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Home Telemonitoring for Type 2 Diabetes

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

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The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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Executive Summary

In June 2008, the Medical Advisory Secretariat began work on the Diabetes Strategy Evidence Project, an evidence-based review of the literature surrounding strategies for successful management and treatment of diabetes. This project came about when the Health System Strategy Division at the Ministry of Health and Long-Term Care subsequently asked the secretariat to provide an evidentiary platform for the Ministry's newly released Diabetes Strategy.

After an initial review of the strategy and consultation with experts, the secretariat identified five key areas in which evidence was needed. Evidence-based analyses have been prepared for each of these five areas: insulin pumps, behavioural interventions, bariatric surgery, home telemonitoring, and community based care. For each area, an economic analysis was completed where appropriate and is described in a separate report.

To review these titles within the Diabetes Strategy Evidence series, please visit the Medical Advisory Secretariat Web site, http://www.health.gov.on.ca/english/providers/program/mas/mas_about.html,

1. Diabetes Strategy Evidence Platform: Summary of Evidence-Based Analyses
2. Continuous Subcutaneous Insulin Infusion Pumps for Type 1 and Type 2 Adult Diabetics: An Evidence-Based Analysis
3. Behavioural Interventions for Type 2 Diabetes: An Evidence-Based Analysis
4. Bariatric Surgery for People with Diabetes and Morbid Obesity: An Evidence-Based Summary
5. Community-Based Care for the Management of Type 2 Diabetes: An Evidence-Based Analysis
6. Home Telemonitoring for Type 2 Diabetes: An Evidence-Based Analysis
7. Application of the Ontario Diabetes Economic Model (ODEM) to Determine the Cost-effectiveness and Budget Impact of Selected Type 2 Diabetes Interventions in Ontario

Objective

The objective of this report is to determine whether home telemonitoring and management of blood glucose is effective for improving glycemic control in adults with type 2 diabetes.

Background

An aging population coupled with a shortage of nurses and physicians in Ontario is increasing the demand for home care services for chronic diseases, including diabetes. In recent years, there has also been a concurrent rise in the number of blood glucose home telemonitoring technologies available for diabetes management. The Canadian Diabetes Association (CDA) currently recommends self-monitoring of blood glucose for patients with type 2 diabetes, particularly for individuals using insulin. With the emergence of home telemonitoring, there is potential for improving the impact of self-monitoring by linking patients with health care professionals who can monitor blood glucose values and then provide guided recommendations remotely. The MAS has, therefore, conducted a review of the available evidence on blood glucose home telemonitoring and management technologies for type 2 diabetes.

Evidence-Based Analysis of Effectiveness

Research Question

Is home telemonitoring of blood glucose for adults with type 2 diabetes more efficacious in improving glycemic control (i.e. can it reduce HbA1c levels) in comparison to usual care?

Literature Search

Inclusion Criteria

- Intervention: Must involve the frequent transmission of remotely-collected blood glucose measurements by patients to health care professionals for routine monitoring through the use of home telemonitoring technology.
- Intervention: Monitoring must be combined with a coordinated management and feedback system based on transmitted data.
- Control: Usual diabetes care as provided by the usual care provider (usual care largely varies by jurisdiction and study).
- Population: Adults ≥18 years of age with type 2 diabetes.
- Follow-up: ≥6 months.
- Sample size: ≥30 patients total.
- Publication type: Randomized controlled trials (RCTs), systematic reviews, and/or meta-analyses.
- Publication date range: January 1, 1998 to January 31, 2009.

Exclusion Criteria

- Studies with a control group other than usual care.
- Studies published in a language other than English.
- Studies in which there is indication that the monitoring of patients' diabetic measurements by a health care professional(s) was not occurring more frequently in intervention patients than in control patients receiving usual care.

Outcomes of Interest

The primary outcome of interest was a reduction in glycosylated hemoglobin (HbA1c) levels.

Search Strategy

A comprehensive literature search was performed in OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, The Cochrane Library, and INAHTA for studies published between January 1, 2007 and January 31, 2009. The search was designed as a continuation of a search undertaken for a systematic review by the Canadian Agency for Drugs and Technologies in Health, originally encompassing studies published from 1950 up until July of 2008 and which reviewed home telemonitoring in comparison to usual care for the management of type 1 and type 2 diabetes.

Summary of Findings

A total of eight studies identified by the literature search were eligible for inclusion (one was excluded post-hoc from analysis). Studies varied considerably on characteristics of design, population, and intervention/control. Of note, few trials limited populations to type 2 diabetics only, thus trials with mixed populations (type 1 and type 2) were included, though in such cases, the majority of patients (>60%) had type 2 diabetes. No studies restricted inclusion or analyses by diabetes treatment type (i.e. populations were mixed with respect to those on insulin therapy vs. not) and studies further varied on whether

intervention was provided in addition to usual care or as a replacement. Lastly, trials often included blood glucose home telemonitoring as an adjunct to other telemedicine components and thus the incremental value of adding home telemonitoring remains unclear. The overall grading of the quality of evidence was low, indicating that there is uncertainty in the findings.

Meta-analysis of the seven trials identified a moderate but significant reduction in HbA1c levels (~0.5% reduction) in favour blood glucose home telemonitoring compared to usual care for adults with type 2 diabetes). Subgroup analyses suggested differences in effect size depending on the type of intervention, however, these findings should be held under caution as the analyses were exploratory in nature and intervention components overlapped between subgroups.

Executive Summary Table 1: Meta-Analyses of Reduction in HbA_{1c} Values for Analyzed Studies

Group	Estimate of effect (95% Confidence Interval)	Statistical Heterogeneity (I^2)
Follow-up values		
All studies	-0.48 [-0.70 to -0.26]	45%
Upload studies	-0.39 [-0.66 to -0.13]	48%
Web entry studies	-0.66 [-0.99 to -0.33]	0%
Change-from-baseline values (ρ=0.5)		
All studies	-0.50 [-0.80 to -0.19]	65%
Upload studies	-0.26 [-0.55 to 0.02]	45%
Web entry studies	-0.78 [-1.14 to -0.43]	0%
Change-from-baseline values (ρ=0.65)		
All studies	-0.52 [-0.82 to -0.21]	73%
Upload studies	-0.25 [-0.51 to 0.01]	46%
Web entry studies	-0.78 [-1.08 to -0.48]	0%
Change-from-baseline values (ρ=0.85)		
All studies	-0.54 [-0.84 to -0.24]	85%
Upload studies	-0.21 [-0.41 to 0.00]	47%
Web entry studies	-0.81 [-1.11 to -0.51]	49%

Conclusions

1. Based on low quality evidence, blood glucose home telemonitoring technologies confer a statistically significant reduction in HbA1c of ~0.50% in comparison to usual care when used adjunctively to a broader telemedicine initiative for adults with type 2 diabetes.
2. Exploratory analysis suggests differences in effect sizes for the primary outcome when analyzing by subgroup; however, this should only be viewed as exploratory or hypothesis-generating only.
3. Significant limitations and/or sources of clinical heterogeneity are present in the available literature, generating great uncertainty in conclusions.
4. More robust trials in type 2 diabetics only, utilizing more modern technologies, preferably performed in an Ontario or a similar setting (given the infrastructure demands and that the standard comparator is usual care), while separating out the effects of other telemedicine intervention components, are needed to clarify the effect of emerging remote blood glucose monitoring technologies.

Background

In June 2008, the Medical Advisory Secretariat began work on the Diabetes Strategy Evidence Project, an evidence-based review of the literature surrounding strategies for successful management and treatment of diabetes. This project came about when the Health System Strategy Division at the Ministry of Health and Long-Term Care subsequently asked the secretariat to provide an evidentiary platform for the Ministry's newly released Diabetes Strategy.

After an initial review of the strategy and consultation with experts, the secretariat identified five key areas in which evidence was needed. Evidence-based analyses have been prepared for each of these five areas: insulin pumps, behavioural interventions, bariatric surgery, home telemonitoring, and community based care. For each area, an economic analysis was completed where appropriate and is described in a separate report.

To review these titles within the Diabetes Strategy Evidence series, please visit the Medical Advisory Secretariat Web site, http://www.health.gov.on.ca/english/providers/program/mas/mas_about.html,

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6. Home Telemonitoring for Type 2 Diabetes: An Evidence-Based Analysis
7. Application of the Ontario Diabetes Economic Model (ODEM) to Determine the Cost-effectiveness and Budget Impact of Selected Type 2 Diabetes Interventions in Ontario

Objective

To determine whether home telemonitoring and management of blood glucose is more efficacious in improving glycemic control for adults with type 2 diabetes in comparison to usual care.

Clinical Need and Target Population

Health care services delivered to patients through home care constitutes an integral part of any chronic disease management model. Due to the rapid emergence of new technologies and an aging population, demand for such services has surged in recent years. Health care providers are struggling to meet the demand of this aging population, with nurse and physician shortages being reported throughout the developed world. According to a 2002 Canadian Nursing Association (CNA) study, it is anticipated that there will be a shortage of 78,000 registered nurses (RN) in Canada by 2011 and a shortage of 113,000 RNs by 2016. (1) Similarly, a 2008 Survey by the Ontario College of Physicians (OCP) estimated that 663,000 to 879,000 Ontarians are currently without a family physician. (2)

Emerging technology platforms such as videoconferencing, teleconferencing, cellular services and the Internet allow health care providers to deliver home care services remotely (known as telemedicine or

telehealth; see Definitions below). While telemedicine is not intended to replace professional health care, it can enhance current care and has the potential to improve access, quality of life (QOL), relevant disease endpoints, patients' feelings of independence and control, and costs compared with usual care for various chronic diseases.

