visible plaque index in Sharma 2011, reported influenza like illness in Chai 2013 and biomarker for diabetes in Goodarzi 2014. See Table 3.

Psychological outcomes

3 studies reported psychological outcomes: perceived control of asthma in Lv 2012, anxiety level in Constant 2014 and Chen 2008. See Table 4.

Secondary outcomes

8 studies (Lin 2012, Costa 2011, Constant 2014, Iribarren 2013, Huang 2013, Khonari 2014, Ramachandran 2013, Ybarra 2012) reported user feedback/evaluation of intervention, 3 studies (Chen 2008, Leong 2006, Tolly 2012) evaluated the costs of the intervention and none measured health service utilisation following the intervention and users' perception of safety. See Table 5 and Table 6.

Adverse events

Only 4 studies (Constant 2014, Ramachandran 2013, Mbuagbaw 2012, Lester 2010) mentioned adverse effects. See Table 7.

We had planned to include studies on disease surveillance and monitoring but none were identified.

4.2. Risk of bias in included studies

We summarised the risk of bias in included studies in Figure 2 and Figure 3. The reasons for judgement were listed in the Characteristics of included studies in the supplementary materials.

4.2.1. Allocation (selection bias)

Random sequence generation

18 studies reported the methods for random sequence generation thus at low risk of bias. Only 7 of them specified the details of the methods, the others simply mentioned it was from "computer generated random numbers". 9 studies had unclear risk of bias. 3 studies (Chai 2013, Huang 2013, Ybarra 2012) were at high risk of bias.

Allocation concealment

Only 7 studies reported proper allocation concealment methods. 1 study (Huang 2013a) had high risk. 22 studies did not mention allocation concealment in the articles.

4.2.2. Blinding (performance bias and detection bias)

Blinding of participants and personnel (performance bias)

Only 1 study blinded the participants. In the other 29 studies, participants were not blinded. 16 studies did not report blinding of personnel. 5 studies mentioned that it was impossible to blind the personnel. 8 studies reported the methods of personnel blinding but 2 (Iribarren 2013, Khonsari 2012) were not considered as effective because blinding of physicians can be compromised due to patient physician communication. Blinding of outcome assessment (detection bias): Subjective outcomes

Since the participants were not blinded in 29 studies, the risk of detection bias for subjective outcomes was judged to be high in 22 studies. 7 studies did not have subjective outcomes thus had low risk of bias. Wang 2014 blinded the participants and had low risk of detection bias for subjective outcomes in which participants were the outcome assessors.

Blinding of outcome assessment (detection bias): Objective outcomes

24 studies had low risk of bias. 6 studies had unclear risk of bias because blinding of laboratory personnel or clinicians was not reported.

4.2.3. Incomplete outcome data (attrition bias)

12 studies had low risk of attrition bias, 14 studies had high risk and 4 studies had unclear risk.

4.2.4. Selective reporting (reporting bias)

22 studies did not have published protocols or clinical registries, thus had unclear risk of reporting bias due to lack of information. Only 4 studies had low risk of reporting bias. Another 4 studies were judged as having high risk.

