

## **Medication adherence during adjunct therapy with statins and ACE inhibitors in adolescents with type 1 diabetes**

Elżbieta Niechciał<sup>1</sup>, PhD; Carlo L. Acerini<sup>2</sup>, MD; Scott T. Chiesa<sup>3</sup>, PhD; Tracey Stevens<sup>2</sup>, BSc; R. Neil Dalton<sup>4</sup>, PhD; Denis Daneman<sup>5</sup>, MD; John E. Deanfield<sup>3</sup>, MD; Timothy W. Jones<sup>6</sup>, MD; Farid H. Mahmud<sup>5</sup>, MD; Sally M. Marshall<sup>7</sup>, MD; H. Andrew W. Neil<sup>8</sup>, DSc; David B Dunger<sup>2,9</sup>, MD; M. Loredana Marcovecchio<sup>2</sup>, MD, PhD; on behalf of the Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT) study group.

<sup>1</sup>Department of Pediatric Diabetes, Endocrinology and Obesity, Poznan University of Medical Sciences, Poznań, Poland

<sup>2</sup>Department of Paediatrics, University of Cambridge, Cambridge, UK

<sup>3</sup>Vascular Physiology Unit, UCL Institute of Cardiovascular Science, London, UK

<sup>4</sup>Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK

<sup>5</sup>Department of Paediatrics, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada

<sup>6</sup>Telethon Kids Institute, The University of Western Australia, Perth, Australia

<sup>7</sup>Institute of Cellular Medicine (Diabetes), Faculty of Clinical Medical Sciences, Newcastle University, Newcastle upon Tyne, UK

<sup>8</sup>Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford, Oxford, UK

<sup>9</sup>Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK.

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**Corresponding author:** Dr M. Loredana Marcovecchio; MD, PhD  
University Department of Paediatrics, Level 8, Box 116, Addenbrooke's Hospital  
Hills Road, Cambridge CB2 0QQ, UK  
Tel.: +44 (0) 1223 768615, Fax: +44 (0) 1223 336996  
Email: mlm45@medschl.cam.ac.uk

## **Abstract**

**Objective:** Suboptimal adherence to insulin treatment is a main issue in adolescents with type 1 diabetes. However, to date, there are no available data on adherence to adjunct non-insulin medications in this population. Our aim was to assess adherence to ACE inhibitors and statins and explore potential determinants in adolescents with type 1 diabetes.

**Research Design and Methods:** 443 adolescents with type 1 diabetes were recruited into the Adolescent Type 1 Diabetes cardio-renal Intervention Trial (AdDIT) trial and exposed to treatment with two oral drugs: an ACE inhibitor, a statin, combinations of both or placebo for 2-4 years. Adherence was assessed every 3 months with the Medication Event Monitoring System (MEMS) and pill count.

**Results:** Median adherence during the trial was 80.2% (interquartile range: 63.6-91.8), based on MEMS, and 85.7% (72.4-92.9) for pill count. MEMS- and pill count-based adherence dropped from 92.9% and 96.3%, respectively, at the first visit, to 76.3% and 79.0% at the end of the trial. The percentage of study participants with adherence  $\geq 75\%$  declined from 84% to 53%. A good correlation was found between MEMS- and pill count-based adherence ( $r=0.82$ ,  $p<0.001$ ). Factors associated with adherence were age, glycemic control and country.

**Conclusions:** We report an overall good adherence to ACE inhibitors and statins during a clinical trial, although there was a clear decline in adherence over time. Older age and suboptimal glycemic control at baseline predicted lower adherence during the trial, and predictably reduced adherence was more prevalent in subjects who subsequently dropped out.

Adherence to a medication regimen, defined as the extent to which a person's medication-taking behavior corresponds with the agreed recommendations from a healthcare provider, is a key determinant of response to therapy and patients' outcomes (1). Adherence is a complex and multifactorial paradigm, which varies depending on the disease and treatment regimen, and is also influenced by physician and patient-related factors (1–3).

In adolescents with type 1 diabetes, suboptimal adherence to diabetes self-management, including insulin therapy, is a main concern (4,5), and it reflects age-related issues as well as the complexity of diabetes management (6,7).

Insulin is the standard treatment for type 1 diabetes, but its doses and timing of administration need to be coordinated, on a daily basis, with the results of blood glucose monitoring, dietary intake, levels of physical activity as well as potential intercurrent illnesses and other factors (6). The burden of adhering to these various behaviors is carried by patients and their families and can affect every aspect of daily life.

Given that glycemic control is often suboptimal during adolescence (8), there is a growing interest in implementing new non-insulin adjunct drug therapies to achieve recommended glycemic targets, and to prevent short- and long-term complications (9). International guidelines are also more widely recommending treatments with blood pressure and lipid lowering drugs during adolescence in the presence of cardiovascular risk factors such as dyslipidemia and hypertension (10,11).

Understanding how these adjunct medications will be accepted and adhered to by young people is needed, not least to inform potential strategies to improve and maintain treatment adherence following their implementation into clinical practice.

Although there is clear evidence for a strong association between adherence to

diabetes treatment and glycemic control and, in turn, complication risk (12), there are no available data on adherence to adjunct non-insulin medications in adolescents with type 1 diabetes.

The Adolescent Type 1 Diabetes cardio-renal Intervention Trial (AdDIT) recruited a contemporary cohort of adolescents with type 1 diabetes from three countries (UK, Canada and Australia) (13). Trial participants were requested to take two oral medications, angiotensin-converting enzyme (ACE) inhibitors and statins, or related placebos, daily for a duration of 2-4 years. Thus, this trial offers a unique opportunity to look at adherence to medications other than standard insulin treatment. As part of the trial, adherence was assessed with the Medication Event Monitoring System (MEMS), which records the date and time of each opening of a pill container, and is currently considered the gold standard for tracking drug dosing history in clinical trials (14,15). Pill count was used as a secondary indirect method to assess adherence. Using data from the AdDIT trial we aimed: 1) to assess rates of adherence and its changes over time; 2) to compare MEMS and pill count as methods of assessing adherence, and 3) to assess factors predicting adherence, in adolescents with type 1 diabetes in the context of a clinical trial.