Paralleling the rise in chronic diseases is the rise in the number of remote monitoring technologies (collectively referred to as 'home telemonitoring technologies') for the monitoring of self-measured blood glucose. Modern blood glucose monitors are commonly equipped with wireless technology and/or are capable of linking-up with modems, enabling users to transmit self-measured blood glucose readings to health care providers or third-party handlers synchronously (in real-time) or asynchronously (when instructed) via the Internet or via telephone/cellular lines.

The Canadian Diabetes Association (CDA) currently recommends self-monitoring of blood glucose (SMBG), with testing at least once per day at variable times, for patients with type 2 diabetes on once-daily insulin (Grade D evidence or consensus based). (3) This recommendation is in concordance with the American Diabetes Association (ADA), although the level of evidence is cited by the ADA as strong (Grade A). (4) Greater uncertainty surrounds SMBG for patients not on insulin. While previous systematic reviews have identified a modest reduction in glycosylated haemoglobin (HbA_{1c}) levels for patients practicing SMBG in comparison to patients not participating in self-monitoring (5;6), most reviewed studies included SMBG as a part of wider self-management initiative. This makes it difficult to separate out the incremental effect of SMBG from other interventional components. Therefore, while the CDA and ADA recommend SMBG for type 2 diabetics, it is recommended only as a means of achieving individualized glycemic goals. (3;4)

With remote data transmission having opened the possibility of adjunctive monitoring of blood glucose levels by a health care professional, there is room for even greater improvement to potentially reach a wider patient base with immediate, guided medicinal and lifestyle recommendations. Such technologies may improve HbA_{1c} levels and other endpoints beyond the levels achieved by simple patient self-monitoring. The Medical Advisory Secretariat (MAS), therefore, set out to review the evidence for home blood glucose telemonitoring technologies for type 2 diabetes.

Definitions

To ensure consistency, it is necessary to define several terms used in this paper.

Telemedicine: Telemedicine (or telehealth) refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education and health-related administrative services. (4;7)

Telehealth: Although evolving, telemedicine is often associated with direct patient clinical services and telehealth is associated with a broader definition of remote healthcare and perceived to be more focused on other health-related services. (8)

Telemonitoring: Telemonitoring (or remote monitoring) refers specifically to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of such data to a monitoring station for interpretation by a physician or third-party assistant. For the purposes of this review, telemonitoring technologies include wireless and modem-compatible blood glucose monitors (herein identified as "upload" devices) that can automatically upload blood glucose readings at the request of the user via Internet or telephone/cellular lines. Also included are "web entry" technologies consisting of websites to which patients enter self-measured biological health data. With both web entry and upload technologies, the onus for data transmission is on the patient (i.e. similar data upload mechanisms are involved).

Also inherent within this definition of telemonitoring is the notion of associated management, that is, timely feedback by health care professionals (those doing the monitoring) to patients based on remotely monitored blood glucose data. Feedback can include guided medicinal or lifestyle recommendations and can be conducted via email, instant messaging, telephone, videoconferencing, cellular phone or SMS text messaging.

HbA_{1c} as a Predictor of Diabetes Complications

Data from the United Kingdom Prospective Diabetes study (UKPDS) has shown that tight glycemic control can significantly reduce the risk of developing serious complications in type 2 diabetics (9). The study demonstrated that for every 1.0 % absolute decrease in HbA_{1c} (a measure of averaged glycosylated haemoglobin levels) there is a 14% relative decrease in all-cause mortality, a 14% relative decrease in myocardial infarction, and a 37% relative decrease in micro-vascular endpoints associated with diabetes. Accordingly, and despite the range of other outcomes examined in diabetes interventions (blood pressure, weight loss, lipid control), the success of diabetes interventions is most widely measured by HbA_{1c}.

Evidence-Based Analysis

Research Question

Is home telemonitoring of blood glucose for adults with type 2 diabetes more efficacious in improving glycemic control (can it reduce HbA_{1c} levels) in comparison to usual care?

Literature Search

Inclusion Criteria

- Intervention: Must involve the frequent transmission of remotely-collected blood glucose measurements by patients to health care professionals for routine monitoring through the use of home telemonitoring technology.
  - Transmission should be made via medical telemonitoring device that can transmit data wirelessly or by modem uplink, or via Internet applications by which patients physically enter self-measured data.
  - This monitoring must be a population-defining element unique to intervention patients.
- Intervention: Monitoring must be combined with a coordinated management and feedback system based on transmitted data.
  - Management and feedback may proceed via telephone, Internet, cellular phone or in person.
  - Feedback should involve medicinal advice (e.g., insulin adjustments) or lifestyle advice (e.g., diet and physical exercise) or a combination of both.
- Control: Usual diabetes care as provided by the usual care provider (usual care largely varies by jurisdiction and study).
- Population: Adults ≥18 years of age with type 2 diabetes (authors of trials which did not specify diabetic type were contacted to determine percentage of type 2 diabetics).
- Follow-up: ≥6 months.
- Sample size: ≥30 patients total.
- Publication type: Randomized controlled trials (RCTs), systematic reviews, and/or meta-analyses.
- Publication date: January 1, 1998 to January 31, 2009.

Exclusion Criteria

- Studies with a control group other than usual care.
- Studies published in a language other than English.
- Studies in which there is indication that the monitoring of patients' diabetic measurements by a health care professional(s) was not occurring more frequently in intervention patients than in control patients receiving usual care (increased monitoring is a key concept of any diabetic telemonitoring intervention).

Outcomes of Interest

- Primary outcome: Glycemic control (i.e., reduction in GHb, HbA or HbA_{1c})

Subgroup Analyses

- Defined a priori.
- By telemonitoring intervention type (wireless/modem-capable blood glucose monitor vs. website data entry).

Search strategy

A comprehensive literature search was performed in OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), The Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published between January 1, 2007 and January 31, 2009. The search strategy is detailed in Appendix 1. The search was designed as a continuation of a search undertaken for a systematic review by the Canadian Agency for Drugs and Technologies in Health (CADTH) (10), originally encompassing studies completed from 1950 up until July of 2008, and which reviewed home telemonitoring in comparison to usual care for the management of type 1 and type 2 diabetes. The additional overlap in time period (January 2007 to July 2008) was meant to account for any lags associated with OVID's publication entry process. The search was not limited to diabetes type 2, as trials often fail to report specific diabetic type in regards to their study populations.

Abstracts were reviewed and studies meeting the inclusion criteria outlined above were obtained. Reference lists were also hand-checked for relevant studies.

HbA_{1c} outcomes from individual studies were meta-analyzed using RevMan 5.0 by the Cochrane Collaboration using a random-effects model to account for between-study differences. Methods for calculating standard deviations for intra-group changes from baseline to final in HbA_{1c} levels are described below (see Statistical Challenges – Meta-analysis below).

Assessment of Quality of Evidence

The quality assigned to individual studies was determined using the MAS' adaptation of the levels-of-evidence hierarchy proposed by Goodman. (11) The overall quality of the evidence was examined according to the GRADE Working Group criteria (see Appendix 2). (12)

- Quality refers to criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the decision about whether an important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest, i.e., the generalizability of the interventions and outcomes.

Table 1 outlines the definitions used in grading the quality of the evidence, as stated by the GRADE Working Group.

Table 1: GRADE criteria defined

Level of Evidence	Definition
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Statistical Challenges – Meta-Analysis

Meta-analyzing pre-post continuous measurements, such as HbA_{1c}, values presents statistical challenges as studies quite often report only baseline (pre) and final values (post) for intervention and control groups, without reporting change-from-baseline values. While the absolute difference between pre and post can be easily calculated (final value minus baseline value), the standard deviation of this intra-group difference, necessary for meta-analysis, is often lacking.

To clarify the statistical challenges relevant to this report, it is important to define some terms:

- The *intra-group change from baseline to final* refers to the mean difference between baseline and final values **within** intervention or **within** control groups (i.e. the difference in pre and post measurements within groups).
- The *inter-group difference* refers to the mean difference in intra-group change from baseline to final (as defined above) **between** intervention and control (i.e. the difference in change-from-baseline values between groups).