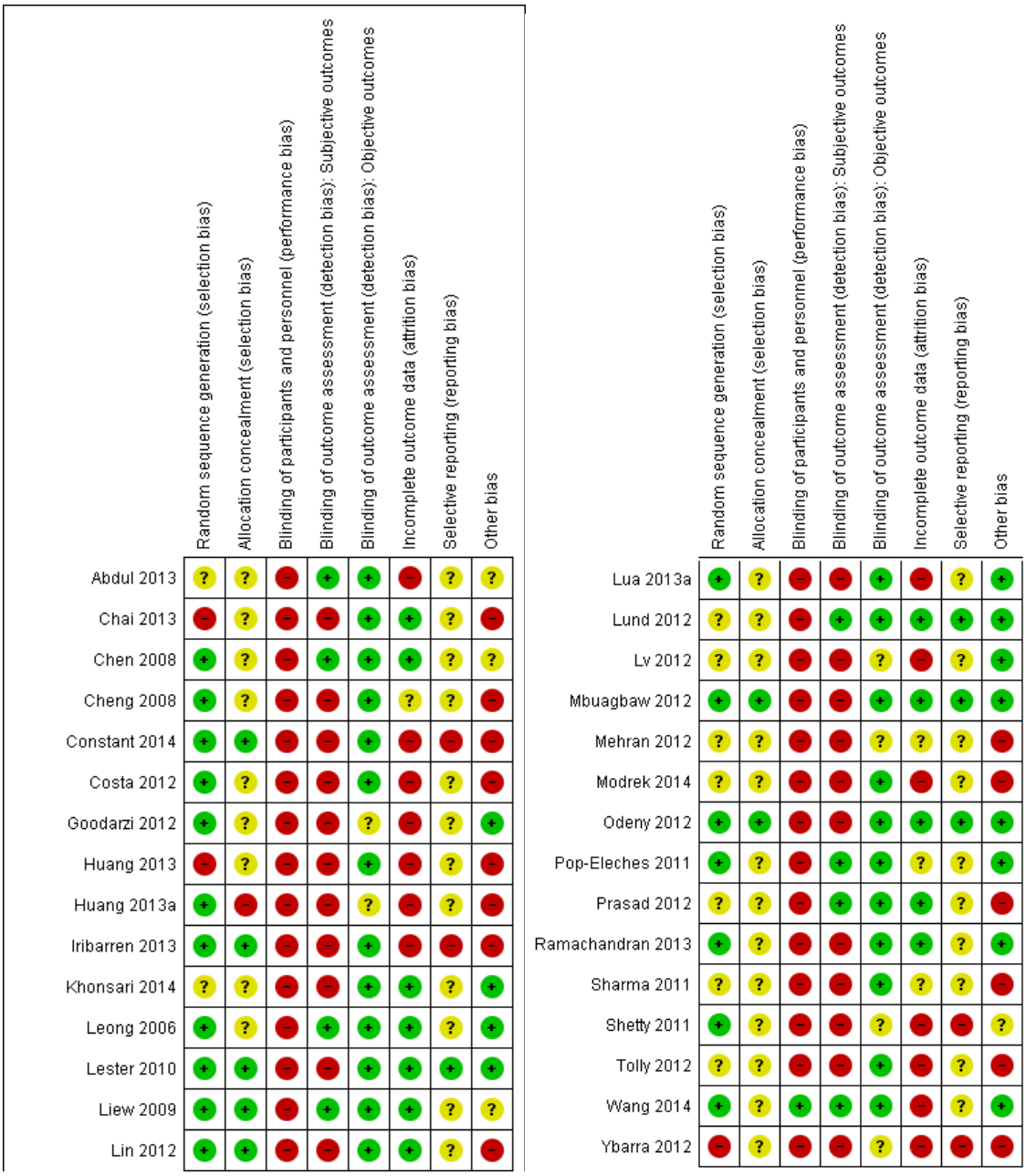

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

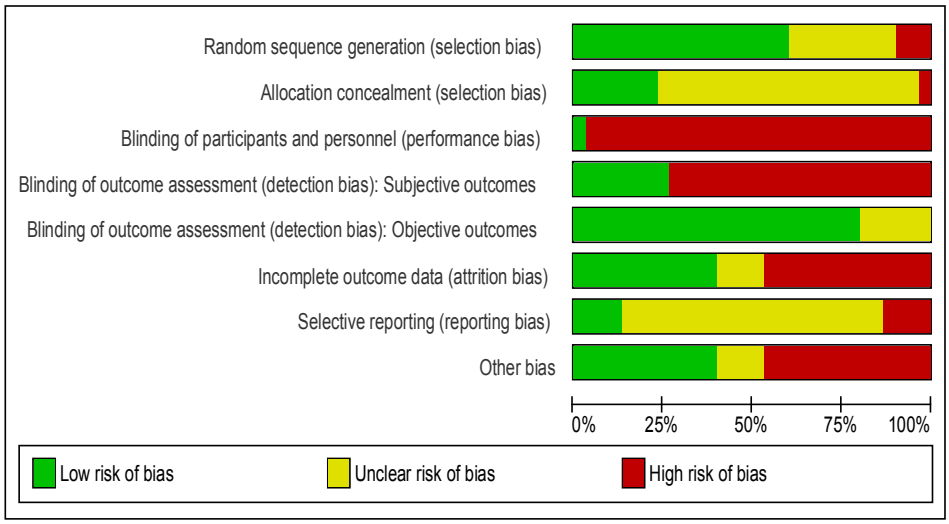

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

4.3. Effects of interventions

4.3.1. Attendance at healthcare appointments

4.3.1.1. Meta-analysis

8 studies involving 5991 participants evaluated the impact on the attendance rate. All the studies were in favour of a beneficial effect of mobile phone interventions but there was substantial heterogeneity. Overall mobile phone interventions, namely SMS and phone call reminders, improved the attendance rate at healthcare appointments compared with no reminder (RR 1.28; 95% CI 1.15 to 1.42; I^2=88%)(8 studies, 5991 participants)(Analysis 1.1, Figure 4). Since a random effect model was used to pool the result, the RR from this analysis was the mean of the distribution of effects from included studies, not the pooled effects of the intervention. There was considerable heterogeneity among the studies (I^2=88%), thus the result had to be taken with caution. The heterogeneity may come from the 3 smaller studies (Lin 2012, Lua 2013a, Prasad 2012) with high risk of bias and large effects. Only 1 study (Odeny 2012) evaluated patient important outcome, the other studies measured surrogate outcomes only.

3 studies (Chen 2008, Leong 2006, Liew 2009) compared two intervention groups (one group received SMS reminder, another received phone call reminder) to the same control group. To include both intervention groups in this analysis, we split the control group into two in proportion to the number of participants in each intervention group and included two pair-comparisons, SMS vs no reminder and phone call vs no reminder, from each study.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Attendance rate at healthcare appointment	8	5991	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.15, 1.42]
1.1.1 SMS reminder	8	4100	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.18, 1.62]
1.1.2 Phone call reminder	3	1891	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.02, 1.17]
1.2 Attendance rate at healthcare appointment	8	6001	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.20, 1.56]
1.2.1 Studies in Asia	6	4391	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.22, 1.76]
1.2.2 Studies in Africa	2	1610	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.98, 1.38]

Analysis 1.1 and 1.2: Meta-analysis of the effect of mobile phone reminder vs no reminder on attendance rate at healthcare appointment

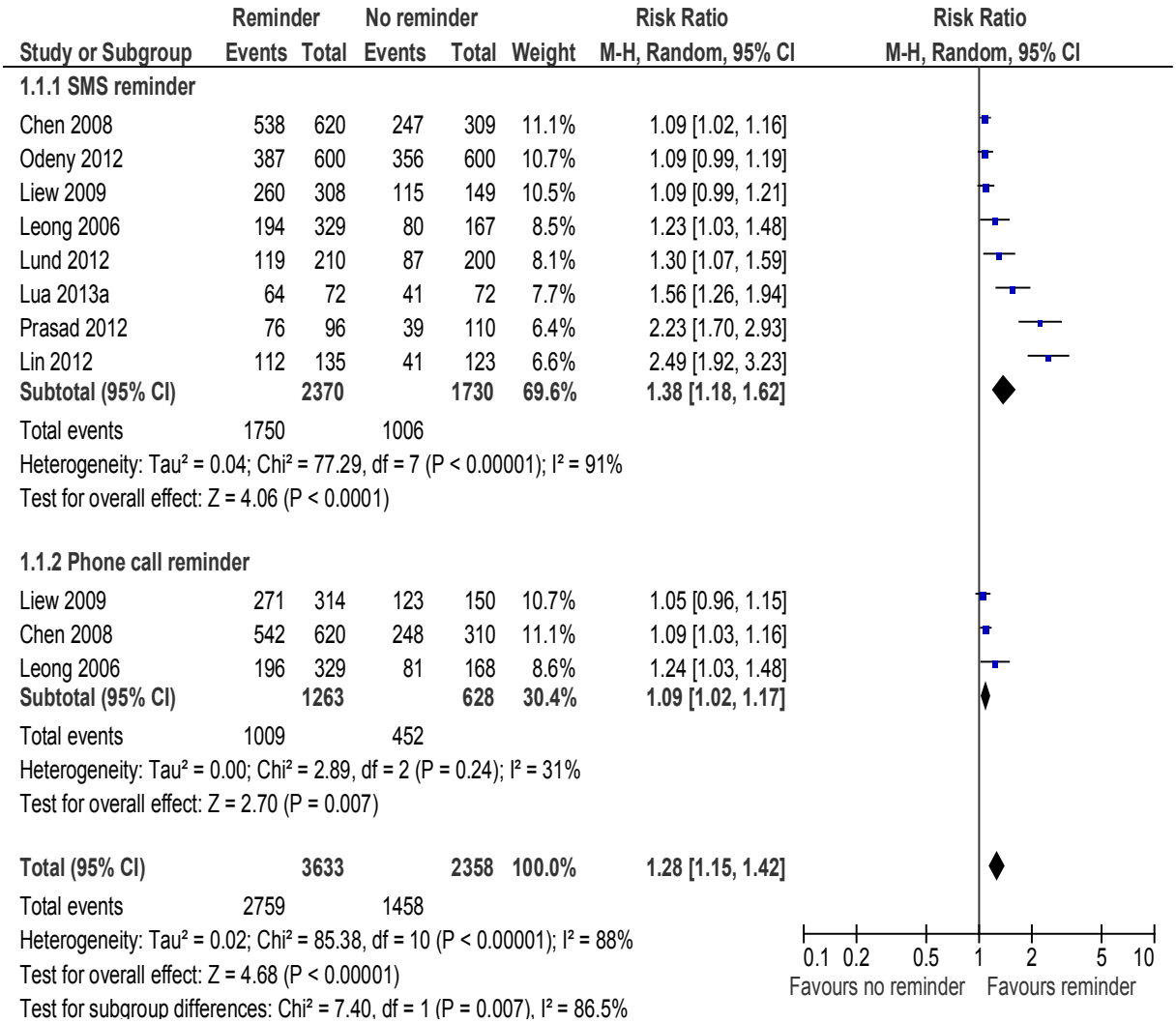

Figure 4. Forest plot of comparison: 1 Mobile phone text message reminder VS no reminder, outcome: 1.1. Attendance rate at healthcare appointment. Subgroup Analysis: SMS VS phone call reminder

In Lin 2012, the participants attend >=4 appointments during the follow up. The attendance rates of the first visit to the fourth visit and the total visits were reported in the article. The unit of analysis of the attendance rate of the total visits is the clinical appointment instead of participant. It increased the sample size by four times and may inflate the result of the meta-analysis. Thus we chose the attendance rate of the fourth visit to include in the meta-analysis because we are interested in the long term effect of the intervention and the unit of analysis is participant.

Lund 2012 is the only cluster RCT included in the meta-analysis. Since ICC was not reported in the article, we used ICC=0.05 to calculate the effective sample size.

4.3.1.2. Subgroup analysis

We performed subgroup analysis according to type of interventions. Both SMS reminder (RR 1.38; 95% CI 1.18 to 1.62; I^2=91%)(8 studies, 4100 participants) and phone call reminder (RR 1.09; 95% CI 1.02 to 1.17; I^2=31%)(3 studies, 1891 participants) improved the attendance rate at healthcare appointments compared with no reminder. The effect of SMS reminder was slightly higher than phone call reminder but there was no significant difference between the two.

We performed another subgroup analysis according to geographic locations. 6 studies were from Asia while 2 were from Africa. The overall effect of studies in Asia (RR 1.46; 95% CI 1.22 to 1.76; I^2=94%) was higher than those in Africa (RR 1.16; 95% CI 0.98 to 1.38; I^2=63%). There was substantial heterogeneity in both subgroups. See Figure in Annex.

We were not able to perform subgroup analysis according to disease conditions because each study was targeting a different disease.

4.3.1.3. Sensitivity analysis

We conducted a sensitivity analysis excluding 5 studies (Prasad 2012, Lua 2013a, Lund 2012, Leong 2006, Chen 2008) with unclear risk of bias in allocation concealment. The effect (RR 1.27; 95% CI 1.03 to 1.56; I^2=93%) was similar to the overall effect including all studies (RR 1.28; 95% CI 1.15 to 1.42). Another sensitivity analysis based on low risk of attrition bias was performed as well, excluding Lua 2013a. The effect (RR 1.25; 95% CI 1.13 to 1.39; I^2=88%) was similar to the overall effect including all studies too.

