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Feasibility of once weekly exenatide-LAR and enhanced diabetes care in Indigenous Australians with type 2 diabetes.

(**L**ong-acting-**O**nce-**W**eekly-**E**xenatide la**R**-SUGAR, **"**Lower SUGAR" study)

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INTRODUCTION

The prevalence of diabetes is 3–4 times higher in Aboriginal Australian and/or Torres Strait Islander peoples (hereafter termed Indigenous Australians) than in other Australians [1]. Indigenous Australians living remotely have an earlier onset of diabetes and more often experience serious complications such as end stage kidney disease, blindness, cardiovascular disease (CVD), and amputations [2-4]. In the worst-affected communities renal failure is over 13 times higher in people aged 35–44 years and mortality from CVD is over 8 times higher in Indigenous Australians[1], leading to individuals leaving their communities and families for medical treatment such as dialysis or major cardiac surgery [5]. Complex interactions of the social determinants of health, significant cultural losses and dispossession, racial discrimination, food insecurity, and an early onset, rapidly progressive form of diabetes have contributed to the impact of diabetes on Indigenous Australians.

Previous large, multicentre clinical trials have demonstrated that a range of medications are effective in reducing blood glucose and consequently the complications of diabetes including CVD and death[6]. Yet, thousands of Australians with diabetes do not meet target levels for blood glucose (4-10mmol/L)[7], particularly Indigenous Australians living remotely [8, 9].

The development of the class of GLP-1 receptor agonists represent one of the major advances in diabetes management in the past decade[10]. As well as leading to glucose lowering, they lead to significant weight loss, along with improvements in other cardiovascular risk factors including blood pressure[11], albuminuria[10] and have beneficial effects on lipid profile[11].

Exenatide-LAR is an incretin analogue, administered weekly, that shares glucoregulatory properties with glucagon-like peptide 1 receptor agonists (GLP-1). It improves glycaemic management, with no increased risk of hypoglycaemia, and leads to weight loss in people with type 2 diabetes [12]. A weekly dosing schedule of exenatide-LAR offers potential benefit of supervised delivery, with the opportunity for regular weekly clinical review, education and treatment titration.

This project was developed in response to a desire for increase in clinical contact expressed by Indigenous Australians in remote communities. The project aimed to demonstrate the feasibility of nurse-led care to help communities manage diabetes. Community leaders, Indigenous Australians living with diabetes and clinicians are working together to develop and overcome barriers of diabetes which has a major impact on Indigenous Australians. After establishing that the research was aligned to community priorities, the research team comprising of leading Indigenous Australians academic researchers and respected community members helped develop the study design. The research was conducted with respect for Indigenous peoples and communities' shared values, diversity, priorities, needs and aspirations with the intention of benefiting Indigenous people and communities as well as researchers[17]. Furthermore, the study was conducted with the understanding to enhance the rights of Indigenous peoples as researchers, research partners, collaborators and participants in research[18].

The primary objective of this study was to assess the feasibility of a model of care comprising weekly exenatide-LAR injection and associated clinical review, education and medication titration in remote Indigenous communities. The secondary objectives of the study were to estimate the strength of potential association of weekly administration of exenatide-LAR with weekly clinical review and a reduction of HbA1c, weight and blood pressure. The study was conceived during clinical service within Indigenous communities, and through engaging with Indigenous people with diabetes and community health leaders to identify healthcare needs and solutions.

MATERIALS AND METHODS

Subjects

Indigenous Australian adults with a pre-existing diagnosis of type 2 diabetes from two remote Indigenous Australian communities, 200-300 kilometres from Alice Springs. Participants were eligible for participation in the study if the following inclusion criteria were met; Indigenous Australians aged 18 years or over with type 2 diabetes, HbA1c greater than 7.5% (58 mmol/L), willing and able to provide informed consent. Participants were unable to participate in the study if any of the exclusion criteria were met; a current history of active drug or heavy alcohol use, history of pancreatitis, risk factors for pancreatitis including known cholelithiasis or triglycerides of > 7 mmol/L, active malignancy, an estimated glomerular filtration rate (eGFR) of less than 45ml/min/1.73m^2 , body mass index less than 25 kg/m^2 , type 1 diabetes , severe gastrointestinal disease including gastroparesis, concurrent use of warfarin, alpha-glucosidase inhibitors, orlistat, opioids, anticholinergics, corticosteroids, GLP1 analogues or dipeptidyl peptidase-4 (DPP4) inhibitors and pregnancy* or breastfeeding (Potentially fertile women were required to have adequate contraception to avoid pregnancy. A pregnancy test (urinary HCG), weekly was performed at each study visit prior to administration of each dose of exenatide-LAR injection in the Community with exenatide-LAR. This was introduced during the study period in women of reproductive age) (Table 1).