To solve the problem of missing standard deviations, the Cochrane Handbook for Systematic Reviews has identified two solutions (http://www.cochrane-handbook.org/), both of which should be explored in any meta-analysis:

1. *Meta-analyze only the inter-group difference in mean final values between intervention and control.* This approach assumes that the inter-group difference in mean final values will be similar to the inter-group difference of the intra-group change from baseline to final if baseline values do not significantly differ between intervention and control. One can test for significant differences at baseline — if they do not differ, this approach is valid.
2. *Use statistical calculations to derive the standard deviations for the intra-group change from baseline to final, then meta-analyze these data.* Repeated (pre and post) measurements made on the same participants tend to be correlated, thus lowering standard errors and creating tighter confidence intervals in comparison to single measurements. A correlation coefficient quantifies this correlation between repeated measurements. This lowering of standard errors explains why meta-analyzing the change-from-baseline values is favourable to meta-analyzing final values only, particularly if there are significant differences between intervention and control at baseline. There are two ways to derive the standard deviations for the intra-group change from baseline to final when information is lacking:
    a. Derive the standard deviation of the intra-group change from baseline to final using P-values, confidence intervals, or standard errors reported from a t-test of the intra-group change from baseline to final. A study which does not report standard deviations for the intra-group change from baseline to final, however, is unlikely to report relevant t-test values. This approach is, therefore, rare.

b. Calculate the standard deviation of the intra-group change from baseline to final by imputing a correlation coefficient. Correlation coefficients can be calculated from studies that report all relevant data (baseline ±SD, final ±SD, intra-group difference ±SD). These correlation coefficients can then be applied to studies lacking relevant information to derive appropriate standard deviations. Alternatively, one can impute varying correlation coefficients and run multiple sensitivity meta-analyses to observe any changes in effect. It is of importance, however, to note that imputation of various values has been historically shown to have little effect on the summary estimates and conclusions of a meta-analysis. (13;14)

For this particular report, both final values and change-from-baseline values were meta-analyzed. Standard deviations for change-from-baseline values were generated by imputing varying correlation coefficients of 0.5, 0.75, and 0.85 and observing the effect on summary estimates and statistical heterogeneity. This range (0.5–0.85) was arbitrarily chosen around a calculated correlation coefficient of 0.64, which was derived from information provided by the authors of the trial by Ralston et al. (15) It should be noted that decreasing the correlation coefficient will result in a more conservative summary estimate, as this will increase trial standard deviations, subsequently resulting in a widening of confidence intervals around individual trial effect sizes and yielding a slight decrease in the overall summary effect size. Choosing a smaller correlation coefficient will also decrease overall statistical heterogeneity by widening confidence intervals.

Studies Included for Meta-Analysis

Most studies reported sufficient information around the primary outcome of HbA_{1c} to allow for inclusion in meta-analysis. Contact with the authors of the trial by Ralston et al. (15) was necessary to obtain relevant standard deviations for trial inclusion. One trial was excluded from meta-analysis post-hoc [Yoon and Kim (16)] for several reasons:

1. Including the trial in meta-analysis introduced excessive statistical heterogeneity (see Figure A6, Appendix 3);
2. The trial was an extreme outlier (confidence intervals did not even span the summary estimate; Figure 6, Appendix 3);
3. The trial's usual care group's HbA1c levels actually rose 0.81%, indicating that usual care was somehow compromised in comparison to the other trials (the authors did not reply to requests for an explanation or additional information); and
4. The trial involved identical authors and setting, and near identical, overlapping recruitment periods as the trial by Kim and Kim (17) (authors did not confirm or deny whether patient populations overlapped).

Figure A6 in Appendix 3 presents a sensitivity analysis with the trial by Yoon and Kim included (comparable to Figure A3 in Appendix 3 with the trial excluded).

Results of Evidence-Based Analysis

The CADTH report (10) identified 26 studies that met the inclusion criteria. While several systematic reviews and/or meta-analyses were identified (summarized in Table 3), no systematic review met the inclusion criteria of this study, making all systematic reviews inapplicable to the current analysis. A total of 17 of the 26 identified studies were identified as RCTs. (18-34) These were used as a basis of the complete literature available for inclusion up to 2007 in this review.

Of those 17 RCTS identified by CADTH, four studies were excluded as they examined only patients with type 1 diabetes (19;21;23;27), two trials were excluded on the basis of small sample sizes (n<30) (18;26), three trials were excluded on the basis of short follow-up (less than six months) (22;29;30), and five were excluded on the basis of inappropriate intervention (primarily telephone support initiated by health care provider) (24;31-34), leaving three studies for inclusion into this systematic review (20;25;28). Back-searching of references identified one trial for inclusion (35) and another trial that was excluded for focusing on type 1 diabetics only (36).

The updated database search identified 499 citations published between January 1, 2007 and January 31, 2009. Of these, 46 were retrieved in full text and of those full texts, three articles initially deemed relevant were later excluded: two on the basis of short follow-up (less than six months) (37;38) and one on the basis of inappropriate intervention (telephone support initiated by health care provider). (39) Four additional trials met the inclusion criteria for this review (15-17;40). The included trial by Yoon and Kim (16) had been reported twice previously (41;42) and thus only the most updated version of the report was included. To summarize, eight trials were included for systematic review (15-17;20;25;28;35;40); the level of evidence for each of these is displayed in Table 2.

Table 2: Level of Evidence of Included Studies

Study Design	Level of Evidence*	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	1
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	7
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

Adapted from the Oxford Centre for Evidence. (11) An additional designation "g" was added for preliminary reports of studies that have been presented at international scientific meetings.

Abbreviations: RCT, randomized controlled trial; Non-RCTs, non-randomized controlled trial (e.g., a cohort study);

Summary of Existing Evidence

Table 3 summarizes the existing evidence-based reviews relevant to home telemonitoring for type 2 diabetes. As previously indicated, no single review met the inclusion criteria of this paper, thus justifying the need for this review. In general, the inclusion criteria of previous reviews were overly sensitive, the literature base consisted largely of observational trials and was incomplete, no review separated out type 2 diabetes, and the methods used for meta-analyses were largely inappropriate.

Table 3: Summary of Existing Evidence on Home Telemonitoring for Diabetes

Study (Year)	Type of Trial # of Trials Search Years	Focus of Review	Applicability to MAS analysis
DelliFraine and Dansky (2008) (43)	SR+MA 6 trials 2001–2007	Home-based telehealth for chronic diseases including diabetes.	Low; few trials identified, mixed diabetic populations.
Tran et al. (2008) (10)	SR+MA 26 trials 1998–2008	Home telehealth for chronic diseases including diabetes.	Moderate; MA used questionable methods, lax inclusion criteria, but literature base considered complete.
Barlow (2007) (44)	SR 34 trials ?-2006	Home telecare for frail elderly people and those with long-term conditions including diabetes.	Low; No MA, very little analysis and interpretation.
Garcia-Lizana and Sarria-Santamaria (2007) (45)	SR 7 trials 1995-2005	Information and communication technologies for managing chronic diseases including diabetes.	Low; No MA, few trials identified.
Pare et al. (2007) (46)	SR 17 trials 1991–2006	Home telemonitoring of patients with diabetes.	Low; No MA, trials largely observational.
Verhoeven et al. (2007) (47)	SR+MA 39 trials 1994–2006	The use of information and communication technology for the management of diabetes with focus on teleconsultation and videoconferencing.	Low; Focus is on teleconsultation and videoconferencing; little relevance to telemonitoring.
Jaana and Paré (2007) (48)	SR 17 trials 1991-2005	Home telemonitoring of patients with diabetes.	Low; No MA, trials largely observational.
Farmer et al. (2005) (49)	SR+MA 26 trials 1966–2004	All telehealth interventions to support blood glucose self-monitoring in diabetes.	Low; MA used questionable methods, lax inclusion criteria, studies with type 1 diabetics included, and older trials.
Balas et al. (2004) (50)	SR + MA 30 trials Not clear (1976–?)	Automated information interventions on diabetes care and patient outcomes.	Low; trials largely observational, mixed diabetic populations.
Montori et al. (2004) (51)	SA+MA 8 trials 1982–2003	Modem transmission of self-monitored blood glucose values in patients with type 1 diabetes	Low; type 1 diabetes only.

Summary of Findings of Literature Review

Appendix 2 summarizes study design, population, and quality characteristics for all included studies.

Summary of Demographics

A total of 2,269 patients were included across the eight identified studies. The reported mean age of participants across trials ranged from 45.5 – 71.0 years, with one study recruiting participants age 55 or older (25) and one recruiting participants age 60 or older. (40) Four of the eight trials (15-17;25;35) limited participants to type 2 diabetics with three of these four (16;17;25;35) being conducted by the same authors in the same setting. The remaining four trials were conducted in mixed diabetic populations (type 1 and type 2). Communications with study authors revealed 87% participants had type 2 diabetes in the trial by Bond et al. (40) and 61% in the trial by Harno et al. (20). Authors for the two remaining trials indicated that study prevalence of type 2 diabetes was likely similar to the population prevalence (~90%) (25;28). Roughly 18% of the entire patient sample were regular insulin users (either alone or with oral medication); however, insulin use in individual study groups varied from 14.5–52%.

Summary of Intervention Characteristics

Additional components of telemedicine were evident across the majority of trials such as videoconferencing, web-based education, and remote monitoring of other biologic (e.g., blood pressure) or lifestyle (e.g., physical activity and diet) measures. Four trials utilized a modem-compatible blood glucose monitor (15;20;25;28), while the other four utilized web-entry of self-measured blood glucose values. (16;17;35;40) All, however, used some form of website or web application, indicating that subgroup analysis was potentially inappropriate (due to overlapping intervention characteristics).

All website entry trials reported that intervention was given in addition to usual care (16;17;35;40). Two studies provided intervention patients with web-enabled computers to carry out the intervention (25;28). All trials reported a feedback or management system by health care professionals via email, instant messaging, telephone, videoconferencing, cellular phone or SMS text messaging.

The number and specialty of health care professionals involved in the intervention differed between trials with little consistency. Trials employed anywhere from one to three health care professionals including case managers, nurses, primary care physicians, dieticians, certified diabetes educators, endocrinologists and professors of nursing.

Frequency of data transmission was poorly reported; however, in this report, it was assumed to be occurring more frequently than visits in the usual care group, unless otherwise specified. Studies reporting frequency noted that data transmission occurred at least monthly, but more likely once per week. (15-17;35) Additional training was often provided to the intervention group on using or understanding the intervention. (15;17;28;35) It is unclear, however, what other components were included in these education sessions. Therefore, some confounding influence may be present, for example, if the intervention group received additional education on proper self-measurement and control of blood glucose.