4.3.2. Adherence to treatment

4.3.2.1. Meta-analysis

11 studies involving 3744 participants evaluated the impact of SMS on the adherence to treatment. 7 could be included in the meta-analysis. 4 studies were in favour of a beneficial effect of SMS reminder and 3 showed non-significant result. There was substantial heterogeneity among studies. Overall SMS reminders improved the adherence to treatment compared with no reminder (RR 1.23; 95% CI 1.05 to 1.45; I^2=63%)(7 studies, 1764 participants) (Analysis 1.3, Figure 5). Since a random effect model was used to pool the result, the RR from this analysis was the mean of the distribution of effects from included studies, not the pooled effects of the intervention. There was substantial heterogeneity among the studies (I^2=63%), thus the result had to be taken with caution. The heterogeneity may come from the 3 smaller studies (Costa 2012, Khonsari 2014, Wang 2014) with small sample and large effect size. 7 studies evaluated clinical outcomes, the other studies measured surrogate outcomes only.

The other 5 studies could not be included into the meta-analysis due to the diversity of the outcome definition and measurement methods. We presented a narrative synthesis of the results below.

The definition of adherence to treatment varied greatly in the included studies. 4 studies defined adherent to treatment as the patients self-reported adherence is >95% (Costa 2012, Lester 2010, Mbuagbaw 2012, Wang 2014). Pop-Eleches 2011 defined it as >90% compliance measured by MEMS. Pop-Eleches 2011 had 4 intervention arms, all on SMS reminders but with different frequency and content. We decided to combine all the 4 intervention groups into one to create a single pair-wise comparison with the control group (no reminder). In Modrek 2014, the participants were given treatment advice depending on the result of malaria rapid diagnostic test, and the outcome was defined as adherent to RDT results or not. Khonsari 2014 used the eight-item Morisky Medication Adherence Scale (MMAS-8-item) to classify adherence into three categories: high, medium and low. We re-defined the scale in Khonsari 2014 into a dichotomous variable, making "high" as "adhere to treatment", "medium" and "low" as "not adhere to treatment". Since the results from the above mentioned studies were dichotomous and defined as adhere to treatment or not, we pooled them into one meta-analysis to evaluate the treatment of SMS reminder vs no reminder on adherence to treatment.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.3 Adherence to treatment	7	1764	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.05, 1.45]
1.3.1 Antiretroviral treatment	4	1195	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.02, 1.28]
1.3.2 Other treatments	3	569	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.97, 4.72]
1.4 Adherence to treatment	7	1764	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.05, 1.45]
1.4.1 Studies in Asia	2	112	Risk Ratio (M-H, Random, 95% CI)	3.08 [1.33, 7.18]
1.4.2 Studies in Africa	4	1623	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.11, 1.31]
1.4.3 Studies in Latin America	1	29	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.45, 1.35]

Analysis 1.3 and 1.4: Meta-analysis of the effect of SMS reminder vs no reminder on Adherence to treatment.

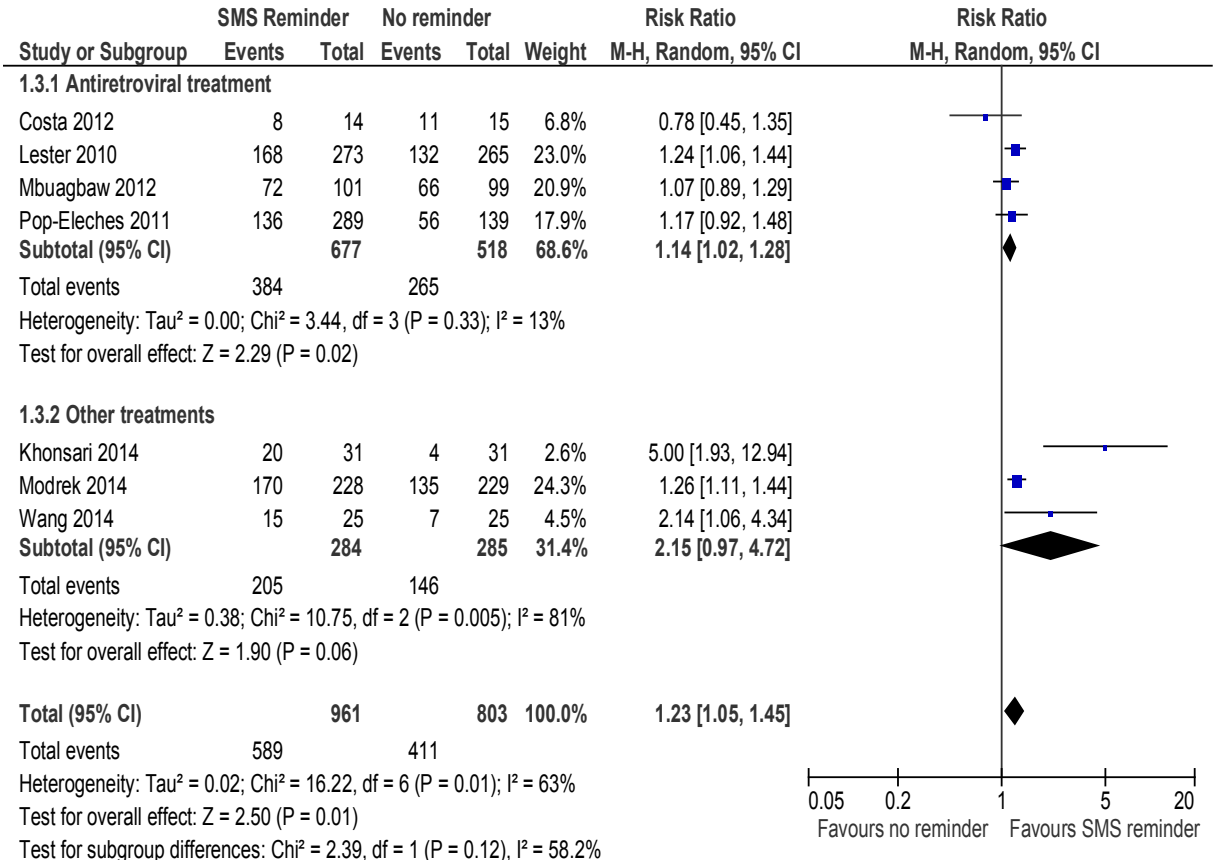

Figure 5. Forest plot of comparison: 1 Mobile phone intervention VS Control, outcome: 1.3 Adherence to treatment.

4.3.2.2. Subgroup analysis

Since there were 4 studies on adherence to antiretroviral treatment, we performed a subgroup analysis according to disease conditions as pre-specified in the protocol. The effect was lower than the overall effect from all included studies but slightly higher compared with no reminder (RR 1.14; 95% CI 1.02 to 1.28; I^2=13%)(4 studies, 1195 participants)(Analysis 1.3; Figure 5). There was low heterogeneity among the studies on antiretroviral treatment but substantial heterogeneity among studies on other treatments (I^2=13%). The heterogeneity may caused by the diversity of disease conditions and follow up durations in these studies. Wang 2014 was on allergic rhinitis treatment with 30 days follow up. Modrek 2014 was on malaria treatment with 4 days follow up. Khonsari 2014 was on acute coronary syndrome with 56 days follow up.

We performed another subgroup analysis based on geographical locations (Analysis 1.4; Figure in Annex). The studies in Africa showed similar effect (RR 1.20; 95% CI 1.11 to 1.31; I^2=0%)(4 studies, 1623 participants) as the overall effect but had no significant heterogeneity.

We were not able to perform subgroup analysis according to type of intervention because all studies were using SMS reminder.

4.3.2.3. Sensitivity analysis

We conducted a sensitivity analysis excluding 5 studies (Costa 2012, Pop-Eleshes 2011, Khonsari 2014, Modrek 2014, Wang 2014) with unclear risk of bias in allocation concealment. The effect (RR 1.16; 95% CI 1.01 to 1.34) was smaller but still statistically significantly different from control group.