Materials and Methods

After consultation with community leaders, Indigenous people with diabetes, community health advisory committee(s), Aboriginal Health Care workers, nurses and doctors, and dissemination of information regarding the study throughout the communities, the communities provided verbal and written support for the study.

Two communities in Central Australia with longstanding specialist clinical outreach services were allocated using a random coin toss method to receive once-weekly exenatide-LAR injection with weekly nurse review and adjustment of medication for 20 weeks (community with exenatide-LAR) or to weekly nurse review in addition to standard care over 20 weeks (community without exenatide-LAR). The primary outcome of the study was the feasibility of the intensive diabetes management model of care with and without weekly supervised exenatide-LAR. Feasibility was defined in this study, as an investigation designed to test the viability of methods and procedures for later use on a large scale or to search for possible effects and associations that may be worth following up in a subsequent larger study[13].

Our principal research questions considered the feasibility of:

(i) recruitment, defined as the proportion of the total population with diabetes in the identified communities that were recruited to the study.

(ii) retention, defined as the proportion of participants who completed the study (known as "study completers") these were participants who attended both first (baseline) and final study visit (6 months).

(iii) adherence, defined as:

(a) the proportion of participants who attended more than half of clinic visits.

(b) the proportion of the appointments attended in study completers.

Secondary outcomes were changes in HbA1c, weight and blood pressure.

Ethics approval

The study was approved by each community with letters of support, and the Central Australian Human Research Ethics Committee (HREC-16-368). All participants provided written informed consent. The clinical trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000913572). The study period for registration of participants was between June 2016 to December 2017.

Intervention

At the time of study conception as well as during the conduct of the trial, long acting GLP-1 receptor agonists were not available for use in Australia for people on oral hypoglycaemic agents or in those who were on insulin. Given that these powerful agents lead to weight loss as opposed to the alternative, which is insulin or sulphonylurea, leading to weight gain, this was thought to be highly advantageous for patients. One of the major concerns for patients with diabetes is weight gain with medications.

After extensive community consultation, both communities expressed their wishes to have access and availability to the study medication.

A study coordinator, who was a chronic diseases nurse, was employed to work on the trial to recruit potential participants from two communities. Participants from the community with exenatide-LAR received once-weekly nurse-supervised exenatide-LAR (2mg powder and solvent for prolonged release suspension for injection, *Bydureon, Astra Zeneca*), diabetes education and titration of other diabetes treatments in line with local management protocols, for 20 weeks [14]. Participants in the community without exenatide-LAR received the same intervention but without exenatide-LAR. Diabetes treatment titration and education was provided by a study nurse, and based on local treatment protocols as outlined in the Central Australian Rural Practitioners Association 6th Edition [15]

and the American Diabetes Association guidelines[6]. This included lifestyle modification, assessment of medication use, identifying and addressing issues affecting adherence, dose titration of insulin (where appropriate) and assessment, prevention and education regarding management of hypoglycaemia, and measurement of weight and blood pressure.

Participant inclusion and exclusion criteria are included in Table 1.

Study conduct

Standard capillary blood glucose meters and testing strips were provided to all participants. Participants were shown how to measure and interpret blood glucose readings. Blood glucose readings were recorded, reviewed at each visit, measured at least weekly by local health care clinic staff and reported to treating clinicians as necessary. Medications adjusted during the study period included routinely available glucose-lowering agents including insulin, as deemed necessary by treating clinicians, but excluded GLP-1 receptor agonistsand DPP4 inhibitors. Other cardiovascular risk factors were managed according to evidence-based clinical practice guidelines.

Biochemical Characteristics

Fasting plasma glucose, HbA1c, fasting lipid profile, urine for measurement of albumin to creatinine ratio (ACR) were performed at Western Pathology, Alice Springs. Laboratory measurements of HbA1c were performed using the standardization of HbA1c measurements recommended by the Royal College of Pathologists Australasia and the Australasian Association of Clinical Biochemists[16].