The duration of intervention equated to length of follow-up (as the intervention was continuous) and ranged from 6 to 30 months.

Summary of Control Characteristics

Control was unanimously reported as usual care across trials, but the providers of usual care differed between studies: internal medicine physician, endocrinologist, primary care physician, or "usual provider." When reported, the frequency of face-to-face consults with usual care providers ranged from two to three consultations per month. Additional care and access to other specialists or education was often available at request or as necessary. The frequency of use of additional services was not reported.

Summary of Outcome Characteristics

All studies reported decline in HbA_{1c} as a primary outcome of assessment.

Quality of the Evidence

Overall, the body of evidence was downgraded from high to low according to study quality and issues with directness as identified using the GRADE quality assessment tool (see Table 4). While blinding of patient to intervention/control is not feasible in blood glucose home telemonitoring trials, blinding of study personnel during outcome assessment and allocation concealment were generally lacking. Further, a statistical imbalance in the number of patients lost to follow-up was evident (data not shown). While trials reported consistent outcomes, the directness or generalizability of studies, particularly with respect to the generalizability of intervention, was questionable as most trials used blood glucose home telemonitoring technologies in concert with other telemedicine intervention components. In addition, the usual care experience and telemonitoring infrastructure may not be generalizable to the Ontario context as these components are highly regional-specific. Lastly, as reported in the Summary of Demographics above, trials included mixed diabetic populations (type 1 and type 2). Populations were further mixed with respect to the percentage of those on insulin therapy. The latter point is important as current recommendations for self-monitoring differ depending on insulin therapy status. (3) These above sources of clinical heterogeneity make it particularly difficult to draw definitive conclusions for adults with type 2 diabetes.

Table 4: GRADE quality assessment for all included studies

Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Effect Size	Overall Quality
Ralston et al. 2009 (15)	RCTs	Lack of allocation concealment and blinding. Statistical imbalance in number of patients lost to follow-up in some trials. Small sample sizes for web entry studies increase the chance that findings are false positive.		Generalizability of intervention in question. Difficult to separate out the effects of strict glucose monitoring vs. other facets of a multi-faceted telehealth intervention. Usual care may not be generalizable to the Ontario experience. Mixed diabetic populations. Mixed populations with respect to insulin therapy.	None	-1.10	
Kim and Kim 2008 (17)						-1.09	
Bond et al. 2007 (40)						-0.57	
Yoon and Kim 2007 (16)						-0.9	**LOW**
Cho et al. 2006 (35)						-0.12	
Harno et al. 2006 (20)						-0.13	
Shea et al. 2006 (25)						-0.40	
McMahon et al. 2005 (28)	**HIGH**	**MODERATE**	**MODERATE**	**LOW**	**LOW**	-1.10	

Abbreviations: RCT, randomized controlled trial.

Summary of Meta-Analyses

The results of meta-analyses on the reduction of HbA_{1c} values for the included studies are summarized in Table 5 (individual forest plots are presented in Appendix 3). As reported in the Methods section, the trial by Yoon and Kim (16) was excluded from meta-analysis.

Meta-analyses of follow-up HbA_{1c} values (Figures 3 – 5, Appendix 3) were consistent with the meta-analysis of change-from-baseline values (Figure 2, Appendix 3) with both sets of analyses suggesting a moderate (~0.5%) reduction in HbA_{1c} values for all blood glucose home telemonitoring technologies in comparison to usual care. Changing the correlation coefficient (ρ) used for imputation during meta-analyses of change-from-baseline values (Figures 3–5, Appendix 3) had little effect on summary estimates; however, increasing the correlation coefficient introduced greater statistical heterogeneity (as expected) by narrowing confidence intervals. This introduced less overlap between individual estimates of effect. Even with a conservative correlation coefficient of 0.5, statistical heterogeneity was high (I^2 of 65%) (Figure 3, Appendix 3).

Subgroup analyses suggested differences in HbA_{1c} reduction between intervention types — modem-capable blood glucose monitors and website entry of self-measured data — when compared to usual care (Figures 2 – 5, Appendix 3). Yet these analyses are difficult to interpret because of the similarity of intervention components (e.g. all study interventions utilized some type of website or web application component) and the possibility of confounding influences present in web entry studies, as all such studies used web entry intervention in addition to usual care while only one upload study reported intervention in addition to usual care. Studies in the web entry subgroup also suffered from notably smaller sample sizes and there is thus an increased chance that their finding of greater effect is exaggerated. For these reasons, the subgroup analyses should only be viewed as exploratory and hypothesis-generating.

Table 5: Results of meta-analyses of studies examining reduction in HbA_{1c} through home telemonitoring in comparison to usual care in adults with type 2 diabetes.

Group	Estimate of effect [95% Confidence Interval]	Statistical Heterogeneity (I^2)
Follow-up values		
All studies	-0.48 [-0.70 to -0.26]	45%
Upload studies	-0.39 [-0.66 to -0.13]	48%
Web entry studies	-0.66 [-0.99 to -0.33]	0%
Change-from-baseline values (ρ=0.5)		
All studies	-0.50 [-0.80 to -0.19]	65%
Upload studies	-0.26 [-0.55 to 0.02]	45%
Web entry studies	-0.78 [-1.14 to -0.43]	0%
Change-from-baseline values (ρ=0.65)		
All studies	-0.52 [-0.82 to -0.21]	73%
Upload studies	-0.25 [-0.51 to 0.01]	46%
Web entry studies	-0.78 [-1.08 to -0.48]	0%
Change-from-baseline values (ρ=0.85)		
All studies	-0.54 [-0.84 to -0.24]	85%
Upload studies	-0.21 [-0.41 to 0.00]	47%
Web entry studies	-0.81 [-1.11 to -0.51]	49%

Conclusions

1. Based on low quality evidence, blood glucose home telemonitoring and management technologies confer a statistically significant reduction in HbA1c of ~0.50% when used adjunctively to a broader telemedicine initiative in comparison to usual care in adults with type 2 diabetes.

2. Regarding Subgroup analyses:
   - Exploratory analysis seems to suggest differences in effect sizes for the primary outcome when analyzing by subgroup; however, subgroup analyses are difficult to interpret given similarities in intervention and possible confounders (e.g. web entry intervention given in addition to usual care in all web entry studies);
   - Subgroup analysis should therefore be viewed as exploratory or hypothesis-generating.

3. Significant limitations and/or sources of clinical heterogeneity are present in the available literature, thus generating great uncertainty in conclusions, specifically:
   - Lack of allocation concealment and blinding,
   - Imbalance in numbers lost to follow-up,
   - Cannot separate out effects of other telemedicine intervention components,
   - Intervention in addition to usual care or replacing,
   - Mixed populations with respect to intervention delivery being in addition to usual care or replacing,
   - Mixed diabetic populations,
   - Mixed populations on insulin,
   - Usual care and technology/infrastructure may not be generalizable to Ontario experience.

4. More robust trials in type 2 diabetics only, utilizing more modern technologies, preferably performed in an Ontario or similar setting (given the infrastructure demands and that the standard comparator is usual care), while separating out the effects of other telemedicine intervention components, are needed to clarify the effect of emerging remote blood glucose monitoring technologies.

Appendices

Appendix 1: Literature Search Strategies

Final Search Strategy – Home telemonitoring for type 2 diabetes

Search date: January 30, 2009
Databases searched: MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library (all via OVID); Ebsco CINAHL, CRD/INAHTA

Database: Ovid MEDLINE(R) <1996 to January Week 3 2009>
Search Strategy

1 exp Diabetes Mellitus/ (114392)
2 (diabetes or diabetic* or NIDDM or IDDM or MODY).ti,ab. (150836)
3 1 or 2 (167013)
4 exp Telecommunications/ (23089)
5 exp Computer Communication Networks/ (35636)
6 (telematic or tele-matic or telemanagement or tele-management or telenursing or tele-nursing or telerehab* or tele-rehab* or teleservic* or tele-servic* or telemedic* or tele-medic* or telehealth or tele-health or telecare or tele-care or tele-home or telehome or telemonitor* or tele-monitor* or telecommunication* or tele-communication* or teleconferenc* or tele-conferenc* or tele-consult* or teleconsult* or email or e-mail or electronic mail or online or web or web-based or internet or internet-based or e-health or ehealth or telephone or videoconferenc* or video-conferenc*).mp. (81258)
7 ((remote or wireless or mobile or cellular or telephone) adj2 (monitor* or consult* or manag*)).mp. (3635)
8 or/4-7 (94434)
9 3 and 8 (1948)
10 limit 9 to (english language and humans and yr="2007 - 2009") (435)
11 limit 10 to (controlled clinical trial or meta analysis or randomized controlled trial) (80)
12 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (35585)
13 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (650)
14 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (67644)
15 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (380904)
16 exp Double-Blind Method/ (54040)
17 exp Control Groups/ (823)
18 exp Placebos/ (9446)
19 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (96228)
20 or/11-19 (490445)
21 20 and 10 (143)