## **Methods**

### **Study population**

The study cohort included 443 adolescents with type 1 diabetes, aged 10-16 years, recruited into the AdDIT trial. The design and results of the AdDIT trial have been previously reported (13). In brief, AdDIT was a multicenter, double-blind, randomized, placebo-controlled trial conducted at 32 centers across the UK, Canada and Australia. AdDIT was designed to explore the potential cardio-renal protection

provided by ACE inhibitors and statins in adolescents with type 1 diabetes at increased risk of vascular complications based on an albumin-creatinine ratio (ACR) in the upper tertile of the normal range (13).

The inclusion criteria for the AdDIT trial were: age between 10 and 16 years; a duration of diabetes of at least 1 year (or a diagnosis within the past year with an undetectable C-peptide level); an adjusted ACR in the upper tertile of the screened population. Exclusion criteria were non–type 1 diabetes, pregnancy or unwillingness to adhere to contraceptive advice and pregnancy testing, severe hyperlipidemia or a family history of familial hypercholesterolemia, hypertension unrelated to diabetic nephropathy, previous exposure to the investigational drugs, unwillingness or inability to adhere to the trial protocol, the presence of coexisting conditions (excluding treated hypothyroidism and celiac disease), proliferative retinopathy, and the presence of renal disease that was not associated with type 1 diabetes (13).

Participants were randomized, using a 2-by-2 factorial design, to receive a variable dose of an ACE inhibitor (Quinapril, 5 or 10 mg), a fixed dose of a statin (Atorvastatin, 10 mg), combinations of both drugs or matched placebos. The drugs were given orally as two tablets daily for a duration of minimum 2 up to maximum 4 years. Trial duration varied based on the time when each participant was enrolled, during the recruitment timescale.

The trial conformed to the provisions of the Declaration of Helsinki and was approved by the Cambridge University Hospitals and participating local research ethics committees. Parents of the participants provided written informed consent, and the trial participants were asked to provide their written assent if they were not yet at an age when they could provide consent.

## **Assessment of adherence**

Electronic monitoring: Quinapril and Atorvastatin and the matched placebos were supplied at each study visit. The tablets were provided in containers with the electronic monitoring caps MEMS (provided by AARDEX, Zug, Switzerland), that recorded the precise date and time of each opening and closing in order to track adherence (13). Each study participant was provided with two bottles containing the study medications/placebos. Participants were asked to keep the tablets in the bottles provided and not to transfer them to other containers. They were informed that their adherence to both drugs was monitored during the trial, and at each study visits they were encouraged to take the medications. However, they did not receive any incentives to promote adherence and no detailed data on adherence to diabetes self-management were collected during the trial.

At each study visit, data from the caps were read by MEMS devices and stored. MEMS adherence was estimated assuming that each cap opening represented a participant taking the correct number of medications from the container during the study period. Participants who did not open their MEMS cap were rated as non-adherent for that day.

Pill count: At every study visit, unused tablets were brought back and counted. By both methods, adherence was assessed at 1 month after randomization and then every three months. It was calculated as the percentage of days on which a tablet was apparently taken by participants remaining active in the study, out of the days in between study visits.

## **Predictors of adherence**

Potential predictors of adherence were chosen 'a priori' from participants' characteristics assessed at baseline and included in the randomization process (13). These included: chronological age, sex, diabetes duration, age at diabetes diagnosis, baseline glycaemic control as assessed by glycated hemoglobin (HbA1c), method of diabetes treatment (multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII)), country (UK, Australia, Canada).

### **Statistical analysis**

Results are presented as percentages, median, and interquartile ranges (IQR). Linear mixed model was used to compare adherence rate across the study visits. Mann-Whitney and Kruskal-Wallis tests were used to compare differences in overall adherence between study groups. Linear regression models were used to assess factors associated with overall adherence. Bland-Altman plots were used to assess agreement between the MEMS and pill count methods. Two-sided p-values less than 0.05 were considered statistically significant. Analyses were performed with SPSS, version 25.

## **Results**

### **Baseline characteristics of the study population**

443 adolescents (203 females and 240 males; 376 white and 67 from other ethnic groups) were randomized into the AdDIT trial at a median age of 13.8 (IQR 12.6-15.0) years and median diabetes duration of 5.0 (3.2-7.8) years across three countries: Australia (n=201, 45%), Canada (n=124, 28%), UK (n=118, 27%). Their baseline median (IQR) HbA1c was 8.3 (7.6-9.3)% [67.2 (59.6-78.1) mmol/mol]; 266 (60%) were on MDI and 177 (40%) on CSII.

These 443 study participants represented around 43% of the eligible screened population and their demographic characteristics were similar to those who refused to take part to the study (data not shown).

Study participants were followed for a median of 2.6 years and their adherence was assessed starting from 1 month after randomization and every 3 months thereafter, until completion of the trial after 2-4 years.

### **Adherence rate based on MEMS vs pill count**

There were no significant differences between adherence to ACE Inhibitor or related placebo and statins or related placebo (Supplementary Figure S1). The average adherence for both drugs was used in all analyses. Levels of adherence between the active drugs vs placebo-placebo groups during the whole trial period were similar (81.6 (66.5-92.2)% vs 79.9 (62.9-91.7)%),  $p=0.54$ .

Overall median adherence (IQR) was 80.2% (63.6-91.8) [mean $\pm$ SD: 75.0 $\pm$ 20.8%], based on MEMS, and 85.7% (72.4-92.9) [mean $\pm$ SD: 80.4 $\pm$ 17.0%], based on pill count. Adherence based on both MEMS and pill count dropped from 92.9% and 96.3%, respectively, at the first visit, to 76.3% and 79.0% at the last visit ( $p$  for trend  $<0.001$ ). As shown in Figure 1, the main decline in adherence occurred during the first 18 months (adherence at 18 months: MEMS= 79.8%; Pill count= 83.2%) ( $p$  for trend  $<0.001$ ), and after that it remained almost stable (Figure 1). The sample size, as reported in Figure 1, decreased over time, mainly due to participants completing the minimum duration of 2 years in the trial. In addition, there were 78 participants who dropped out at different time points and 37 participants who stopped treatment earlier than expected but remained in the study. Adherence during the trial was lower in participants who subsequently dropped out or stopped medications compared to



the rest of the trial population remaining active in the trial (72.4 (53.2-90.3)% vs 82.0 (66.2 -92.2)%),  $p=0.02$ . When including these non-active participants, with their adherence considered equal to 0 in the analysis, overall adherence during the trial was 4.4% lower compared to the adherence calculated only for participants remaining in the study (Supplementary Figure S2).