Adverse Events

Potential adverse events were assessed and recorded weekly. Adverse events of interest were nausea and hypoglycaemia. Nausea is the most commonly reported adverse event reported with GLP-1 receptor agonists. Minor hypoglycaemia was classified as symptoms of hypoglycaemia (with or without capillary glucose confirmation), not requiring third party assistance. Severe hypoglycaemia was classified as symptoms of hypoglycaemia (with or without capillary glucose confirmation) requiring third party assistance[6].

Statistical Analysis

Due to the feasibility nature of the study, no prior power analysis was conducted. Data were summarized as medians with interquartile range, or counts and proportions, and analysed using Wilcoxon rank sum tests or $\chi 2$ tests as appropriate. The change in HbA1c was estimated using bootstrapped median regression adjusted for the baseline HbA1c value. The treatment effects estimates were reported as median differences with respective 95% confidence intervals (95%CI). Statistical analysis was performed using Stata v16IC statistical software (StataCorp, College Station, TX, USA).

RESULTS

Thirty-eight Indigenous Australians were recruited, 23 from the community with exenatide-LAR and 15 from the community without exenatide-LAR (Figure 1). No participants had used exenatide-LAR previously. In the community with exenatide-LAR, two individuals withdrew consent, one came off the study due to pregnancy, one was ineligible at screening due to a body mass index (BMI) <25 kg/m^2 and five participants were lost to follow up (Figure 1). In the community without exenatide-LAR, two were lost to follow up (Figure 1). Baseline characteristics for all participants recruited are shown in Table 2 and for those who completed the study in Table 3.

Feasibility of Recruitment

At the beginning of the study, presentations were made to community members, health advisory committee of the local community, and clinic staff about the trial. Posters were hung on community spaces, an investigator presented on the local radio informing the local region about the study and inviting potential eligible participants to consider being part of the trial. A list of eligible participants in the two communities with diabetes were obtained. Out of a potential 1143 Indigenous Australians living in the two communities, 221 had diabetes. Following a pre-screen by the study team to determine inclusion and exclusion criteria from electronic medical records, eligible participants were contacted. Out of these 221, 38 eligible patients (17%) were recruited into the study.

Feasibility of Retention

13 participants from the community with exenatide-LAR and 9 participants from the community without exenatide-LAR completed the study (referred to as study completers) (Figure 1), resulting in a dropout rate of approximately 40%.

Baseline characteristics of the study completers versus non-study completers were not statistically different except for height (Supplementary table 1). Baseline characteristics for those recruited (Table

2) and study completers (Table 3) were similar between the communities except for height (Table 3, p=0.031).

Feasibility of Adherence (a) the proportion of participants who attended more than half of clinic visits.

In study completers, the proportion of participants who attended more than half of visits in the community with exenatide-LAR was 11 out of 13 (85%) compared to 6 out of 9 (67%) clinic visits in the community without exenatide-LAR.

Feasibility of Adherence (b) the proportion of the appointments attended for study completers.

In study completers, the median (interquartile range) individual number of visits attended (of a maximum possible 21) in the community with exenatide- LAR was 15 (IQR 13, 18), corresponding to 71% (IQR 62%, 86%) of all possible visits. In study completers, the median number of visits in the community without exenatide-LAR was 13 (IQR 9, 16), corresponding to 62% (IQR 43%, 76%), p=0.50.

Adverse events

Adverse events are summarized in Table 4 and included diarrhoea, gastroenteritis, hypoglycaemia, nausea, vomiting, injection-site nodules and injection site pruritus. None of the individuals withdrew from the study due to intolerability of the medications**.** One participant became pregnant due to failed contraception. Medications per site at Baseline and Final Visit are listed in Supplementary Table 2. Medications of all participants from Baseline vs Final Visit are listed in Supplementary Table 3.

The total number of adverse events in the community with exenatide-LAR was 30. The total number of adverse events in the community without exenatide-LAR was 4. In the community with exenatide-LAR, 1 gastroenteritis viral event, 3 hypoglycaemic events, 12 diarrhoea events and 4 nausea events 8 events of injection-side nodules and 2 events of injection site pruritus were recorded. In the community without exenatide-LAR, 2 hypoglycaemic events, 1 nausea event and 1 vomiting event were recorded.

Proportion of hypoglycaemic episodes in the Exenatide- LAR vs without Exenatide-LAR

In study completers, self-reported hypoglycaemic episodes in the community with exenatide-LAR were reported by 3 out of 13 participants, (23% of participants) compared to 2 out of 9 (22% of participants) in the community without exenatide-LAR. There were no episodes of severe hypoglycaemia recorded.