Database: EMBASE <1980 to 2009 Week 05>
Search Strategy

1 exp Diabetes Mellitus/ (237565)
2 exp Diabetic Patient/ (2727)
3 (diabetes or diabetic* or NIDDM or IDDM or MODY).ti,ab. (220746)
4 or/1-3 (276058)
5 exp telecommunication/ (8637)
6 exp internet/ (28100)
7 exp e-mail/ or exp interactive voice response system/ or exp mobile phone/ or exp telephone/ or exp videoconferencing/ or exp wireless communication/ (13692)

8 (telematic or tele-matic or telemanagement or tele-management or telenursing or tele-nursing or telerehab* or tele-rehab* or teleservic* or tele-servic* or telemedic* or tele-medic* or telehealth or tele-health or telecare or tele-care or tele-home or telehome or telemonitor* or tele-monitor* or telecommunication* or tele-communication* or teleconferenc* or tele-conferenc* or tele-consult* or teleconsult* or email or e-mail or electronic mail or online or web or web-based or internet or internet-based or e-health or ehealth or telephone or videoconferenc* or video-conferenc*).mp. (84109)
9 ((remote or wireless or mobile or cellular or telephone) adj2 (monitor* or consult* or manag*)).mp. (2032)
10 or/5-9 (86079)
11 4 and 10 (2078)
12 limit 11 to (human and english language and yr="2007 - 2009") (450)
13 Randomized Controlled Trial/ (165071)
14 exp Randomization/ (26467)
15 exp RANDOM SAMPLE/ (1395)
16 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (297798)
17 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (670)
18 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (64531)
19 Double Blind Procedure/ (71178)
20 exp Triple Blind Procedure/ (12)
21 exp Control Group/ (2779)
22 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (212600)
23 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (429709)
24 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (282757)
25 or/13-24 (795016)
26 12 and 25 (161)

CINAHL

Query Limiters/Expanders Last Run Via Results
S24 (S11 and S23) Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 275
S23 (S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22) Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 111203
S22 control* N2 clinical trial* Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 2100
S21 (MH "Control (Research)") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 146
S20 (MH "Placebos") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 4899
S19 (MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 15799
S18 meta analy* or metaanaly* or pooled analysis or (systematic* N2 review*) or published studies or medline or embase or data synthesis or data extraction or cochrane Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 28061
S17 (MH "Systematic Review") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 4278
S16 (MH "Meta Analysis") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 7342
S15 rct Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 1095
S14 health technology N2 assess* Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 183
S13 random* or sham* Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 84738
S12 (MH "Random Assignment") or (MH "Random Sample+") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 37065
S11 (S3 and S10) Limiters - Publication Year from: 2003-2009; English Language
Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 1689
S10 (S4 or S5 or S6 or S9) Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 95421
S9 (monitor* or consult* or manag*) and (S7 and S8) Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 5198
S8 monitor* or consult* or manag* Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 231567
S7 remote or wireless or mobile or cellular or telephone Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 26250
S6 (telematic or tele-matic or telemanagement or tele-management or telenursing or tele-nursing or telerehab* or tele-rehab* or teleservic* or tele-servic* or telemedic* or tele-medic* or telehealth or tele-health or telecare or tele-care or tele-home or telehome or telemonitor* or tele-monitor* or telecommunication* or tele-communication* or teleconferenc* or tele-conferenc* or tele-consult* or teleconsult* or email or e-mail or electronic mail or online or web or web-based or internet or internet-based or e-health or ehealth or telephone or videoconferenc* or video-conferenc*) Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 86695
S5 (MH "Computer Communication Networks+") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 46760
S4 (MH "Telecommunications+") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 32197
S3 (S1 or S2) Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 49864
S2 diabetes or diabetic* or NIDDM or IDDM or MODY Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 49753
S1 (MH "Diabetic Patients") or (MH "Diabetes Mellitus+") Search modes - Boolean/Phrase Interface - EBSCOhost

Database - CINAHL;Pre-CINAHL 38905

Appendix 2: Study Characteristics

Table A1: Patient and design characteristics

Study	Patient Population	Setting	Intervention	Freq. BG Data Trans.	Control	Freq. Face-to-Face Consults*	Length Follow-Up†	Primary Outcomes (Secondary)
Ralston et al. 2009	n=83 (9 lost to follow-up with various methods of imputation for ITT analysis for adjusted analyses only); Diabetes type 2; Inclusions: - ≥18 years - HbA_{1c} in last 12 months ≥7.0% - ≥two visits to University of Washington's general internal medicine clinic in last year Exclusions: - participation in pilot study - major psychological illness - did not speak English - had a resident as a primary physician - were followed primarily in a special clinic -lack of Internet access - severe cognitive, language, or hearing impairment	Seattle; 1 internal medicine clinic; Recruitment period: Aug 2002 to May 2004.	In addition to usual care. Up-front education session by care manager. Transmission of self-BG readings and other biologic data through web-based application with weekly review and email feedback by care manager (conferring with primary care providers as necessary).	Once a week.	Usual care from an internal medicine physician.	NR	12 m	HbA_{1c} (total cholest. and BP).
Bond et al. 2007	n=62 (No loss to follow-up); Diabetes type 1 (13%, n=8); Diabetes type 2 (87%, n=54); Inclusions: - ≥60 years - dx of type 1 or type 2 diabetes for ≥ 1 yr; - living independently in the community - oral fluency in English; Exclusions: - moderate or severe cognitive, visual, or physical impairment - presence of severe co-morbid disease.	Seattle; Multicenter; Recruitment period: Sept 2004–2005 and Feb 2005– 2006.	n=31; In additional to usual care. Website entry of self-BG readings and other biological or lifestyle markers with nurse monitoring and e-mail or IM feedback plus weekly education by PI.	NR	n=31; Usual provider care with no additional educational or training. Access to educational materials/classes through face-to-face provider consultations or Internet if requested.	NR	6 m	HbA1c, BP, weight, cholesterol and HDL levels.

Study	Patient Population	Setting	Intervention	Freq. BG Data Trans.	Control	Freq. Face-to-Face Consults*	Length Follow-Up†	Primary Outcomes (Secondary)
Yoon and Kim 2008	n=60 (9 lost to follow-up with PP analyses presented); Diabetes type 2; Inclusions: - able to perform BG self-testing and access websites - have own cellular phone; Exclusions: - Clinical history of a severe illness - renal insufficiency with a creatinine level >1.5mg/dl - had been using insulin pumps	Korea; 1 outpatient clinic; Recruitment period: Jan 2003 to Aug 2006.	n=30 (5 lost to follow-up thus 25 analysed); In addition to usual care. Website entry of self-BG and other lifestyle or biological markers with weekly SMS text feedback by endocrinologist and/or nursing professor.	At least monthly; warnings if data not sent weekly.	n=30 (4 lost to follow-up thus 26 analysed); Clinic's usual advice about medication and lifestyle modifications from endocrinologist. Additional care if necessary or requested.	Several visits during 12 m period.	12 m	HbA1c, 2HPPT, FBG.
Kim and Kim 2007	n=40; (6 lost to follow-up with PP analyses presented); Diabetes type 2; Inclusions: - BMI >23 kg/m2 - able to perform BG self-testing, self-injection and access websites - have own cellular phone; Exclusions: - Clinical history of a severe illness - renal insufficiency with a creatinine level >1.5mg/dl - had been using insulin pumps	Korea; 1 outpatient clinic; Recruitment period: Jan 2003 to Dec 2006.	n=20 (2 lost to follow-up thus 18 analysed); In addition to usual care. Up-front diabetes education program. Website entry of self-BG and other lifestyle or biological markers with weekly SMS text feedback by diabetic educator and/or professor of nursing. Outpatient visits once every 3 months.	At least monthly; warnings if data not sent weekly.	n=20 (4 lost to follow-up, 16 analysed); Up-front diabetes education program. Clinic's usual advice about medication and lifestyle modifications from endocrinologist. Additional care if necessary or requested.	4–5 visits during 12 m period.	12 m	HbA1c, 2HPPT, FBG.
Cho et al. 2006	n=80 (9 lost to follow-up but last endpoints carried forward ITT analysis); Diabetes type 2; Inclusions: - ≥30 years Exclusions: - disabling conditions or diseases - hepatic dysfunction - a creatinine level >0.133 mmol/l - severe complications of diabetes - treatment with an intensified insulin regimen - lack of Internet knowledge - history of similar intervention.	Korea; 1 outpatient clinic; Study period: Feb 2002 to Aug 2004.	n=40; In addition to usual care. Up-front diabetes education program. Website entry of self-BG and other lifestyle or biological markers with weekly SMS text feedback by endocrinologist, nurse, and/or dietician. Outpatient visits once every 3 months.	At least monthly; warnings if data not sent weekly.	n=40; Up-front diabetes education program. Clinic's usual advice about medication and lifestyle modifications from endocrinologist. Additional care if necessary or requested.	Once every 3 months.	30 m	HbA1c levels, HbA1c fluctuation index (FBG, total cholesterol, triglycerides, HDL, creatinine) .