The correlation between MEMS- and pill count-based adherence was 0.82 ( $p<0.001$ ) (Figure 2a). Bland Altman plots showed good agreement between the two methods with a bias of 5.3% (95% confidence interval: -28.2; 17.9) (Figure 2b).

### **Levels of adherence over study treatment visits based on MEMS data**

When analyzing the data using different categories of adherence ( $\geq 75\%$ , 50-75%, 25-50% and  $<25\%$ ), most participants had a median adherence rate above 75% during the trial period (Figure 3). However, the percentage of active participants with adherence  $\geq 75\%$  decreased from 84% at the beginning of the study to 56-58% after 18-24 months and to 53% after 48 months. In parallel the proportion of participants with adherence rates between 50% and 75%, 50% and 25% and less than 25% increased from 13% to 28%, 1.8% to 14% and 0.7% to 4.6%, respectively.

### **Baseline factors associated with adherence based on MEMS data**

Adherence decreased across age groups (10-12, 12-15 and 15-17 year-old group): 81.4 (70.1-93.4)% vs 79.3 (60.8-91.0)% vs 78.9 (60.8-91.7)%, although the between-group difference reached only borderline statistical significance ( $p=0.07$ ).

No differences in adherence during the study period were found between participants with a diabetes duration, at the baseline visit, less than 5 years (80.6 (65.7-91.8)%) compared to those with a duration of 5-10 years (80.4 (66.8-91.8)%),  $p=0.56$ . No

differences were found between males (79.8 (63.4-91.0)%) and females (80.4 (64.3-92.6)%),  $p=0.63$ .

When comparing adherence between the three countries involved in the AddIT trial, Australia showed a slightly higher median adherence (83.4 (70.1-92.9)%) compared to the UK (78.9 (61.7-91.6)%) and Canada (73.8 (56.8-88.3)%),  $p$  for trend=0.001.

However, the decline in adherence during the trial period was observed in all three countries: at the first study visit, median adherence was 93.3% for Australia, 92.9% for the UK and 89.0% for Canada, whereas by the last study visit it dropped to 79.8%, 76.1 and 73.0%, respectively.

Levels of adherence varied in relation to glycemic control at the baseline study visit, with the lowest adherence in participants with an HbA1c >8.5% (>69 mmol/mol): 76.9 (56.9-88.8)%, compared to those with an HbA1c between 7.5 and 8.5% (58-69 mmol/mol): 81.9 (66.5-91.7)% and less than 7.5% (<58 mmol/mol): 88.1 [75.2-93.9]%,  $p=0.001$  (Supplementary Table 1 and Supplementary Figure S3). There were no significant differences in adherence between participants on MDI and those on CSII: 80.2 (60.6-92.2)% vs 80.5 (67.6-91.9)%,  $p=0.84$ .

In univariate linear regression models, baseline factors significantly associated with adherence were chronological age, with a lower adherence in older study participants; country of origin, with the highest adherence in Australia; glycemic control, with the lowest adherence associated with the highest HbA1c levels (Table 1). In a multiple regression model, HbA1c and country remained independently associated with adherence (Table 1).

## **Discussion**

This is the major study providing data on adherence to medications other than insulin in a large contemporary cohort of adolescents with type 1 diabetes, recruited across three countries, and enrolled in a clinical trial involving taking two adjunct oral medications daily, for a total duration of 2-4 years.

Median adherence to both ACE inhibitors and statins during the AdDIT trial was around 80%, although there was a deterioration in adherence over time.

Adherence to medications in adolescents, in clinical practice and in clinical trials, varies widely from 10 to 90%, with most studies reporting rates less than 50%, particularly in those with chronic rather than acute conditions (16). The physical and psychological changes occurring during adolescence, along with demographic and socioeconomic factors and the intrinsic characteristics of the underlying disease, can all contribute to poor adherence in this age group (17).

Type 1 diabetes is a good example of a chronic disease where adherence to treatment strategies and self-management can be challenging, particularly during adolescence (18). Current diabetes self-management is based on MDI or CSII, which need to be balanced with frequent blood glucose monitoring, diet, physical activity as well as other factors, such as intercurrent illnesses (18). Observational studies based on self-reports, questionnaires, HbA1c and, more recently, on continuous glucose monitoring and insulin pumps, indicate suboptimal adherence to insulin treatment and other self-management behaviors among children and adolescents with type 1 diabetes (19–24). In one of these studies, adherence to individual components of treatment regimens varied from 29% for dietary recommendations to 52% for insulin administration and 69% for blood glucose monitoring (24). In addition, around 65% of insulin pump-wearing children miss one or more meal time boluses of insulin per

week (20). These data are a concern given that non-adherence to diabetes regimen can result in suboptimal glycemic control and increased episodes of diabetic ketoacidosis and, in the long term, lead to higher rates of vascular complications and reduced life expectancy (25).

In contrast to these real life data, AdDIT provides valuable information to adherence to adjunct oral medications in the context of a clinical trial. Although, non-adherence to ACE inhibitors or statins does not have the same impact of non-adherence to insulin in terms of risk for acute complications, understanding factors affecting adherence to these medications is important to maximize their benefit when used in clinical practice. This is important given that use of these drugs from an early age may improve long-term outcomes of young people with type 1 diabetes.

Although overall adherence was better than expected, during the AdDIT trial, there was a deterioration in adherence to both ACE Inhibitors and statins over time, and after 2 years of treatment 58% of participants showed an adherence of at least 75% and this percentage dropped to 53% after 4 years. This is in line with previous findings from other studies, and likely reflect loss of participants' motivation, feeling of lack of immediate benefits, as well as the age-related factors (5,17,26). Overall, these data highlight the need of strategies to reinforce adherence over time to gain the maximum benefit from any intervention during a clinical trial and in the real word setting.

The AdDIT trial provides valuable data on how adherence can vary based on the methods of assessment. Several methods can be used to assess adherence, and

they are broadly classified as direct and indirect methods (27). Direct methods, based on the measurement of the level of the administered drug or its metabolites in biological samples, are the most accurate, but also most expensive and impractical ways to assess adherence. In contrast, indirect methods rely on patient self-reports or questionnaires, rates of prescription refills, pill counts and are considered less precise and more prone to errors (1,28). Pill count is one of the most used indirect methods to assess drug adherence but it can be susceptible to misrepresentation and overestimate patient's adherence (27,29). The MEMS method, which records the date and time of each opening of a pill container, is considered a more accurate indirect method and the gold standard for tracking drug dosing history in clinical trials (14,15). MEMS has been used to investigate adherence in adult populations with various conditions (30), but only in a few clinical trials involving pediatric populations. These were mainly studies with small sample sizes and short periods of exposures to medications, ranging from 1 up to 12 months (31–33).