Secondary outcomes: Glycaemic management, weight and blood pressure

In study completers, the median difference in the change in HbA1c from baseline to final visit, adjusted for baseline HbA1c value, between the community with exenatide-LAR and the community without exenatide-LAR was -3.1%, 95% CI [-5.80%, -0.38%; p=0.03] (Figure 2).

In study completers, the final median HbA1c of those who attended >50% of visits in the community with exenatide-LAR was 8.1%, (IQR 7.7%, 9.4%) [65 mmol/L (IQR 61-79)mmol/L], compared to a median HbA1c of those in the community without exenatide-LAR of 10.9%, (IQR 9.1%, 12.5%) [96 mmol/L (IQR 76 – 113)mmol/L]. The median difference in the change in HbA1c of those who attended >50% of visits, between the community with exenatide-LAR and the community without exenatide-LAR, from baseline to final visit, adjusted for baseline HbA1c value was -3.35%, 95% CI [-6.42%, -0.29%; p=0.034].

In study completers, only 4 complete weight datapoints (baseline and final visit) from the community with exenatide-LAR and 11 from the community without exenatide-LAR were recorded. The median difference in weight between the community with exenatide-LAR and the community without exenatide-LAR, from baseline to final visit adjusted for baseline weight value, was 1.1kg, 95%CI [-8.11 kg, 10.3kg; p=0.80].

In study completers, the median change in systolic blood pressure, mmHg, from baseline for the community with exenatide-LAR was -3.3 mmHg (n=13, IQR -16.2, +6.2mmHg), compared to the community without exenatide-LAR, -8.3 mmHg (n=9, IQR -16.7, +10.3mmHg). The median change in diastolic blood pressure, mmHg, from baseline for the community with exenatide-LAR was -2.7 mmHg (n=13, IQR -7.3, +4.6mmHg), compared to the community without exenatide-LAR, -3.5 mmHg (n= 9, IQR -9.7, 3.8mmHg).

DISCUSSION

This study demonstrates that a new model of care for managing type 2 diabetes in remote Indigenous communities, involving weekly nurse review with or without exenatide- LAR injections, is feasible. The secondary outcomes demonstrated a greater improvement in glycaemic management in the community with exenatide-LAR compared to the community without exenatide-LAR. Weekly exenatide-LAR injections were associated with greater clinic attendance suggesting that the offer of supervised medication dosing provided added incentive to attend.

Implication of the study findings

This is the first cluster randomised interventional study of a glucose lowering injectable medication completed in remote Indigenous Australian communities. Although the need for robust clinical evidence base in this high-risk patient population is clear, the majority of published research is descriptive, with limited number of interventional studies [19]. The design of the study demonstrates that a pragmatic approach to the evaluation of new treatments for complex chronic condition such as diabetes is possible.

Social determinants of health including poverty, over-crowded housing, access to primary and specialist health care are important to consider in chronic disease management[20]. Long-term, high-quality chronic disease management in remote Indigenous populations is essential to aim for but is faced by challenges [21]. When staffing is consistently maintained and individuals are engaged and willing to accept care, clinical management structures with training and workshops for staff importantly for Indigenous Health care workers can result in improvement in the proportion of individuals achieving glycaemic targets [22-24] . Specialist outreach care can also lead to improved outcomes for people with diabetes [8]. The current study demonstrates the feasibility of an alternative diabetes model of care with supervised weekly injectable medication which is safe and can lead to significant improvements in glycaemic management in remote Indigenous communities.

Comparison to other studies

Previous studies have shown glucose lowering benefits of exenatide-LAR [10, 25-27]. Recent trials using GLP 1 agonists have shown both glucose lowering and added CVD protection[28]. This study highlights the importance of a model of care that incorporates the use of one of these agents safely and effectively in a high-risk population.

Previous studies in remote communities looking at chronic disease management have shown that multifactorial community-based intervention programs addressing lifestyle factors may lead to improvements in risk factors for chronic conditions [29]. Furthermore, culturally safe, community level health-worker led models of diabetes care for high risk patients may be effective in improving glucose levels in remote Indigenous Australian communities [30, 19]. The polypill study did not show a significant improvement in cardiovascular risk factors when compared to enhanced usual care [31], but was associated with significant improvements in adherence. There is a scarcity of clinical trials performed in remote settings, and the obstacles to performing clinical research is this setting are myriad. Recruitment and retention of study participants in this peripatetic group of people can be difficult,

and the logistics relating to research in isolated, remote and climatically harsh setting makes clinical research particularly challenging.