Study	Patient Population	Setting	Intervention	Freq. BG Data Trans.	Control	Freq. Face-to-Face Consults*	Length Follow-Up†	Primary Outcomes (Secondary)
Harno et al. 2006	n=175 (Drop-outs NR); Diabetes type 1 (49%; n=86); Diabetes type 2 (61%; n=107); Exclusions: - technical reasons - other diseases or lifestyle problems - refusal or withdrawal.	Finland; 2 primary care centres and 2 university hospital outpatient clinics; Study period: October 2001 start date.	n=101; Web-based e-health application plus modem transmission of BG data with SMS feedback by diabetes care team for pts with internet or cellular phone.	NR	n=74; General practitioner visits about once every three months or more if deemed clinically necessary.	Once every 3 months.	12 m	HbA1c levels, systolic BP, diastolic BP, fasting glucose, cholesterol, HDL, LDL, triglyceride, creatinine, and BMI.
Shea et al. 2006	n=1,665 (310 lost to follow-up with baseline carried forward ITT analysis as well as PP analysis presented); Diabetes type 1 and 2; Inclusions: -≥55 years -Medicare beneficiary - dx diabetes and on treatment with diet, oral hypoglycemic agent or insulin - residence in a federally designated medically underserved area - oral fluency in English or Spanish; Exclusions: - moderate or severe cognitive, visual, or physical impairment - presence of severe co-morbid disease.	New York City; Study period: Dec 2000 – October 2003	n=844 (174 lost follow-up); Web-enabled computer which supported modem transmission of BG data, videoconferencing, education modules and messaging feedback from nurse case managers. Case managers were supervised by a diebetologist.	NR	n=821 (136 lost to follow-up); Usual care from primary care provider who had received current diabetes guidelines.	NR	12 m	HbA1c levels and BP (LDL).
McMahon et al. 2005	n=104 (20 lost to follow-up with last endpoint carried forward ITT analysis) Diabetes type 1 and 2; Inclusions: - HbA1c ≥9.0%, - age >18 years - ability to understand written and spoken English - willingness to use intervention equipment - have access to a telephone - have a Veteran's Affairs-based primary care provider	Boston; Multicentre; Trial period not reported.	n=52; Up-front education session. In addition to usual care. Web-enabled laptop and access to website which supported modem transmission of BG and BP data plus IM with nurse or certified diabetes educator case managers. Website also contained diabetes education modules.	Custom to patient.	n=52; Up-front education session. Usual care by primary care provider as needed.	As needed.	12 m	HbA1c and BP levels (fasting triglycerides, LDL and HDL cholesterol).

***** Frequency of face-to-face consultations refers to frequency of in-person visits to usual diabetes care practitioner for control group. If, however, intervention was provided in addition to usual care, this frequency also refers to frequency of visits for the intervention group.

† Length of follow-up is equal to length of intervention as intervention was provided across entire period of patient observation.

Abbreviations: 2HPPT, two hours post-prandial test; BG, blood glucose; BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HDL, high-density lipids; IM, instant messaging; ITT, intention-to-treat; LDL, low-density lipids; NR, not reported; PI, principal investigator; PP, per-protocol; Pts, patients; SMS, short message service.

Table A2: Quality Characteristics

Study	Randomization	Blinding	Analysis	Percentage Lost to Follow-Up (Number)	Sample Size Calculation and Power
Ralston et al. 2009	Participants assigned using a computer random number generator. Allocation to the study group concealed from the study coordinator and the participant until after recruitment phone calls.	Blinding reportedly not feasible.	ITT analyses presented using various imputation methods for adjusted analyses only.	7% (3) intervention, 14.6% (6) control.	Trial designed for β of 0.8 to detect a difference of 0.5% in HbA1c levels (two-sided α of 0.05; SD of mean HbA1c 1.26; mean change in Z score SD in HbA1c levels 0.87).
Yoon and Kim 2008	No description of randomization or allocation concealment.	No blinding reported.	PP analyses.	16.7% (5) intervention, 13.3% (4) control.	For repeated measures analysis of variance (for an effect size of 0.60, at β of 0.8 and α of 0.05), 25 subjects in each group required for 1% reduction of HBA1c levels at post-test compared to pre-test.
Bond et al. 2007	Participants were randomized using a stratified two-tier strata that was based on HbA1c level and gender. No description of allocation concealment.	No blinding reported.	ITT analysis.	0	Assuming the SD of change is the same for both groups using an estimated 12-month attrition rate in the 10–20% arrange, 62 participants are required (including a 15% attrition rate), based on a 0.5 correlation between pre-intervention/post-intervention scores, would provide for a moderate effect size of 0.55 with β of 0.8.
Kim and Kim 2007	No description of randomization or allocation concealment.	No blinding reported.	PP analyses.	10.0% (2) intervention, 20.0% (4) control.	For repeated measures analysis of variance (for an effect size of 0.60, at β of 0.8 and α of 0.05), 34% of unpaired t-test samples (rho = 0.60, one time of pre-test, four times of post-test), 15 subjects in each group required for a 1% reduction of HBA1c levels at post-test compared to pre-test.
Cho et al. 2006	Adaptive randomization. No description of allocation concealment.	No blinding reported.	ITT analysis with last endpoint carried forward.	12.5% (5) intervention, 10% (4) control.	No calculation reported.
Harno et al. 2006	No description of randomization or concealment.	No blinding reported.	Unclear.	Unclear.	No calculation reported.
Shea et al. 2006	Randomization controlled by study coordinating center (therefore concealment was maintained). Subjects were randomized within clusters defined by primary care provider patient panels.	Personnel conducting baseline and follow-up examination were blinded to patient intervention status.	Both ITT with baseline values carried forward and PP analyses presented.	20.6% (174) intervention, 16.6% (136) control.	Assumptions: an overall attrition rate of 20%, reliability of the outcome variables of 0.9, cluster inter-correlations ranging from 0.05–0.2, α of 0.05, and two-tailed test for each primary outcome. Based on calculations performed assuming different scenarios regarding variances and effect sizes, power was at least 0.80 for the detection of clinically meaningful changes in the outcomes. Sample size was increased during recruitment to compensate for early drop-out in the intervention group.
McMahon et al. 2005	Participants were randomized to one of two study groups through use of a random variables generator and a series of sealed envelopes.	Trial reports no blinding of research staff recording outcome measures.	ITT analysis with last endpoint carried over.	15.4% (8) intervention, 23.1% (12) control.	A sample size of 50 in each group was required to have β of 0.8 and α of 0.05 to detect a between group difference of 0.8% for HbA1c.

ITT, intention-to-treat; PP, per-protocol; SD, standard deviation.

Appendix 3: Forest Plots

Figure A1: Baseline HbA_{1c} values for included studies

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bond 2007	7	1.1	31	7.11	0.91	31	8.9%	-0.11 [-0.61, 0.39]
Cho 2006	7.7	1.5	40	7.5	1.3	40	6.2%	0.20 [-0.42, 0.82]
Harno 2006	7.82	1.31	101	8.21	1.55	74	11.2%	-0.39 [-0.83, 0.05]
Kim and Kim 2007	7.66	0.7	16	8.16	1.9	18	2.8%	-0.50 [-1.44, 0.44]
McMahon 2005	10	0.8	52	9.9	0.8	52	18.8%	0.10 [-0.21, 0.41]
Ralston 2009	8.2	0.66	39	7.9	1.14	35	11.4%	0.30 [-0.13, 0.73]
Shea 2006	7.35	1.41	670	7.42	1.58	685	36.8%	-0.07 [-0.23, 0.09]
Yoon 2008	8.09	1.72	25	7.59	1.09	26	3.9%	0.50 [-0.29, 1.29]
Total (95% CI)			**974**			**961**	**100.0%**	**-0.01 [-0.17, 0.15]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.10$, df = 7 (P = 0.25); $I^2 = 23\%$

Test for overall effect: Z = 0.10 (P = 0.92)