4.3.2.4. Narrative synthesis

Huang 2013 measured pre- and post-test missed doses and delayed doses, reporting the percentage of participants who had a decrease in delayed doses and missed doses. Since having a decrease in delayed doses and missed doses may not relate to high adherence rate, we did not include it in the meta-analysis even though the outcome is dichotomous. The study found that there was higher percentage of participants experienced decreased incidence of delayed doses and missed doses in the SMS reminder group compared with no reminder group (P<0.001). 2 studies measured adherence as continuous variable reporting percentage or mean of adherence to treatment (Huang 2013a, Iribarren 2013, Shetty 2011). Huang 2013a found did not find significantly higher adherence rates in the intervention group during the 3-month follow up. In Iribarren 2013, adherence rate was not reported due to

missing data in the control group. Shetty 2011 reported only the adherence to diet and physical activity prescriptions (inter-group difference was not significant), not on drug prescriptions. Lua 2013a measured adherence using the Malay Modified Morisky Adherence Scale, reporting mean response scores ranging from 0 to 1. It found no significant differences in medication adherence between groups at baseline and follow up.

Huang 2013a was the only study using phone call as adherence reminder. It measured adherence as continuous variable reporting percentage adherence to treatment. It did not find significantly higher adherence rates in the intervention group during the 3-month follow up.

4.3.3. KAP scores in education programs

4.3.3.1. Meta-analysis

3 studies (Lua 2013a, Goodarzi 2012, Sharma 2011) reported KAP scores in mean and standard deviation. Since they were measuring the same outcome but using different scales, we used standard mean difference to estimate the overall effect of the SMS intervention. Lua 2013a reported awareness score instead of practice score in the outcome. Since the details of the score were not available, we excluded it from the meta-analysis on practice score. The knowledge score (SMD 0.66; 95% CI 0.30 to 1.01; I^2=66%)(3 studies, 387 participants)(Analysis 1.5; Figure 6), attitude score (SMD 0.53; 95% CI 0.33 to 0.74; I^2=0%)(3 studies, 387 participants) (Analysis 1.6; Figure 7) and practice score (SMD 0.72; 95% CI 0.05 to 1.39; I^2=84%)(2 studies, 243 participants)(Analysis 1.7; Figure 8) improved significantly in the SMS group compared with the control group. There was substantial heterogeneity in the knowledge score and practice score, because the effect from Goodarzi 2012 was higher than other studies. There was no significant heterogeneity in attitude score.

4.3.3.2. Narrative synthesis

The mean attitude score in Lua 2013a was significantly higher in the intervention group. Chai 2013 measured KAP scores as average number of correct questions and Mehran 2012 reported the median and inter-quartile range. Both studies found significantly better results in the intervention group in knowledge and attitude scores, but not in practice score.

4.3.4. Other outcomes

Due to the variation in outcomes, we were not able to pool the results of clinical outcomes, behaviour changes, psychological outcomes and secondary outcomes. The results were summarised in Table 1 to 7 in the Annex Part II.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.5 Knowledge score in education programs	3	387	Std. Mean Difference (IV, Random, 95% CI)	0.66 [0.30, 1.01]
1.6 Attitude score in education programs	3	387	Std. Mean Difference (IV, Random, 95% CI)	0.53 [0.33, 0.74]
1.7 Practice score in education programs	2	243	Std. Mean Difference (IV, Random, 95% CI)	0.72 [0.05, 1.39]

Analysis 1.5; 1.6; and 1.7: Meta-analysis of the effect of SMS reminder vs no reminder on KAP scores in education programs.

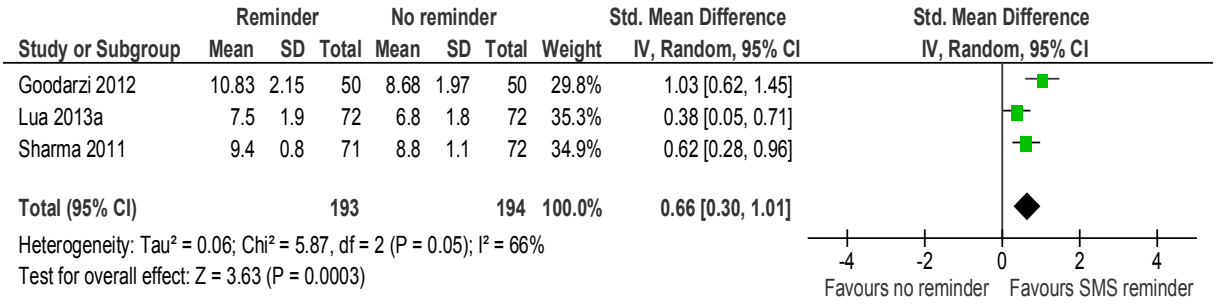

Figure 6. Forest plot of comparison: 1 Reminder VS no reminder, outcome: 1.5 Knowledge score

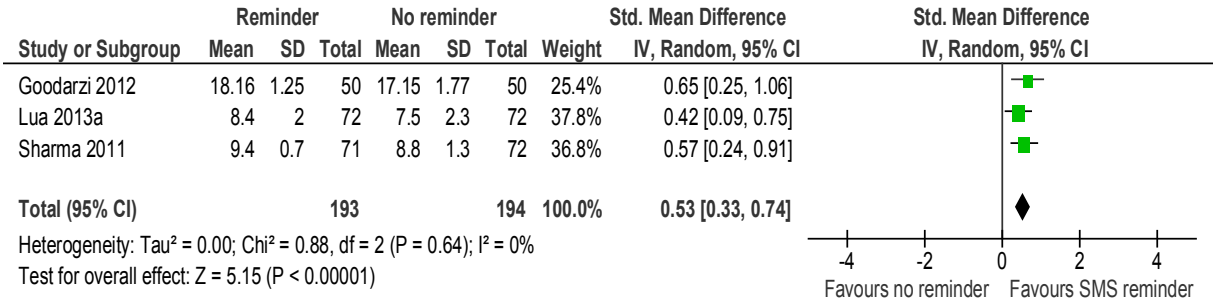

Figure 7. Forest plot of comparison: 1 Reminder VS no reminder, outcome: 1.6 Attitude score

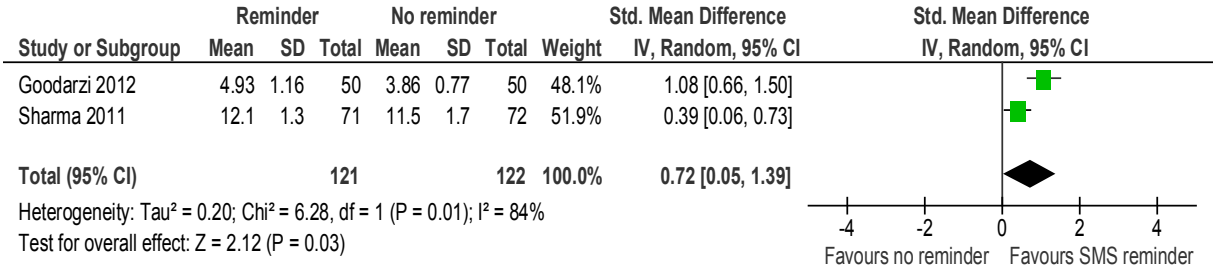

Figure 8. Forest plot of comparison: 1 Reminder VS no reminder, outcome: 1.7 Practice score

4.3.4.1. Behaviour changes

5 studies reported behaviour changes as outcomes. Only Chai 2013 found significantly better effect in the intervention group compared with control group, while 3 other studies (Odeny 2012, Tolly 2012, Ybarra 2012) found no significant difference between the two groups. Abdul 2013 found significant effect in the phone call reminder group, but not in the SMS group on repeat Pap smear. See Table 1 in Annex Part II.

4.3.4.2. Clinical outcomes

6 studies using mobile phone as adherence reminder reported clinical outcomes. 3 studies (Huang 2013a, Mbuagbaw 2012, Wang 2014) did not find significant difference between intervention and control groups. 2 studies (Iribarren 2013, Shetty 2011) did not report between group comparison of clinical outcomes. Khonsari 2014 found highly significant difference in heart functional status between the two groups but no difference in ACS-related readmission and death rate. See Table 2 in Annex Part II.