Strengths and limitations

While a randomised, placebo-controlled trial would provide more robust findings, the realities of research in remote Indigenous Australian communities makes such approaches challenging. Despite this, with limited numbers of participants, we have demonstrated findings that are in concordance with earlier studies in populations far removed from this study setting. We would like to acknowledge the importance of economic evaluations in clinical trials however it would be difficult to properly evaluate this on the basis of this feasibility study. Performing clinical trials in remote Indigenous communities presents a unique set of challenges. Important considerations include allowing sufficient time for developing relationships, trust and engagement between research staff and community members. There was significant dropout in the study of 40% which limits the interpretation of the findings. There was also a period of suspension of approximately two months in recruitment and follow up, following resignation of the initial study coordinator until new study coordinators were recruited. This had an impact on the retention of the pre-existing study participants. These are some reasons which may explain the high dropout rate in our study. Despite this greater than 50% of the clinic visits were attended in 85% of individuals in the Community with exenatide-LAR and 67% in the Community without exenatide-LAR. The fact that addition of supervised weekly exenatide-LAR was associated with more clinic attendance may indicate possibly that the offer of supervised medication dosing provided added incentive to attend. Future studies in this setting should address this issue by adequately powering for dropout, and by working closely with communities to encourage participation and follow up. Importantly, the project led to access of a previously unavailable once weekly medication with potential benefit in terms of diabetes management.

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CONCLUSIONS

This study for the first time demonstrates the feasibility of supervised once weekly exenatide-LAR as part of an intensive diabetes management program in a remote Indigenous community setting. The results highlight the potential benefits of this approach in Indigenous communities which have some of the highest rates of diabetes complications, including kidney disease and CVD in the world. The

findings of the project show that this model of care is feasible and that long-term, such models of care can be sustainable or transferrable with appropriate funding and support.

AUTHOR CONTRIBUTIONS

Elif I Ekinci (study design, application for funding, HREC application, data collection and analysis, statistical analysis, writing), Felicity Pyrlis (recruited participants at one of the sites, contributed to study design and conduct), Mariam Hachem (data collection, statistical analysis and writing), Louise Maple-Brown (study design, application for funding, HREC application, writing), Alex Brown (study design, application for funding, HREC application, writing), Graeme Maguire (study design, application for funding, HREC application, writing), Leonid Churilov (statistical analysis, write-up), Neale Cohen (study design, application for funding, HREC application, data collection and analysis, statistical analysis, writing**).**

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Figure Legends:

Figure 1. Study profile

Participants who completed the study protocol with an initial and final HbA1c measurement were considered evaluable, and therefore data from 9 participants in the Community without exenatide-LAR and 13 participants in the Community with exenatide-LAR were included in the final analysis.

Figure 2. Change in HbA1c (%) from baseline

Median (IQR) change in HbA1c (%) from baseline in the community without exenatide-LAR and the community with exenatide-LAR for those who completed the trial.

Table 1. Study Inclusion and Exclusion Criteria.

Inclusion Criteria	*Exclusion Criteria*
• Indigenous Australians aged 18 years or over with type 2 diabetes • HbA1c greater than 7.5% (58 mmol/L) • Willing and able to provide informed consent	• a current history of active drug or heavy alcohol use • history of pancreatitis • risk factors for pancreatitis including known cholelithiasis or triglycerides of > 7 mmol/L • active malignancy • an estimated glomerular filtration rate (eGFR) of less than 45ml/min/1.73m^2 • body mass index less than 25 kg/m^2 • type 1 diabetes • pregnancy* or breastfeeding • severe gastrointestinal disease including gastroparesis • concurrent use of warfarin, alpha-glucosidase inhibitors, orlistat, opioids, anticholinergics, corticosteroids, GLP-1 receptor agonists or dipeptidyl peptidase-4 (DPP4) inhibitors.