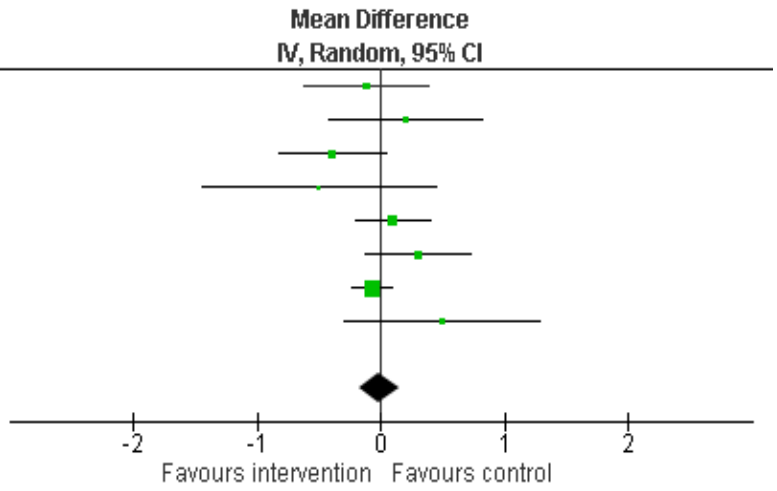
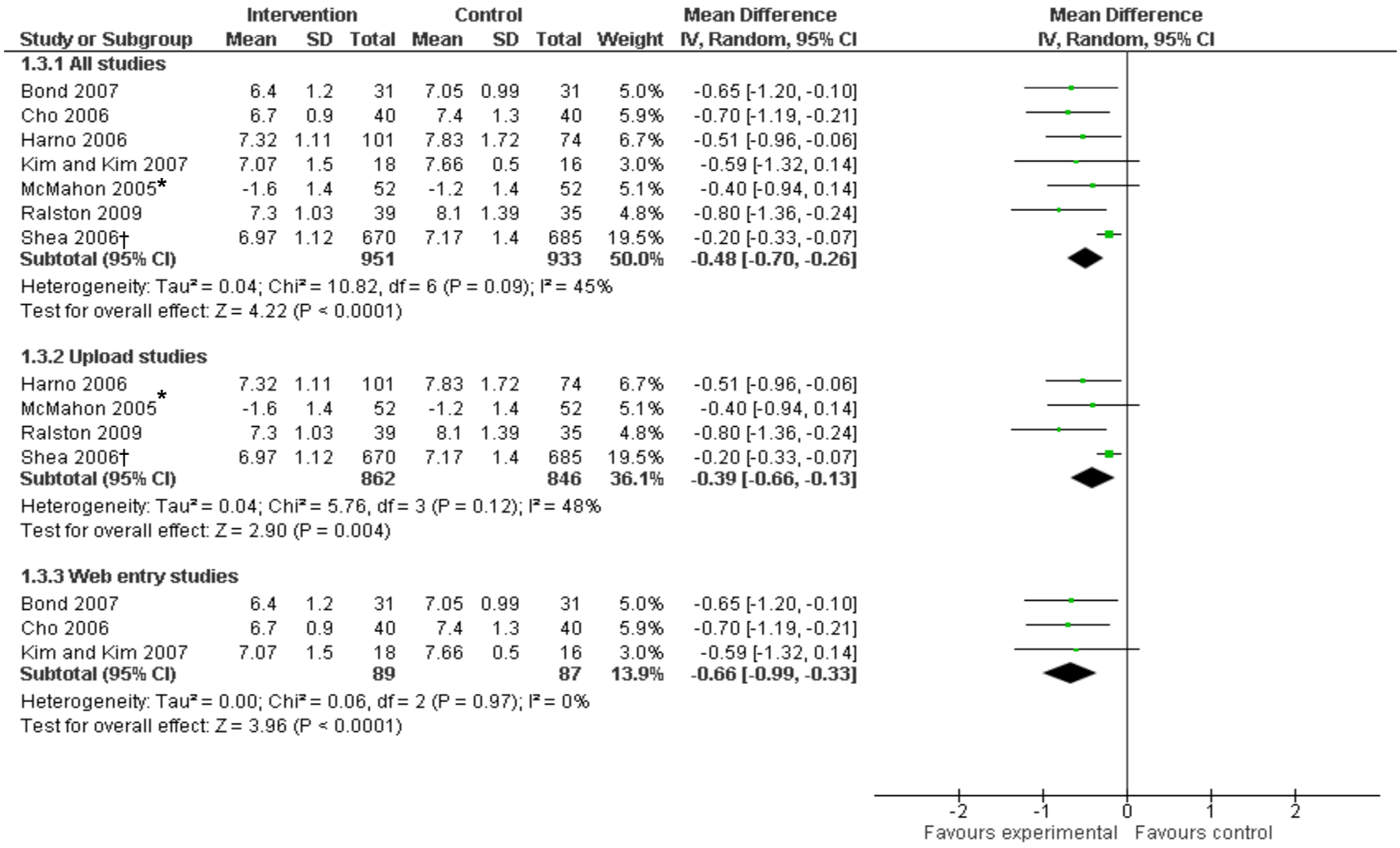
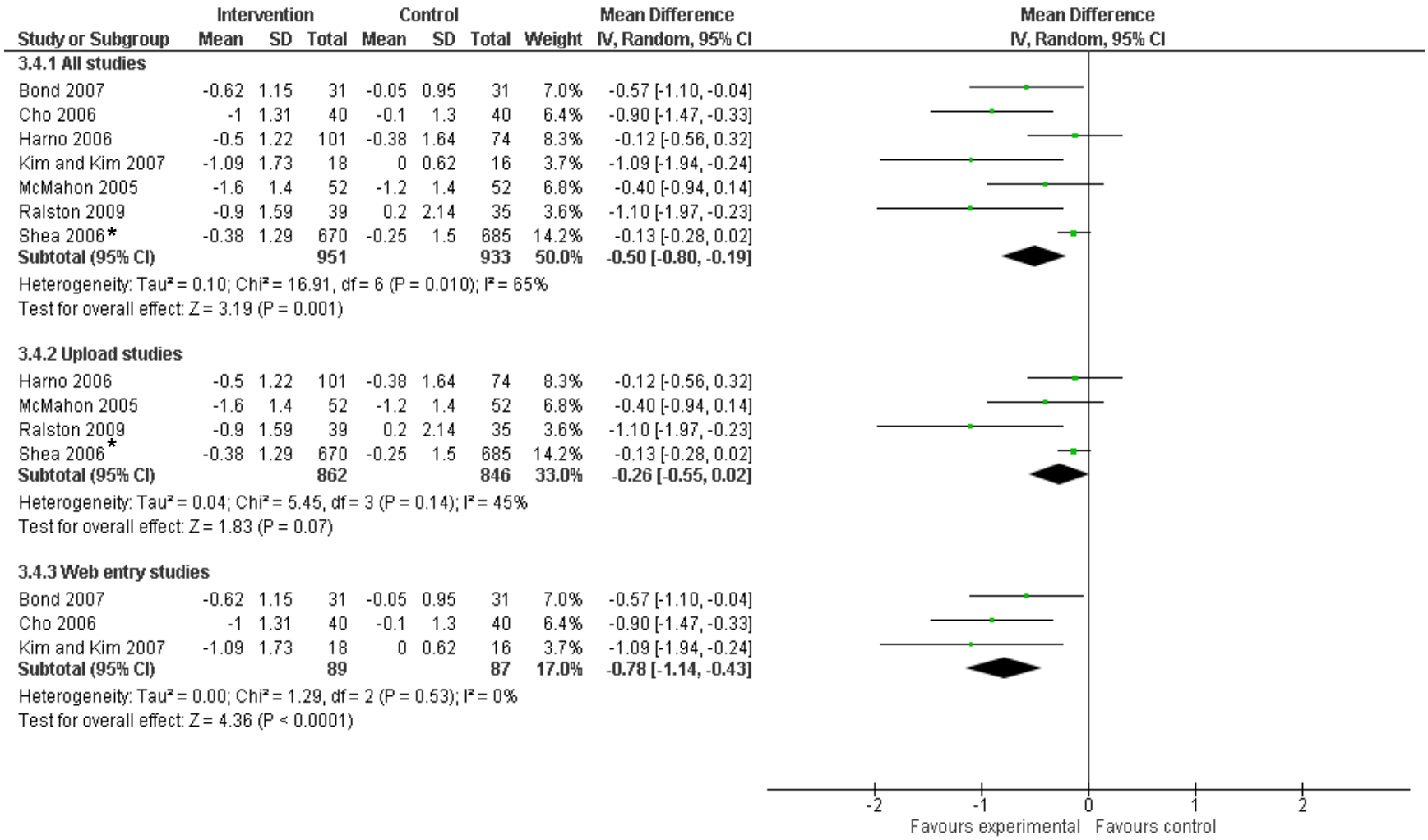


Figure A2: Difference in follow-up HbA1c values between blood glucose home telemonitoring and usual control for all studies (excluding Yoon and Kim 2008), by subgroup



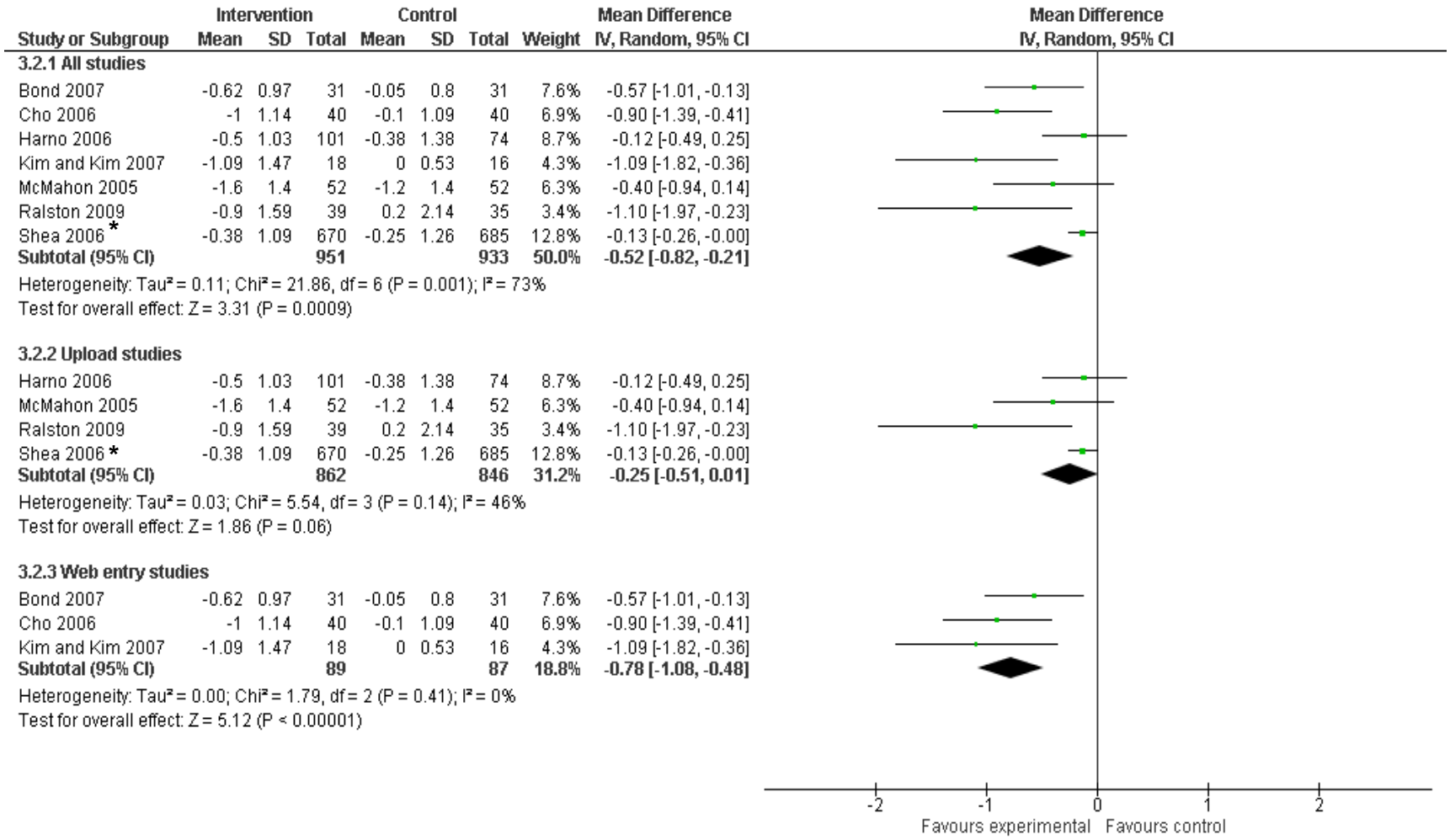
* Values presented are change-from-baseline values (follow-up values not reported).
† Values presented are from sample which completed follow-up only (i.e., per-protocol analysis); ITT sample had baseline values carried over (no intermediate endpoints) and there was a statistically significant difference in drop-out between intervention and control.