5 studies using mobile phone to deliver education or behaviour change programs reported clinical outcomes. 2 studies (Chai 2013, Goodarzi 2012) found intervention group had significantly better outcomes than control group but the risk of detection bias in these 2 studies were high and unclear. 2 other studies (Lv 2012, Sharma 2011) with low risk of detection bias did not find significant difference between the two groups. Ramachandran 2013 found the cumulative incidence of type 2 diabetes was lower in intervention group but no difference in anthropometric measurements and lipid profile except lower HDL. See Table 3 in Annex Part II.

4.3.4.3. Psychological outcomes

3 studies reported psychological outcomes. Cheng 2008 and Lv 2012 found significantly better effect in the intervention group compared with control group. Constant 2014 found significant decrease in anxiety level in the SMS group but no difference in negative emotion scores. See Table 4 in Annex Part II.

4.3.4.4. Secondary outcomes

Mobile phone intervention had very high acceptability among the participants. In the 9 studies that evaluated user acceptability of the intervention, over 90% of participants thought the intervention was useful and would like it to continue. In Ybarra 2012, the acceptability was lower, at 69%. See Table 5 in Annex Part II.

The cost of intervention was evaluated in 4 studies. 2 studies on attendance (Chen 2008, Leong 2006) found the SMS reminder cost 0.31 Yuan and RM 0.45 per attendance, more cost-effective than phone call reminder (0.48 Yuan and RM 0.82). 2 studies on education found SMS reminder cost $2.41 per additional HIV tester and €1.67 for asthma patient monitoring. See Table 6 in Annex Part II.

4.3.4.5. Adverse outcomes

Only 4 studies reported adverse events. 2 studies (Constant 2014, Lester 2010) reported there was no adverse event attributable to the intervention. In Ramachandran 2013, 8/271 participants said the SMS disturbed them. Mbuagbaw 2012 reported one female felt it had compromised her undisclosed AIDS status. See Table 7 in Annex Part II.

4.3.5. Publication bias

There was potential publication bias indicated by the asymmetry of the funnel plots, though the number of studies was not sufficient to confirm the bias. Results in this review may bias towards positive effect of the intervention. See Figure 11 and 12 and in Annex Part III.

V. DISCUSSION

We carried out a systematic review on the effect of mobile phone interventions in improving health behaviour and health status in developing countries. We did an extensive search on four electronic databases and included 30 published trials in the review. The included studies were from 3 different continents, 20 from Asia, 8 from Africa and 2 from Latin America, where most of the developing countries are located. They covered 16 different diseases and 7/23 (23%) were on HIV. Since the studies were carried out in different countries and targeting different populations with various disease conditions and of different methodological quality, there was substantial heterogeneity among the studies. Due to the variation in outcome definition and measurement methods, we were only able to pool the results in 3 outcomes: attendance at healthcare appointments, adherence to treatment and KAP scores in education programs. The other outcomes were summarized descriptively.

5.1. Main results

Mobile phone reminder was effective in improving attendance rate compared with no reminder (RR 1.28; 95% CI 1.15 to 1.42; I^2=88%)(8 studies, 5991 participants) The effect of SMS reminder was slightly higher than phone call reminder and it was more cost-effective. SMS reminder improved the adherence to treatment compared with no reminder (RR 1.23; 95% CI 1.05 to 1.45; I^2=63%)(7 studies, 1764 participants). It had a smaller but more robust

effect on adherence to antiretroviral treatment (RR 1.14; 95% CI 1.02 to 1.28; I^2=13%)(4 studies, 1195 participants). Sending SMS in education programs improved the knowledge score (SMD 0.66; 95% CI 0.30 to 1.01; I^2=66%)(3 studies, 387 participants), attitude score (SMD 0.53; 95% CI 0.33 to 0.74; I^2=0%)(3 studies, 387 participants) and practice score (SMD 0.72; 95% CI 0.05 to 1.39; I^2=84%)(2 studies, 243 participants) significantly compared with the control group. There was no strong evidence that SMS intervention had an effect on patient important outcomes such as health behaviour changes or clinical outcomes. Mobile phone intervention had very high acceptability among the participants. Adverse events were rarely reported.

5.2. Strengths

We searched four databases using comprehensive search strategy, identified 4936 citation for selection. Two reviewers independently assessed the citations and reached consensus on the trial selection. We carefully assessed the risk of bias in included studies and did extensive data extraction. Existing reviews included mostly trials from developed countries and focusing on a single disease or a certain type of intervention. Our review targeted developing countries specifically because mobile phone intervention can be a cost-effective way in improving health in resource-limited settings. We did not put limits on disease conditions and types of intervention, thus the review covered all possible aspects of mobile phone interventions in health.

5.3. Limitations

Although all the included studies were RCTs, they were generally of low methodological quality. 25 studies rated as high or unclear risk in more than half of the items in the risk of bias assessment. The heterogeneity among included studies was considerable due to the variation in disease condition, outcome assessment, sample size, etc. The strength of evidence was compromised because of the low quality and heterogeneity of the studies. All the studies focused on surrogate markers and very few reported patient important outcomes. There was potential publication bias which may bias the results towards the positive effects of intervention. The results from this review had to be taken with caution.

VI. CONCLUSION

Results showed that mobile phones could bridge the communication gap between clinicians and patients in developing countries and act as a useful tool to improve attendance rate at clinical appointments, adherence to treatment and effect of education programs. Mass

delivery of SMS by automated computer system is a promising way to improve health behaviour and health status in resource-limited settings.

VII. RECOMMENDATIONS

Better-designed high-quality studies are needed to evaluate the real effect of mobile phone interventions in improving health behaviour and health status. Future studies should use more objective methods to measure outcomes to lower the risk of detection bias caused by lack of participant-blinding. Patient important outcomes and long-term effects of the intervention need to be further investigated. Adverse event reporting and cost-effective evaluation should be included in the reporting. Issues of confidentiality need to be taken into account when designing the trials.

Systematic reviews including both RCTs and observational studies on the effect of mobile phone intervention in health would be worth doing to gather more evidences.

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Annex

Part I. Search strategy

CENTRAL	08 April 2014
In Trials cellular phone[MeSH Terms] OR text messag* OR texting OR short messag* OR multimedia messag* OR multi-media messag* OR mms OR (sms NOT (somatostatin* OR sphingomyelin*)) OR ((messag* OR text* OR voice call* OR phone call*) AND (cellular phone* OR cell phone* OR mobile phone*)):ti,ab,kw	

PubMed	09 April 2014
randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR drug therapy [sh] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract] NOT (animals[MeSH Terms] NOT humans[MeSH Terms]) AND cellular phone[MeSH Terms] OR text messag*[Title/Abstract] OR texting[Title/Abstract] OR short messag*[Title/Abstract] OR multimedia messag* OR multi-media messag*[Title/Abstract] OR mms[Title/Abstract] OR (sms[Title/Abstract] NOT (somatostatin* OR sphingomyelin*[Title/Abstract])) OR ((messag* OR text*[Title/Abstract] OR voice call*[Title/Abstract] OR phone call*[Title/Abstract]) AND (cellular phone*[Title/Abstract] OR cell phone*[Title/Abstract] OR mobile phone*[Title/Abstract] OR mobile telephon*[Title/Abstract] OR wireless phone*[Title/Abstract] OR wireless telephon*[Title/Abstract]))	

EMBASE	09 April 2014
'mobile phone'/exp OR 'wireless communication'/exp OR (text AND messag*) OR 'texting' OR 'texted' OR (short AND messag*) OR (multimedia AND messag*) OR (multi media AND messag*) OR (mms AND (multimedia OR 'multi media')) OR (sms NOT (somatostatin* OR sphingomyelin)) OR (messag* OR text* OR (voice AND call*) OR (phone AND call*) AND (cellular OR cell OR mobile OR wireless) AND (phone* OR telephon*)):ti:ab AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti)	

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cellular phone OR mobile phone OR cellular telephone* OR mobile telephone* OR text messag* OR texting OR texted OR short messag* OR multimedia messag* OR sms OR mms OR phone call* OR voice call* In regional indexes	

Part II. Summary of outcomes tables.