***** Potentially fertile women were required to have adequate contraception to avoid pregnancy. A pregnancy test (urinary HCG), weekly was performed at each study visit prior to administration of each dose of exenatide-LAR injection in the Community with exenatide-LAR. This was introduced during the study period in women of reproductive age

Table 2. Baseline characteristics of all participants

	Community without exenatide-LAR	**Community with exenatide-LAR**
N	13	19
Female (%)	11 (84.6%)	13 (68.4%)
Age (years)	45.4 (38.2, 52.7)	51.3 (41.9, 58.6)
HbA1c (%)	11.6 (10.9, 13.1)	10.2 (8.4, 11.0)
HbA1c (mmol/L)	103 (96-119)	88 (68-97)
Waist (cm)	112.0 (96.0, 124.0)	119.5 (109.1, 130.0)
Weight (kg)	83.2 (73.8, 109.3)	98.4 (88.7, 124.6)
Height (m)	1.63 (1.58, 1.67)	1.70 (1.67, 1.82)
BMI (kg/m^2)	31.7 (26.3, 40.5)	32.2 (28.9, 40.0)
Duration of Diabetes (years)	7 (6, 13)	8 (6, 12)
Total Cholesterol (mmol/L)	4.0 (3.6, 4.9)	4.0 (3.5, 4.7)
HDL (mmol/L)	0.8 (0.8, 0.9)	0.9 (0.70, 1.0)
LDL (mmol/L)	1.9 (1.7, 2.4)	2.1 (1.7, 2.5)
Triglycerides (mmol/L)	2.4 (1.6, 3.6)	2.1 (1.1, 2.9)
Creatinine (umol/L)	74 (62, 92)	67.5 (58, 74)
Sodium (mmol/L)	135 (132, 137)	135 (134, 137)
Potassium (mmol/L)	4.8 (4.2, 5.7)	4.3 (4.2, 4.5)
ALT (U/L)	21 (18, 41)	28.5 (23.5, 38.5)
AST (U/L)	19 (16, 36)	20 (15, 27)
Fasting glucose (mmol/L)	17.5 (15.8, 18.6)	15.3 (13.2, 19.8)
ACR (mg/mmol/L)	22.1 (7.0, 230.3)	9.35 (3.6, 127.7)

Urea (mmol/L)	6.3 (4.9, 6.8)	5.5 (4.5, 7.5)
CKD EPI eGFR ml/min/1.73m^2	90 (67, 109)	98 (83, 105)
Systolic BP (mmHg)	126.3 (122.3, 133.0)	127.0 (113.3, 134.0)
Diastolic BP (mmHg)	83.3 (80.0, 88.3)	77.5 (69.7, 84.7)
Heart Rate (bpm)	90.0 (83.0, 100.0)	89.0 (75.0, 97.7)

Data are presented as median and interquartile range or as proportions.

Table 3. Baseline characteristics of final participants for efficacy assessment (study completers).

	Community without exenatide-LAR	Community with exenatide-LAR	p-value
N	9	13	
Female (%)	8 (88.9%)	8 (61.5%)	0.17
Age (years)	45 (38, 52)	51 (42,64)	0.14
HbA1c (%)	11.6 (11.1, 12.8)	10.2 (9.0, 11.0)	0.089
HbA1c (mmol/L)	103 (98-116)	88 (75-97)	0.089
Waist (cm)	112 (95.5, 124)	119.5 (108,136)	0.22
Weight (kg)	94.1 (76.6, 109.3)	97.4 (87.1, 119.6)	0.40
Height (m)	1.64 (1.60, 1.67)	1.70 (1.67, 1.83)	0.032
BMI (kg/m^2)	31.7 (26.1, 37.7)	34.4 (31.0, 40.0)	0.46
Duration of Diabetes (years)	7 (6, 14)	8.5 (7, 12)	0.74
Total Cholesterol (mmol/L)	4.2 (3.9, 4.9)	4.4 (3.6, 5.1)	0.78
HDL (mmol/L)	0.8 (0.8, 0.9)	0.9 (0.8, 1.0)	0.32
LDL (mmol/L)	2.1 (1.8, 2.6)	2.1 (1.8, 2.5)	0.97
Triglycerides (mmol/L)	2.4 (1.6, 3.6)	2.3 (1.3, 2.9)	0.24
Creatinine (umol/L)	74 (54, 91)	69.5 (62.5, 82)	0.97