In the AddIT population two indirect methods were used, namely pill count and MEMS, and this comparison confirmed that pill count tends to overestimate adherence, as previously reported (27,29). This overestimation with pill count occurred even though the study participants were aware of their adherence being monitored with the MEMS caps. Reasons for this attempt to mislead about adherence may include inadequate knowledge about the aim or benefits of treatment as well as dissatisfaction with treatment (1).

The AddIT trial also offered the opportunity to assess potential factors associated with adherence in the context of a clinical trial. Adherence to a medical regimen can be affected by caregiver-related factors, patients characteristics, relationships between healthcare professionals and patients, social and cultural circumstances and

disease- and treatment-related factors (2,3). Frequently, patients are able to memorise only 50% of discussed issues during clinical visits (34) and may have insufficient knowledge about drug usage, and that could lead to patients not taking the appropriate prescribed doses, missing doses or discontinuing treatment (1).

Another potential main barrier to adherence to prescribed drugs are disbelief related to the diagnosis, fear of side effects, high frequency of dosing, number of concurrent medications, routes of drug administration and long-term treatment (3).

Medication adherence in children and adolescents is generally more complex than in adults, and this is reflected by worse adherence rates reported in pediatric than in adult studies (35). Younger children require involvement of a third party in the management of their medical condition (17), while adolescents face a particular life phase, characterized by many challenges potentially conflicting with optimal adherence (36).

In the AdDIT trial, adherence was lower in older than younger participants, in line with the results of previous studies suggesting a decline in adherence during the transition from childhood to adolescence (37). This may reflect specific developmental changes occurring during adolescence and less parental involvement in diabetes management (38), which is a known step as children grow up and express their desire of being more independent.

Surprisingly, we did not find any effect of diabetes duration on adherence rates, in contrast to other studies reporting a decline with longer disease duration (37). Our findings could be explained by the relatively short and narrow range of diabetes duration in our study population.

Despite the implementation of a standardized protocol in the AdDIT trial, there were differences in adherence across countries, with a slightly higher adherence to therapy

in Australia than in the UK and Canada. Variations in adherence between countries have been previously reported and could be related to socio-demographic and socio-economic factors, differences in health care systems and medical care, and physician-patient communication (1,2,39).

Suboptimal glycemic control was also associated with lower adherence to the adjunct oral medications during the AdDIT trial, likely reflecting participants' specific characteristics and behaviors which affect not only adherence to insulin regimes but also to any additional treatment strategies. Adolescents with type 1 diabetes face several obstacles to treatment adherence, including psychosocial issues, model of family functioning, communication, and regimen-associated barriers (36). They are also at high risk of depression, anxiety, other mood or eating disorders (18). All these factors have previously been associated with poor adherence to insulin treatment (36), and may similarly impact adherence to adjunct oral medications.

The association between suboptimal glycemic control and lower adherence across all randomized groups during the AdDIT trial raises the question as to whether more complex treatment approaches, which should be directed mainly towards those patients not achieving recommended glycemic targets, could bring real benefits.

Currently, several adjunct non-insulin treatments are being investigated with the aim of improving glycemic control in people with type 1 diabetes, as well as addressing weight control, preserving beta cell function and inducing vascular protection (9–11).

These include use of gliptin and sodium-glucose co-transporters 2 inhibitor agents, as well as other drugs to reduce cardiovascular risk factors, such as statins and ACE inhibitors. However, before the implementation of more complex drug therapies, strategies examining and overcoming the issues of poor adherence in those

adolescents already non-adhering to current insulin treatment regimen are required (3).

Some limitations of the present study need to be acknowledged. Although the study population was demographically well representative of the larger multinational AddIT screening population of over 4000 adolescents with type 1 diabetes, the adherence data related to a selective group who agreed to participate in a clinical trial and were aware that adherence to the adjunct medications was monitored. This likely resulted in a greater adherence than that observed in daily clinical practice, where there is no specific standardized monitoring system in place, and thus the findings are less generalizable to a real-world setting. Participants remained active in the study for a variable duration, from a minimum of 2 to a maximum of 4 years, leading to adherence data available only for around 30% of the study population for the whole 4-year trial duration. Although the MEMS method seems superior to pill count or other indirect methods, it could still have disadvantages such as misleading the system when opening the container without taking the drug or taking the wrong number of tablets or multiple doses out of the container at the same time (27). In addition, we did not collect data on socioeconomic status or psychosocial factors (family, peers, social support, acceptance/understanding of disease and treatment, mental status, self-esteem), which have previously been reported to affect adherence in children and adolescents in some, although not all studies (26,40). Finally, we were unable to assess the effect of other potential predictors of adherence, such as ethnicity (40), given that the participants were predominantly White.

## **Conclusions**



Overall, AdDIT has provided valuable insights into medication adherence in the context of multiple drug treatment for young people with T1D. The AdDIT trial showed an overall good adherence rate in a population of adolescents with type 1 diabetes in a clinical trial setting, but also confirmed that deterioration of adherence over time can be an issue. Older age and higher HbA1c at baseline predicted adolescents with lower adherence during the trial, highlighting two targets for strategies aiming at improving adherence both in clinical trials and in daily clinical practice. Although type 1 diabetes is a complex condition, based on the present data the implementation of adjunct oral therapies in type 1 diabetes in the future seems feasible, but will require specific strategies addressing potential barriers to adherence and ways of overcoming them.

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### **Author contributions**

Dr Marcovecchio has full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

EN was involved in the literature review, data interpretation and analysis and wrote the first draft of the manuscript. CLA contributed to data acquisition and interpretation and critical review of the manuscript. STC and TS contributed to data acquisition and analysis, critical review of the manuscript. RND, DD, JED, TWJ, FHM, SMM, HAWN, DBD, contributed to the study concept and design, data interpretation and critical review of the manuscript. MLM contributed to study design and concept, data interpretation, performed statistical analysis, wrote and reviewed the manuscript.

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### **Conflict of interest**

None in related to the present work.