Table 1. Summary of outcomes: behavior changes

Study ID	Country of recruitment	Disease	Follow up time	Intervention	Control	Behaviour Changes	Results
Abdul 2013	Malaysia	cervical cancer	56	SMS	Recall by letter	uptake of pap smear within 8 week after recall	Women who received recall via phone call were more likely to repeat Pap smear (OR=2.38, CI=1.56-3.62). SMS group had no significant increase.
Chai 2013	China	H1N1	20	SMS	No reminder	uptake of H1N1 vaccine	respondents in the H1N1 group had 1.77 times higher odds (95% CI¼1.39, 2.26) of reporting receipt of a 2009 H1N1 vaccination than respondents in the tobacco group on the post-SMS survey.
Odeny 2012	Kenya	HIV	42	SMS	No reminder	early resumption of sexual activity	proportion of men who resumed sex in the SMS group remained slightly higher (248/600; 41.3%) than in the control group (231/600; 38.5%), but the difference was not statistically significant (RR = 1.07, 95% CI: 0.93 to 1.23, P = 0.3).
Tolly 2012	South Africa	HIV	60	SMS	No reminder	tested for HIV or not	All participants who received SMSs are more likely to test for HIV in comparison with the control group, although the odds are not statistically significant.
Ybarra 2012	Turkey	smoking	105	SMS	No reminder	sustained abstinence from smoking 3 months after quit day	Three-month cessation rates, based upon ITT analyses, were statistically similar for the 2 arms: 11% intervention group versus 5% control group (χ21=1.4, P=.24; R2 = 2.0, 95% CI 0.62-6.3)

Table 2. Summary of outcomes: clinical outcomes (adherence)

Study ID	Country of recruitment	Disease	Purpose	Number of participants	Follow up time	Interven-tion	Control	Clinical outcomes	Results
Huang 2013a	China	HIV	Adherence to treatment	196	90	Phone call	No reminder	CD4 count, weight change, WHO clinical staging, and opportunistic infections	There were no statistically significant differences in mean CD4 count, weight change, WHO clinical staging, and opportunistic infections between the intervention and control groups in both treatment-naive and treatmentexperienced patients.
Iribarren 2013	Argentina	TB	Adherence to treatment	37	60	SMS	No reminder	TB status according to medical records	Conversion Rates cannot be compared due to high % of missing data. Treatment success was high in both groups, 17/18 in SMS group and 17/19 in control group completed treatment successfully.
Khonsari 2014	Malaysia	acute coronary syndrome	Adherence to treatment	62	56	SMS	No reminder	Heart functional status, hospital readmission and death rate	There was a highly significant difference in heart functional status between the control and intervention groups, $\chi 2$ (1) = 16.957, $p<0.001$. For the ACS-related readmissions and death rate, the p-value was 0.056 and 0.246.
Mbuagbaw 2012	Cameroon	HIV	Adherence to treatment	200	180	SMS	No reminder	weight, BMI, opportunitistic infections, all cause mortality	There is no significant difference among the two groups for all the clinical outcomes.
Shetty 2011	India	Diabetes	Adherence to treatment	215	365	SMS	No reminder	improved health outcomes measured as HbA1c, other glycaemic measures and lipid profile	Reported only comparison within group, not between groups.
Wang 2014	China	Allergic rhinitis	Adherence to treatment	50	30	SMS	No reminder	severity of AR(self assessed)	improvement in NAR was not significantly different between the control and SMS groups.

Table 3. Summary of outcomes: clinical outcomes (education)

Study ID	Country of recruitment	Disease	Purpose	Number of participants	Follow up time	Interven-tion	Control	Clinical outcomes	Results
Chai 2013	China	H1N1	Education	1998	20	SMS	Attention control	reported influenza like illness	respondents in the H1N1 group had 0.12 times lower odds (95%CI¼0.06, 0.25) of reporting influenza-like illness than those in the tobacco group on the post-SMS survey (after controlling for the difference in knowledge of 2009 H1N1 symptoms between the groups and compared with the pre-SMS survey)
Goodarzi 2012	Iran	type 2 diabetes	Education	100	90	SMS	No reminder	blood glucose, lipids, BUN, creatinin, HbA1C	There was a significant change in HbA1C (p = 0.024), LDL (p = 0.19), cholesterol (p = 0.002), BUN (p ≤ 0/001), micro albumin (p < 0.001) for the exp. group
Lv 2012	China	Asthma	Education	150	84	SMS	No reminder	severity of asthma: FEV; airway inflammation	FEV1%: no significant differences were observed in the change rates among the three groups. There were no significant differences among the three groups in the changes of eosinophil counts and neutrophil counts in blood and sputum
Ramachandran 2013	India	type 2 diabetes	Education	537	NA	SMS	No reminder	incidence of type 2 diabetes, BMI, waist circumference, systolic and diastolic blood pressure, lipid profile	The cumulative incidence of type 2 diabetes was lower in those who received mobile phone messages than in controls (hazard ratio 0·64, 95% CI 0·45–0·92; p=0·015). There was no significant effect on BMI, waist circum-ference, blood pressure, or serum cholesterol and triglycerides, but the effect on HDL cholesterol was significant.
Sharma 2011	India	Dental health	Education	150	28	SMS	No reminder	visible plaque index of children	The VPI score was not significantly different between the two groups, although the SMS group showed a greater decrease in VPI.

Table 4. Summary of outcomes: psychological outcomes

Study ID	Country of recruitment	Disease	Follow up time	Intervention	Control	Behaviour Changes	Results
Cheng 2008	Taiwan, China	serum screening for Down syndrom	21	SMS	No reminder	anxiety level measured using the Spielberger State-Trait Anxiety Inventory (STAI)	The state anxiety scores measured after SMS report sent to SMS group had declined significantly in SMS group.
Constant 2014	South Africa	medical abortion	NA	SMS	No reminder	changes in anxiety, emotional discomfort and stress experienced between baseline and follow-up	anxiety decreased more in the SMS group than in the control group (β=1.3; 95% CI=0.3 to 2.4; p=0.013). Differences in SBNE and IBNE between baseline and follow-up were not significant for the two study groups.
Lv 2012	China	Asthma	84	SMS	No reminder	perceived control of asthma	The mean change of patients' PCAQ-6 score in the SMS group was significantly higher than in the control group (p = 0.018).

Table 5. Summary of outcomes: user evaluation of intervention

Study ID	Country of recruitment	Disease	Number of participants randomised	Outcome Details	Results
Constant 2014	South Africa	medical abortion	469	acceptability of the intervention	186/190 (98%) said that the messages helped them through their abortion, and 188/190 (99%) said that they would recommend them to a friend
Costa 2011	Brazil	HIV	29	Impressions and satisfaction regarding the SMS messages received	Helped to take medications: 11/11 Satisfactory Would like to continue receiving SMS: 10/11 Yes
Huang 2013	Taiwan, China	general	1240	user satisfaction with the intervention	Overall satisfaction with the SMS 4.3/5
Iribarren 2013	Argentina	TB	37	acceptability of SMS intervention	Not evaluated by the participants, but by researchers.
Khonsari 2014	Malaysia	acute coronary syndrome	62	Patients' perception of the applied system	29/31 or 93.5% said the system was useful and 64.5 % felt that it had helped them in taking their medications. Over 80% of participants requested for the SMS reminders to be continued
Lin 2012	China	cataract	258	would like the SMS program to continue or not	132 of 135 (97.8%) of parents in the intervention group reported they would like the SMS program to continue
Ramachandran 2013	India	type 2 diabetes	537	acceptability of intervention	messages were generally welcomed, median score 5 out of 6.
Shetty 2011	India	Diabetes	215	acceptability and the preferred contents of the message	Evaluated by the researcher as highly acceptable based on the number of messages and the frequency requested by the patients.
Ybarra 2012	Turkey	smoking	151	acceptability of the intervenion	41/59 (69%) somewhat or strongly liked the program and 46/59 (78%) somewhat or very likely to recommend the program to others