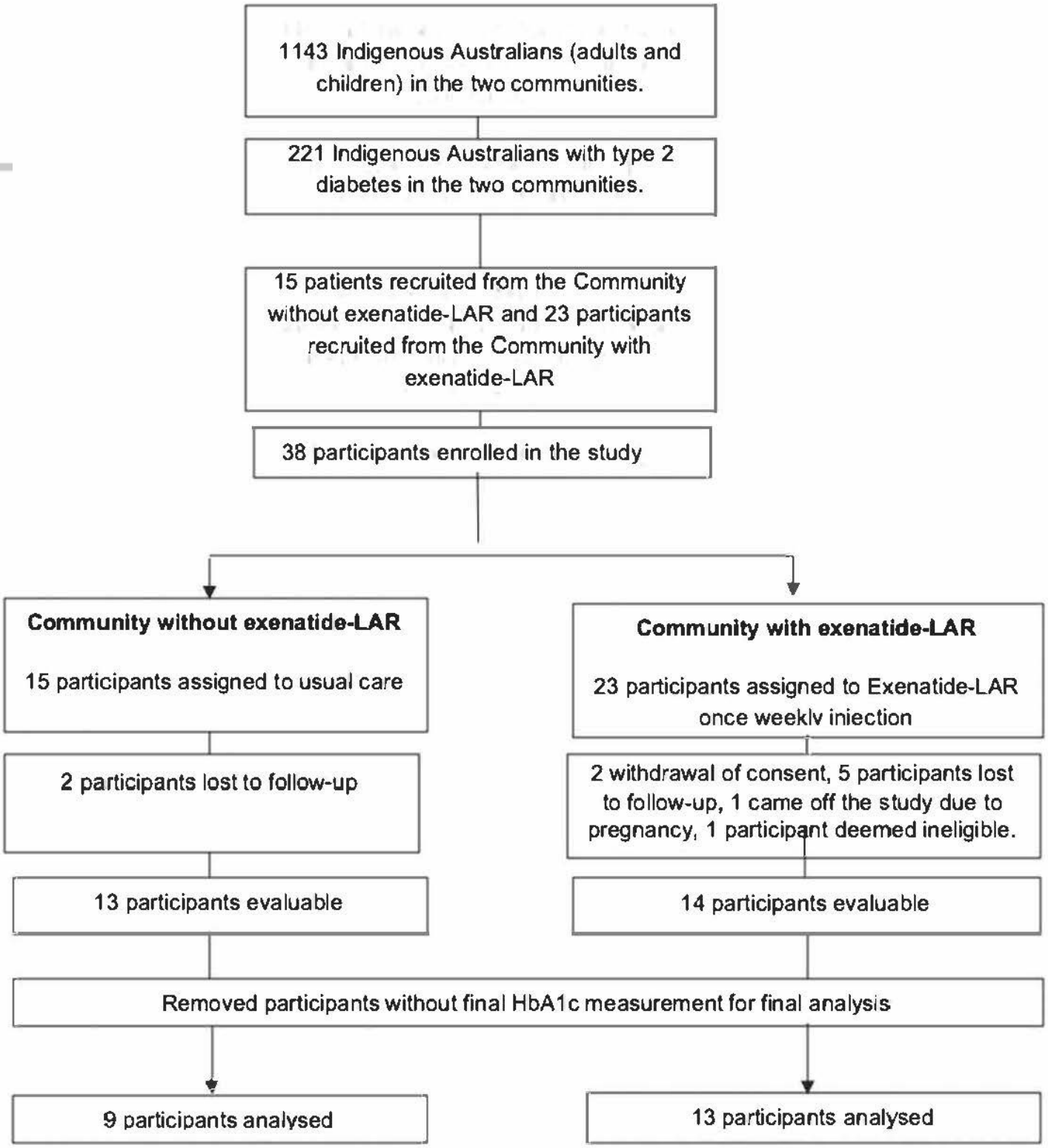
Sodium (mmol/L)	135 (134, 137)	135 (133, 137)	0.85
Potassium (mmol/L)	4.5 (4.3, 4.7)	4.3 (4.0, 4.4)	0.11
ALT (U/L)	21 (18, 41)	27.5 (21, 40)	0.59
AST (U/L)	24 (16, 36)	19 (14, 27)	0.48
Fasting glucose (mmol/L)	16.0 (9.2, 17.7)	15.3 (13.2, 20.2)	0.46
ACR (mg/mmol/L)	86.3 (8.5, 230.3)	27.6 (4, 178.2)	0.37
Urea (mmol/L)	6.5 (5.2, 7.2)	5.8 (4.9, 7.7)	0.62
CKD EPI eGFR ml/min/1.73m^2	98 (67,110)	89 (77, 101)	0.62
Systolic BP (mmHg)	126.3 (125,133)	127 (115.3, 136.8)	0.86
Diastolic BP (mmHg)	85.7 (82.3, 88.3)	78.3 (68.5, 88.3)	0.23
Heart Rate (bpm)	90 (83, 100.3)	89.0 (73.5, 91.5)	0.27

Data presented as medians and interquartile range, or as proportions, comparisons performed using a Wilcoxon rank-sum test, with $p<0.05$ denoted as statistically significant.