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## Tables and Figures

**Table 1. Baseline predictors of adherence during the trial**

	<b>Beta coefficient</b>	<b>P-value</b>
<b>Univariate linear regression models</b>		
Sex (female vs male)	-0.04	0.41
Age (years)	-0.10	0.03
Age at diagnosis (years)	-0.007	0.88
Diabetes duration (years)	-0.05	0.34
HbA1c (mmol/mol)	-0.21	<0.001
Diabetes treatment (MDI vs CSII)	0.05	0.35
Country (Australia vs UK vs Canada)	-0.18	<0.001
<b>Multivariate linear regression model</b>		
Age (years)	-0.09	0.05
HbA1C (mmol/mol)	-0.20	<0.001
Country (Australia vs UK vs Canada)	-0.19	<0.001

Dependent variable is median adherence over time; independent variables are as collected at the baseline study visit. MDI: multiple daily injections; CSII: continuous subcutaneous insulin infusion

## Figure legend

### **Figure 1.** Adherence during the trial period based on MEMS and pill count

Results at each study visit are reported as medians. N of participants are those still active at each follow up study visit with available adherence data. At the first 1-month visit. P for over time changes in each group: <0.001

**Figure 2.** Comparisons between adherence assessed by MEMS and pill count: A) Scatter plot of pill count vs MEMS,  $r=0.82$ ,  $p<0.001$ . B) Bland-Altman plots of the two adherence methods