Table 6. Summary of outcomes: cost of intervention

Main outcome	Study ID	Country of recruitment	Disease	Number of participants randomised	Outcome Details	Results
Attendance	Chen 2008	China	all	1859	cost per attendance	cost per attendance for the SMS group was 0.31 Yuan, for the telephone group was 0.48 Yuan.
Attendance	Leong 2006	Malaysia	All	993	cost of mobile phone reminder	cost per attendance for the SMS group was RM 0.45, for the telephone group was RM 0.82.
Education	Tolly 2012	South Africa	HIV	2553	cost per additional tester	cost per additional tester=$2.41 (SMS)
Education	Ostojic 2005	Croatia	Asthma	16	cost of the monitoring (per week, per patient)	cost of follow-up by SMS was €1.67

Table 7. Summary of outcomes: adverse events

Main outcome	Study ID	Country of recruitment	Disease	Number of participants randomised	Outcome Details	Results
Education	Constant 2014	South Africa	medical abortion	469	Adverse events	No adverse events were associated with the intervention
Education	Ramachandran 2013	India	type 2 diabetes	537	The intervention disturb their daily life or not	8/271 (3%) of people at any review stated that receiving the messages was disturbing them.
Adherence to treatment	Mbuagbaw 2012	Cameroon	HIV	200	Adverse events	One female in the intervention arm felt it had compromised her undisclosed status.
Adherence to treatment	Lester 2010	Kenya	HIV	538	Adverse events	No adverse event directly attributable to the mobile phone SMS communication

Part III. Additional figures.

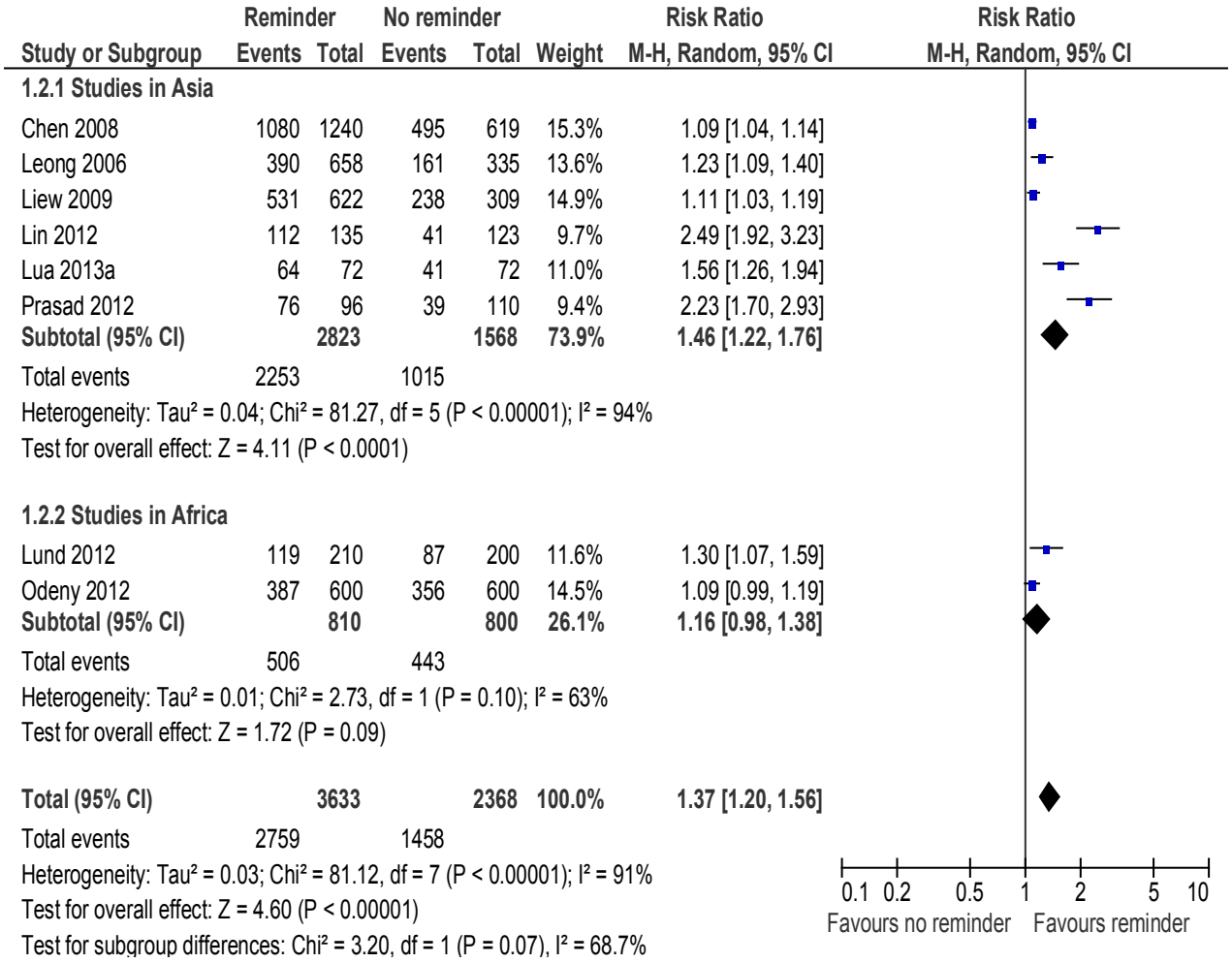

Figure 9. Forest plot of comparison: 1 Mobile phone intervention VS Control, outcome: 1.2 Attendance rate at healthcare appointment. Subgroup analysis according to geographical locations.