Table 4. Adverse Events

	Community without exenatide-LAR	**Community with exenatide-LAR**
Total Number of Adverse Events	4	30
Gastroenteritis viral	0	1
Hypoglycaemia	2	3
Diarrhoea	0	12
Nausea	1	4
Vomiting	1	0
Injection Site Nodules	0	8
Injection Site Pruritus	0	2

Data shown as total number of adverse events within each group.



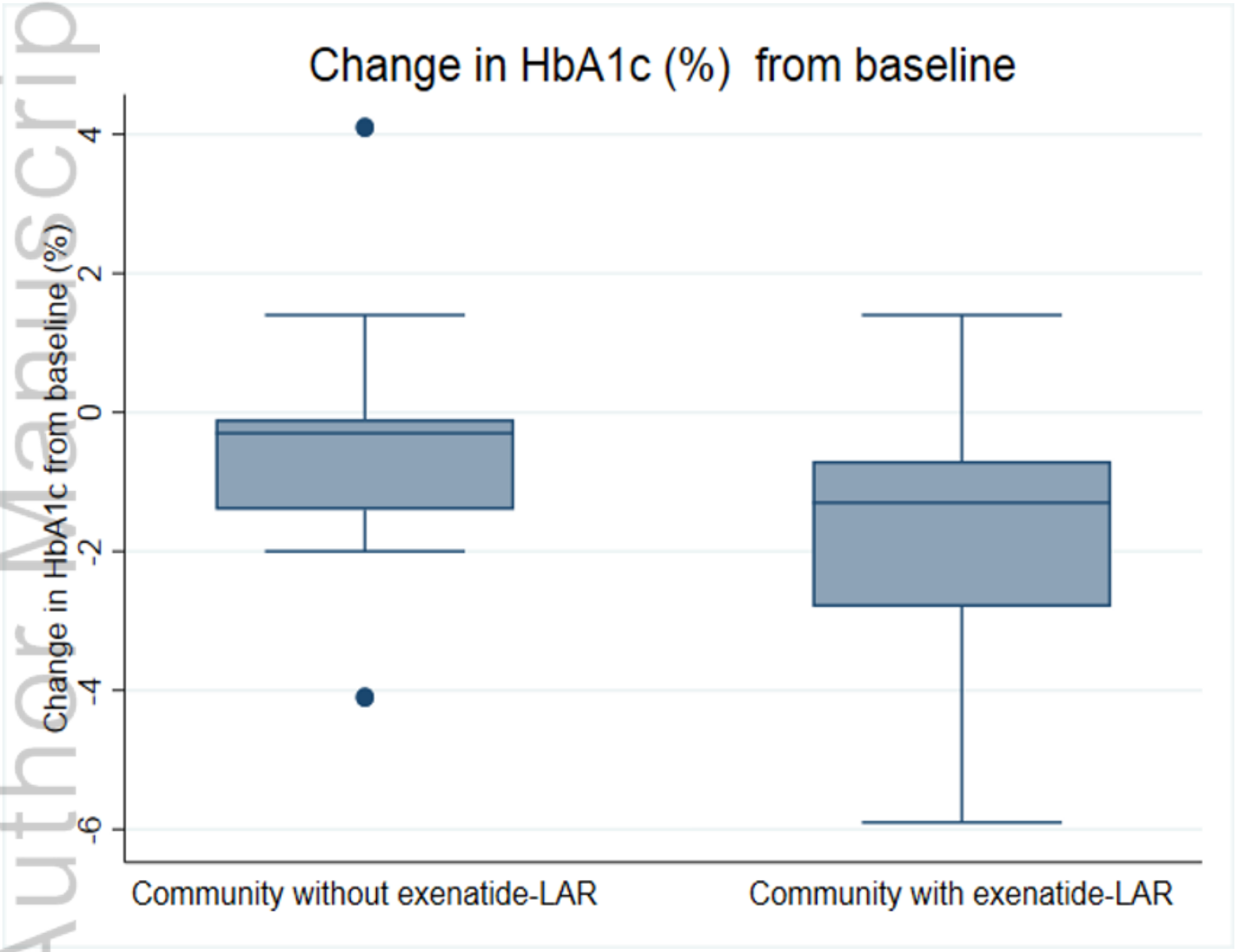


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Table 1. Study Inclusion and Exclusion Criteria.

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