**Figure 3.** Percentage of participants showing different levels of adherence, from  $\geq 75\%$  to  $<25\%$



Figure 1

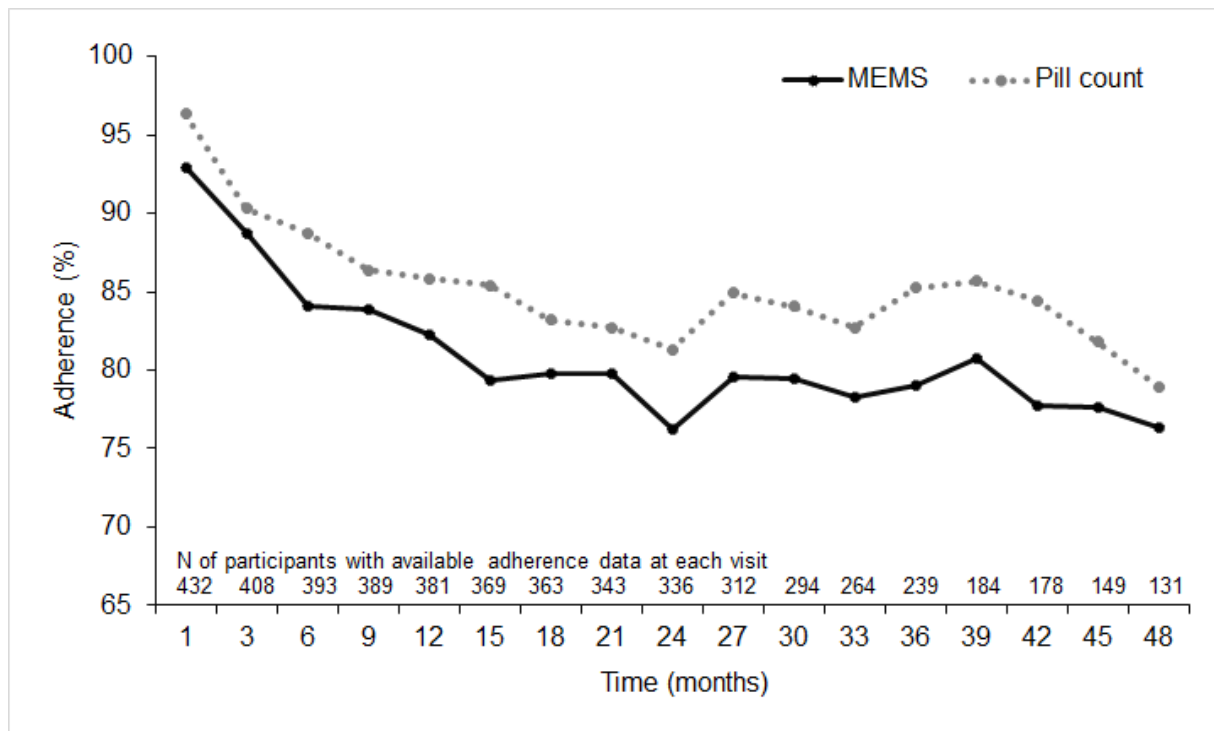


Figure 2a

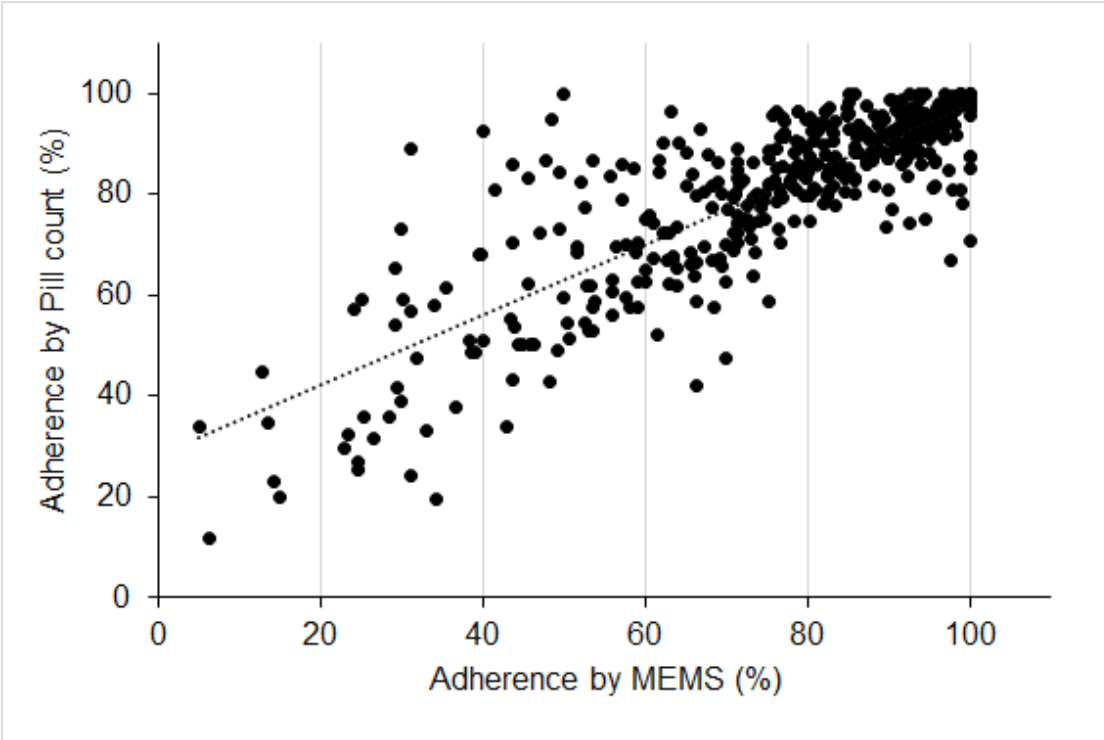


Figure 2b

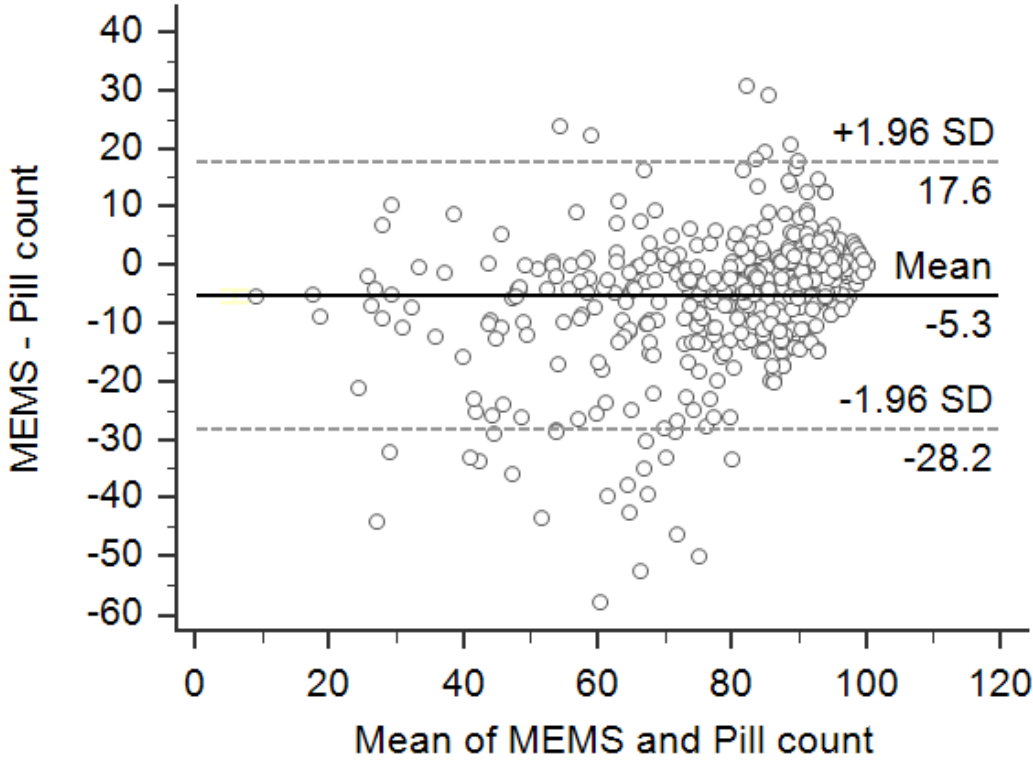
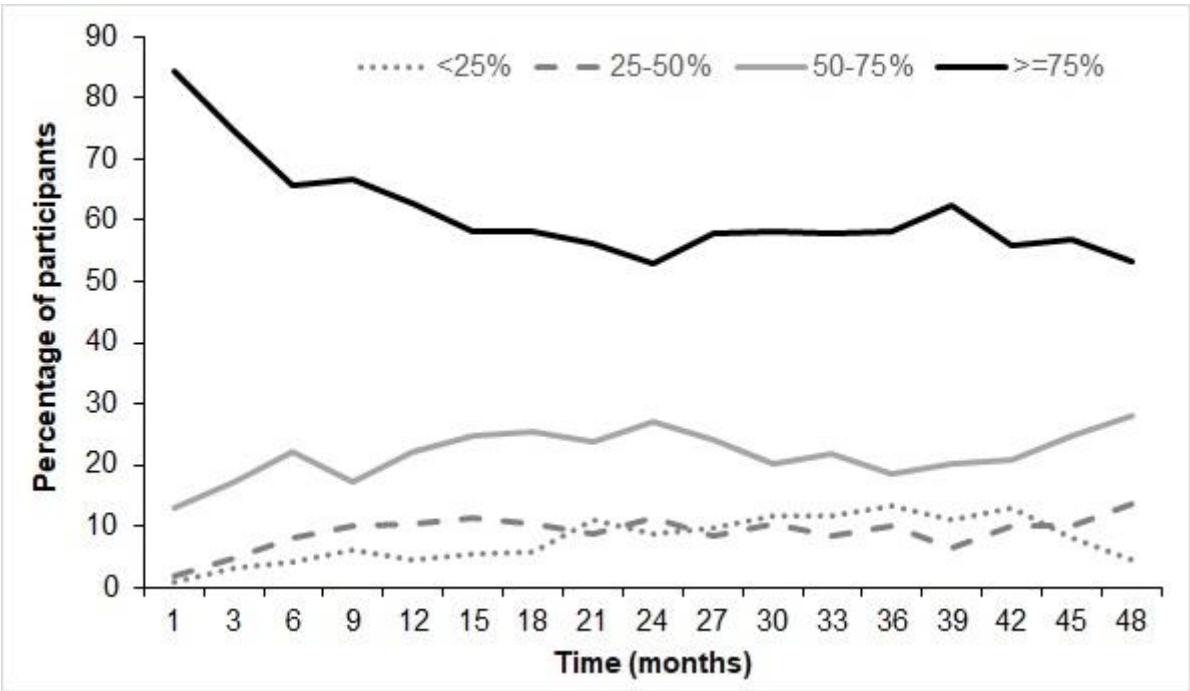