Figure A3: Difference in change-from-baseline HbA_{1c} values between blood glucose home telemonitoring and usual control for all studies (excluding Yoon and Kim 2008), by subgroup (ρ=0.5)



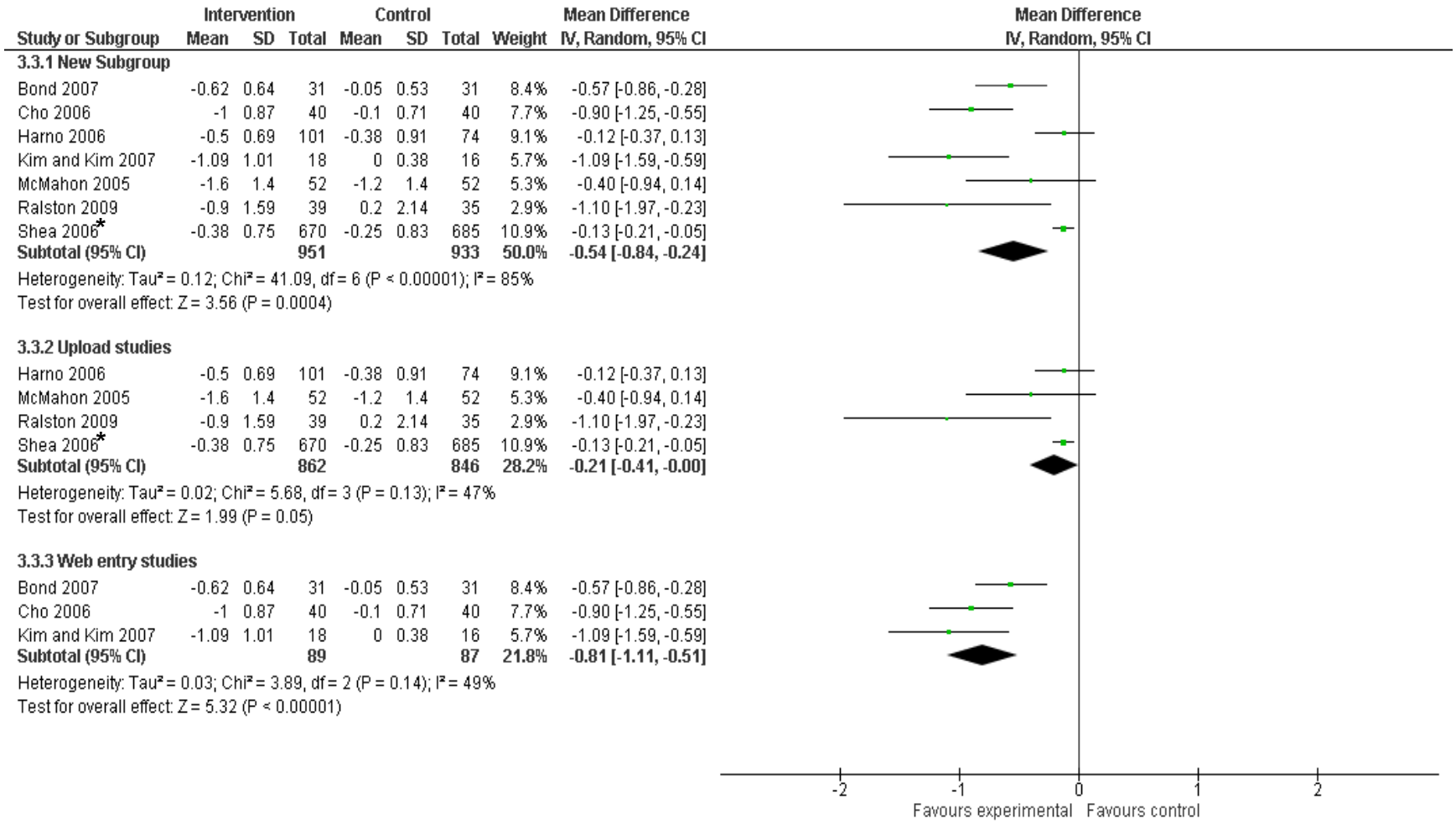
* Values presented are from sample which completed follow-up only (i.e., per-protocol analysis); ITT sample had baseline values carried over (no intermediate endpoints) and there was a statistically significant difference in drop-out between intervention and control.

Figure A4: Difference in change-from-baseline HbA_{1c} values between blood glucose home telemonitoring and usual control for all studies (excluding Yoon and Kim 2008),by subgroup (ρ=0.65)



* Values presented are from sample which completed follow-up only (i.e., per-protocol analysis); ITT sample had baseline values carried over (no intermediate endpoints) and there was a statistically significant difference in drop-out between intervention and control.

Figure A5: Difference in change-from-baseline HbA_{1c} values between blood glucose home telemonitoring and usual control for all studies (excluding Yoon and Kim 2008), by subgroup (ρ=0.85)



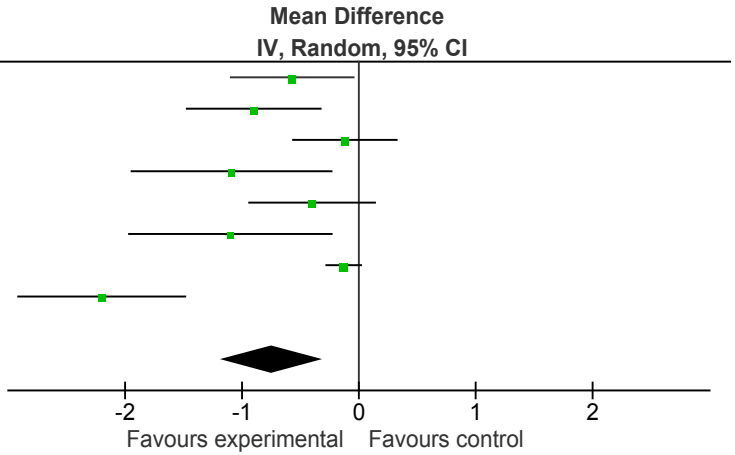
* Values presented are from sample which completed follow-up only (i.e., per-protocol analysis); ITT sample had baseline values carried over (no intermediate endpoints) and there was a statistically significant difference in drop-out between intervention and control.

Figure A6: Difference in change-from-baseline HbA_{1c} values between blood glucose home telemonitoring and usual control for all studies, including Yoon and Kim 2008 (ρ=0.5)

	Intervention			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bond 2007	-0.62	1.15	31	-0.05	0.95	31	13.2%	-0.57 [-1.10, -0.04]
Cho 2006	-1	1.31	40	-0.1	1.3	40	12.7%	-0.90 [-1.47, -0.33]
Harno 2006	-0.5	1.22	101	-0.38	1.64	74	13.9%	-0.12 [-0.56, 0.32]
Kim and Kim 2007	-1.09	1.73	18	0	0.62	16	10.0%	-1.09 [-1.94, -0.24]
McMahon 2005	-1.6	1.4	52	-1.2	1.4	52	13.0%	-0.40 [-0.94, 0.14]
Ralston 2009	-0.9	1.59	39	0.2	2.14	35	9.9%	-1.10 [-1.97, -0.23]
Shea 2006	-0.38	1.29	670	-0.25	1.5	685	16.0%	-0.13 [-0.28, 0.02]
Yoon 2008	-1.39	1.49	25	0.81	1.07	26	11.3%	-2.20 [-2.91, -1.49]
Total (95% CI)			**976**			**959**	**100.0%**	**-0.75 [-1.18, -0.31]**

Heterogeneity: Tau² = 0.30; Chi² = 44.74, df = 7 (P < 0.00001); I² = 84%

Test for overall effect: Z = 3.37 (P = 0.0008)



† Values presented from sample which completed follow-up only (i.e., per-protocol analysis); ITT sample had baseline values carried over (no intermediate endpoints) and there was a statistically significant difference in drop-outs between intervention and control.

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