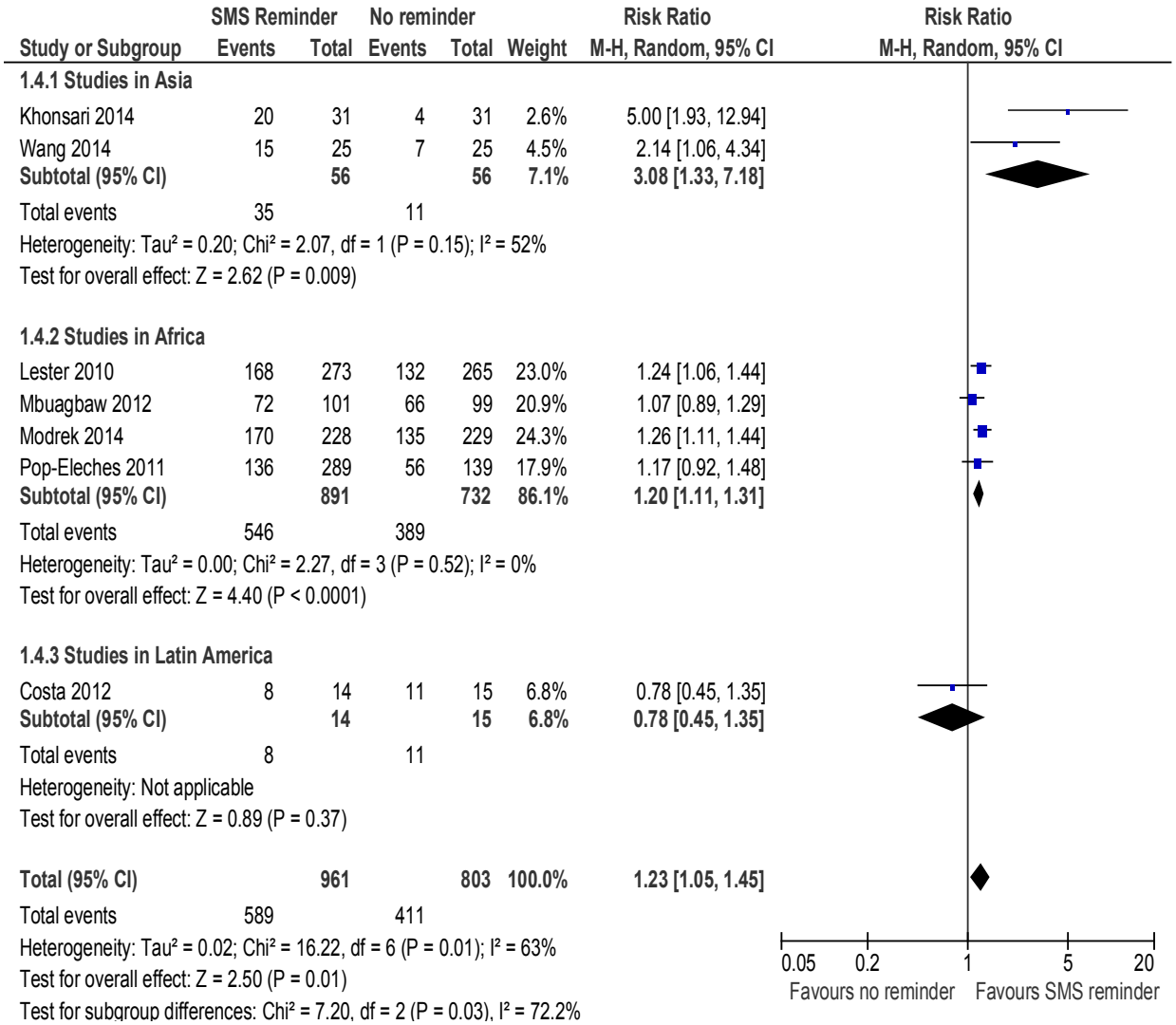

Figure 10. Forest plot of comparison: 1 Mobile phone text message reminder VS no reminder, outcome: 1.4 Adherence to treatment. Subgroup analysis according to geographical locations

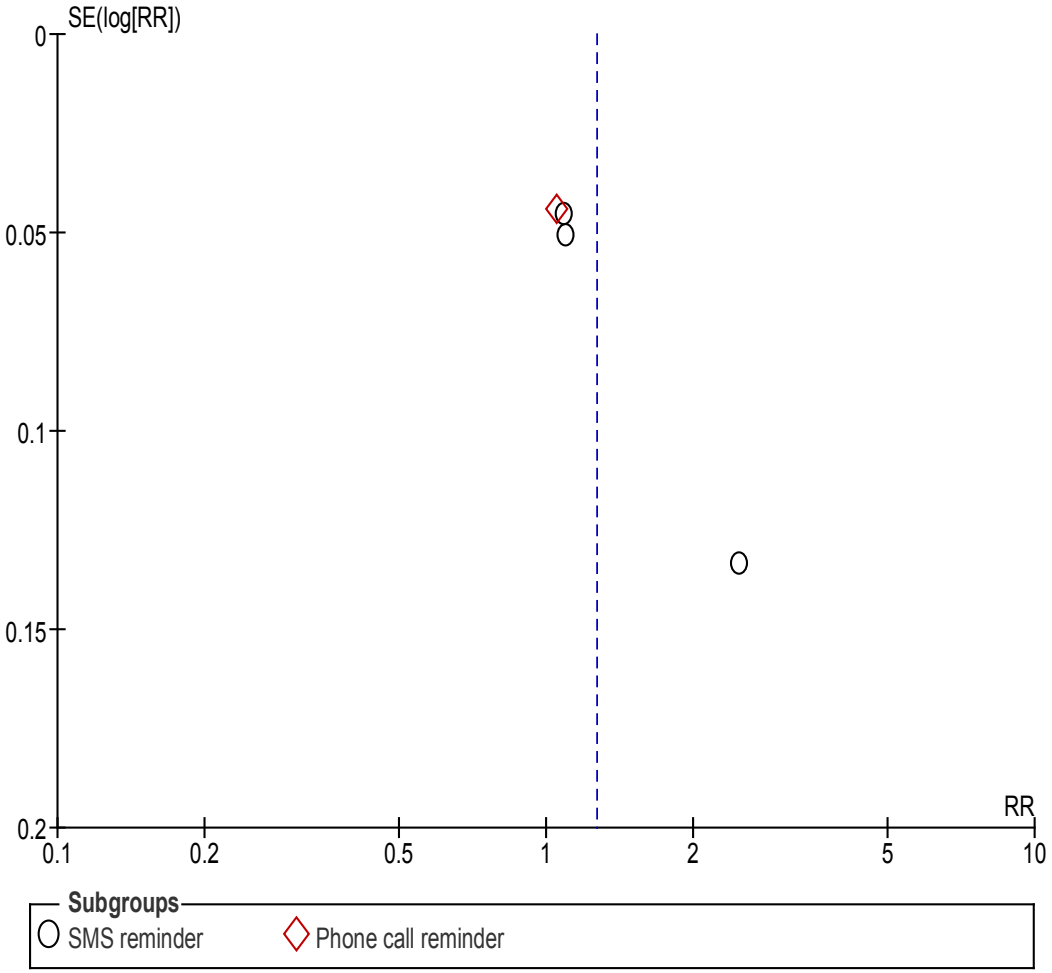

Figure 11. Funnel plot of comparison: 1 Mobile phone intervention VS Control, outcome: 1.1 Attendance rate at healthcare appointment.

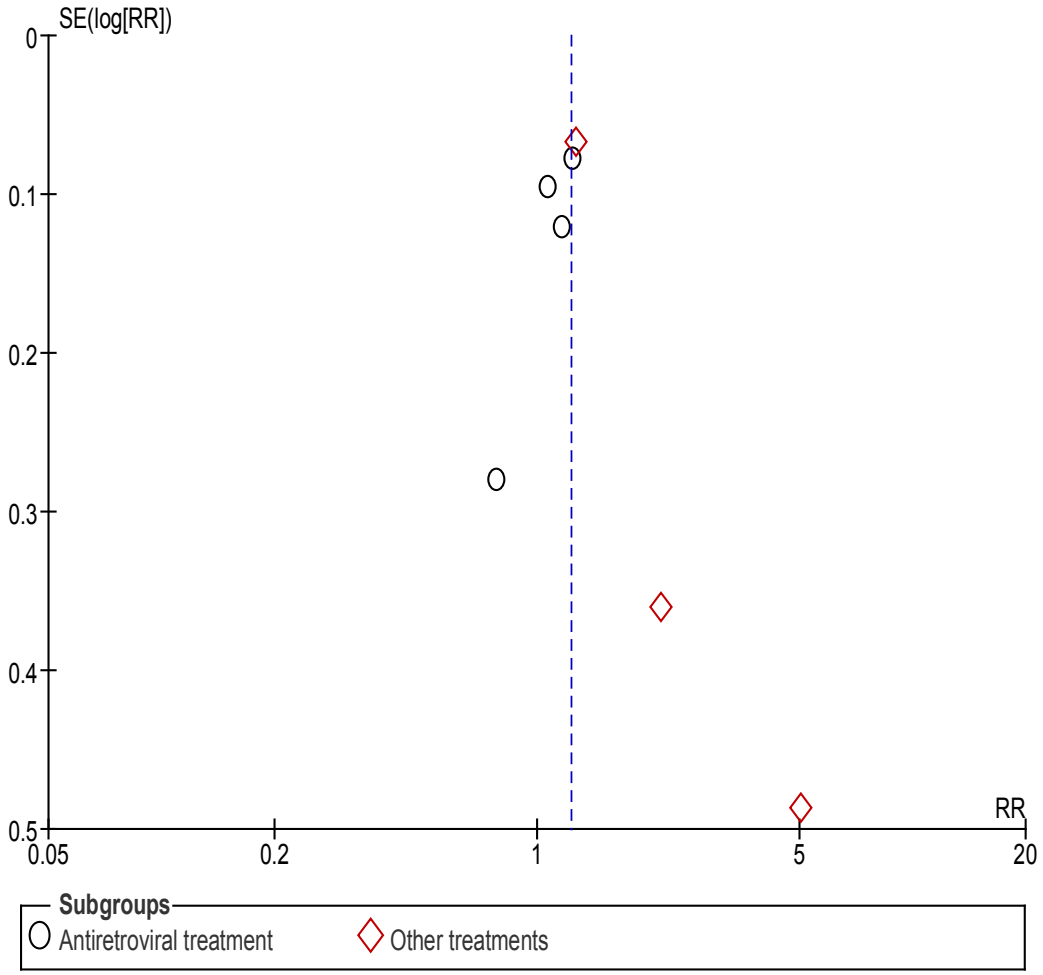

Figure 12. Funnel plot of comparison: 1 Mobile phone intervention VS Control, outcome: 1.3 Adherence to treatment.