Figure 3



## Online-only Supplemental material

**Table S1. Median adherence at the first and the last visit by sex, age, duration, HbA1C, countries**

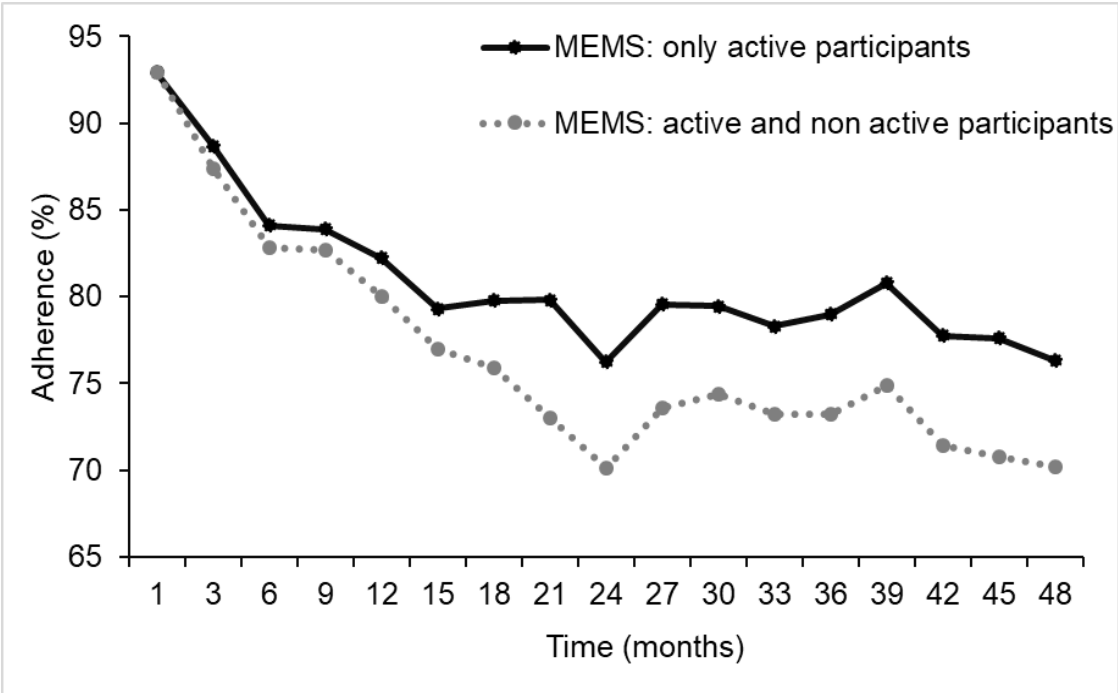
	Adherence at 1st visits (%)	Adherence at last visit (%)
<b>Whole study population</b>	92.9 (82.1-100.0)	76.7 (55.7-85.9)
<b>Sex</b>		
Female, n=203	92.9 (84.6-100.0)	79.6 (54.7-84.9)
Male, n=240	92.9 (80.0-100.0)	76.3 (56.6-90.1)
<b>Age, years</b>		
10 to 12, n=148	100.0 (85.7-100.0)	82.1 (70.9-86.0)
13 to 14, n=175	92.9 (78.6-100.0)	79.3 (60.8-92.)
15 to 17, n=120	92.6 (78.8-100.0)	73.0 (43.9-85.3)
<b>Diabetes duration, years</b>		
≤5, n=222	92.9 (80.0-100.0)	76.3 (62.4-84.8)
> 5 to 10, n=221	93.3 (83.3-100.0)	79.7 (43.5-92.9)
<b>HbA1C % [mmol/mol]</b>		
<7.5% [<58 mmol/mol], n=94	93.8 (85.7-100.0)	81.4 (69.0-92.9)
7.5-8.5% [58-69 mmol/mol], n=159	92.9 (82.7-100.0)	75.6 (63.3-84.8)
>8.5% [>69 mmol/mol], n=190	92.6 (78.6-100.0)	72.5 (47.3-87.6)
<b>Diabetes treatment</b>		
MDI, n=266	92.9 (81.8-100.0)	77.2 (47.3-85.7)
CSII, n=177	92.9 (82.7-100.0)	76.7 (61.6-87.5)
<b>Country</b>		
Australia, n=201	93.3 (85.7-100.0)	79.8 (64.4-86.5)
UK, n=118	92.9 (85.7-100.0)	76.1 (55.0-92.9)
Canada, n=124	89.0 (73.7-100.0)	73.0 (46.4-86.5)

Data are Median (interquartile range). CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections

**Figure S1. Comparison of adherence rate between statin (ore related placebo) and ACE Inhibitors (ore related placebo) during the trial period**



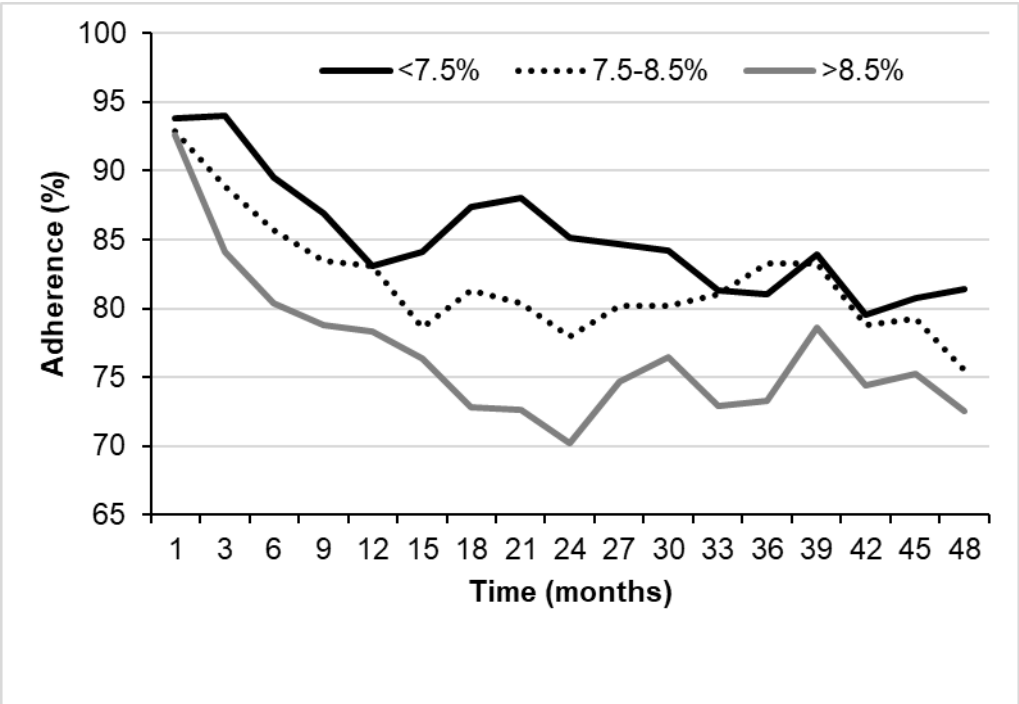
**Figure S2. Adherence during the trial period based on MEMS for active study participants and for combined active and non-active participants**



time (months)	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
MEMS: only active participants	92.9	88.7	84.1	83.9	82.2	79.3	79.8	79.8	76.3	79.6	79.5	78.3	79.0	80.8	77.8	77.6	76.3
MEMS: active and non-active participants	92.9	87.4	82.8	82.7	80.0	77.0	75.9	73.0	70.1	73.6	74.4	73.3	73.3	74.7	70.0	70.6	70.2

Results at each study visit are reported as medians. P for over time trend <0.001  
 For non-active participants at any specific time point, adherence was set equal to 0

**Figure S3. Adherence by HbA1c groups during the trial period**



Lines are median levels of adherence for each HbA1c group: <7.5% (<58 mmol/mol); 7.5-8.5% (58-69 mmol); >8.5% (>69 mmol/mol).

## 1. Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT) study group:

**Carlo L. Acerini** (University of Cambridge, Cambridge, UK), **Frank Ackland** (Northampton General Hospital, Northampton, UK), **Binu Anand** (West Suffolk Hospital, NHS Foundation Trust, Bury St Edmunds, UK), **Tim Barrett** (Birmingham Children's Hospital and University of Birmingham, Birmingham, UK), **Virginia Birrell** (James Cook Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK), **Fiona Campbell** (Leeds General Infirmary, The Leeds Teaching Hospitals NHS Trust, Leeds, UK), **Marietta Charakida** (King's College London, London, UK), **Tim Cheetham** (Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle, UK), **Scott T. Chiesa** (University College London, London, UK), **John E. Deanfield** (University College London, London, UK), **Chris Cooper** (Stepping Hill Hospital, Stockport NHS Foundation Trust, Stockport, UK), **Ian Doughty** (Royal Manchester Children's Hospital, Manchester, UK), **Atanu Dutta** (Stoke Mandeville Hospital, Aylesbury, UK), **Julie Edge** (John Radcliffe Hospital, Oxford, UK), **Alastair Gray** (University of Oxford, Oxford, UK), **Julian Hamilton-Shield** (University of Bristol and University Hospitals Bristol NHS Foundation Trust, Bristol, UK), **Nick Mann** (Royal Berkshire Hospital, Reading, UK), **M. Loredana Marcovecchio** (University of Cambridge, Cambridge, UK), **Sally M. Marshall** (Newcastle University), **H. Andrew W. Neil** (University of Oxford, Oxford, UK), **Gerry Rayman** (Ipswich Hospitals NHS Trust, Ipswich, UK), **Jonathon M. Robinson** (Royal Albert Edward Infirmary, Wroughton, Wigan and Leigh NHS Foundation Trust, Wigan, UK), **Michelle Russell-Taylor** (Wycombe Hospital, Buckingham Healthcare NHS Trust, High Wycombe, UK), **Vengudi Sankar** (Royal Bolton Hospital, Bolton NHS Foundation Trust, Bolton, UK), **Anne Smith** (Northampton General Hospital, Northampton, UK), **Nandu Thalange** (Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK), **Chandan Yaliwal** (Royal Berkshire Hospital, Reading, UK).

**Paul Benitez-Aguirre** (The Children's Hospital at Westmead and University of Sydney, Sydney, NSW, Australia), **Fergus Cameron** (Royal Children's Hospital, Murdoch Children's Research Institute and The University of Melbourne, Melbourne, VIC, Australia), **Andrew Cotterill** (University of Queensland, Brisbane, QLD, Australia), **Jennifer Couper** (Women's and Children's Hospital and University of Adelaide, Adelaide, SA, Australia), **Maria Craig** (The Children's Hospital at Westmead, University of Sydney, and University of New South Wales, Sydney, NSW, Australia), **Elizabeth Davis** (Princess Margaret Hospital for Children and University of Western Australia, Perth, WA, Australia), **Kim Donaghue** (The Children's Hospital at Westmead and University of Sydney, Sydney, NSW, Australia), **Timothy W. Jones** (Princess Margaret Hospital for Children and University of Western Australia, Perth, WA, Australia), **Bruce King** (University of Newcastle, Newcastle, NSW, Australia), **Charles Verge** (Sydney Children's Hospital and University of New South Wales, Sydney, NSW, Australia), **Phil Bergman** (Monash Children's Hospital, Clayton, VIC, Australia), **Christine Rodda** (University of Melbourne, Melbourne, VIC, Australia).

**Cheril Clarson** (London Health Sciences Centre and Western University, London, ON, Canada); **Jacqueline Curtis** (The Hospital for Sick Children and University of



Toronto, Toronto, ON, Canada), **Denis Daneman** (The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada), **Farid H. Mahmud** (The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada); **Etienne Sochett** (The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada).

## **2. AddIT TRIAL STEERING COMMITTEE MEMBERS**

Chair-**Prof Sally Marshall** (Newcastle University); **Prof Jane Armitage** (University of Oxford); **Prof Polly Bingley** (University of Bristol), Prof William Van't Hoff (Great Ormond Street Hospital, London), **Prof David Dunger** (University of Cambridge), **Prof Neil Dalton** (King's College London), **Prof Denis Daneman** (University of Toronto), Prof Andrew Neil (University of Oxford), **Prof John Deanfield** (University College London), **Prof Tim Jones**, (University of Western Australia), **Prof Kim Donaghue** (University of Sydney)

## **3. AddIT DATA MONITORING AND ETHICS COMMITTEE MEMBERS**

Chair- **Prof Colin Baigent** (University of Oxford); **Dr Jon Emberson** (University of Oxford); **Prof Marcus Flather** (University of East Anglia Norwich); Professor Rudy Bilous (James Cook University Hospital, Middlesbrough).

## **4. AddIT STUDY COORDINATORS:**

Stella Silvester and Rowena Weighell, University of Cambridge, UK; Yesmino Elia, The Hospital for Sick Children, Toronto, Canada; Dr Charles Czank, Telethon Institute for Child Health Research, University of Western Australia, Perth, Australia.