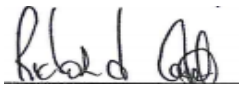
INCA-SUN Statistical Analysis Plan

Study Title: Inhaler Adherence in Severe Unstable Asthma (INCA-SUN)

Final Version approved by Prof Richard Costello, P.I.:

 14/3/2019

1 Introduction

1.1 Background

Many patients with asthma remain poorly controlled despite the use of inhaled corticosteroids and long-acting beta agonists. Poor control may arise from inadequate adherence, incorrect inhaler technique or because the condition is refractory. Without having an objective assessment of adherence, clinicians may inadvertently add extra medication instead of addressing adherence. This study aims to assess if incorporating objectively recorded adherence from the Inhaler Compliance Assessment (INCA) device and lung function into clinical decision making provides more cost-effective prescribing and improves outcomes.

1.2 Objective

The investigators hypothesize that aligning adherence with the patient's own clinical course achieves better asthma control and identifies risks for future loss of control, compared to current best practice. The study has an adherence optimisation phase, weeks 1-12 followed by a medication management phase, weeks 12 to 32.

The investigators will compare two asthma education interventions, standard Guideline recommended practice and feedback from the individual's own INCA device, which assess inhaler adherence and relates adherence with changes in PEFR and symptom scores over time.

The primary aim of the study is to assess the impact of incorporating objective adherence information into Guideline recommended medication management.

A secondary aim is to assess the long-term effectiveness of this approach on control and exacerbations.

Specific objectives of the study are outlined below:

1.3 Primary endpoints:

- To compare difference in appropriate asthma medication prescription at the end of the study. In this case, appropriate refers to therapy after two GINA-recommended cycles of review and medication changes with prior knowledge of adherence.
- To compare actual adherence to ICS/LABA therapy. This will be assessed by the between-group (active and control) difference in the mean actual adherence to twice daily salmeterol/fluticasone use over the last 12 weeks of the study.

1.4 Secondary Endpoints

1.4.1 Patient-reported outcomes

- To compare the asthma control test (ACT), Asthma Quality of Life Questionnaire scores, peak expiratory flow rate (PEFR) between the active and control groups

1.4.2 Clinical outcomes

- To examine and compare the proportion of patients reaching stated clinical goals in the active and control groups.
- To compare the proportion of patients who are refractory, defined as having actual adherence ≥80%, ≥1 exacerbations, PEFR am/pm <80% and ACT ≤19.
- To compare the proportion of patients who are non-adherent and remain uncontrolled, that is, actual adherence <80%, PEFR am/pm <80% and ACT ≤19.
- To compare the time to first exacerbation (defined by ≥20% fall in PEFR and at least doubling of reliever use for three consecutive days or prescribed rescue oral steroid) between the active and control groups.
- To compare the proportion of patients with inhaler-related side effects, including oral candidiasis, between the active and control groups.
- To compare changes in blood eosinophils, periostin and fractional exhaled nitric oxide (FeNO) between the active and control groups.
- To investigate the relationship of biomarker changes in relation to adherence.
- To compare the proportion of patients who were clinically stable (i.e., proportion of patients who required no daily reliever use in the month prior to study end) between the active and control groups.
- To investigate the relationship between changes in FeNO (characterised into FeNO ≥45 ppb or FeNO <45 ppb) and adherence.
- To investigate the relationship between 7 day FeNO suppression and clinical and biomarker outcomes.

1.4.3 Economic outcomes

- To conduct a cost-effectiveness and cost-utility analysis of the Inhaler Compliance Assessment (INCA) educational intervention compared with the control arm.. In addition, conduct an economic evaluation of a national implementation of the INCA-SUN programme (budget impact analysis).
- To compare the average time lost to work between the active and control groups.

1.5 Study Design

INCA-SUN is a multicentre, parallel group, prospective randomised controlled trial. Patients will be recruited through secondary care in 10 sites throughout Ireland and the UK (6 Irish, 4 UK).

The study consists of a screening phase, followed by six clinic visits, with additional visits to the study nurse to dispense medication. Study outcomes are assessed at visits 5 and 6 (weeks 20 and 32).

1.6 Required sample size

The sample size required was estimated based on the two primary endpoints, and the study sample size chosen as the larger of the two estimates. In all cases a two-sided significance level of 0.05 was assumed. Additional sample size calculations for secondary endpoints were performed and are included in Appendix A.

1.6.1 Primary outcome 1: proportion of patients prescribed whose therapy is stepped up.

The INCA-1(1) study found that 60% of patients remained poorly controlled at the end of the study period, and were thus eligible for step-up therapy. Of these fewer than 50% met clinical indications for the prescription of ant-IgE monoclonal antibody treatment (omalizumab), giving approximately 30% of patients suitable for biologic therapy. However, the majority of these patients (approx. 60%) were also poorly adherent, suggesting that if adherence assessment were incorporated into medication management, the number of patients referred for biological therapy would be reduced to approximately 10%.

We estimated the sample size needed to detect a between group difference of 20%, where the proportion of patients eligible for step up is 30% in the control group and 10% in the active group.

Based on a chi-squared test comparing two independent proportions, the sample size required to detect such a difference with 90% power is 82 per group. Allowing for a 10% dropout rate, this gives a total required sample size of 181.

1.6.2 Primary outcome 2: Mean adherence rate in weeks 20-32

Based on the results of the INCA-1 study, we expect a between-groups difference in actual adherence rate at the end of the study of approximately 10% (Pooled s.d. 25%).

The sample size required to detect this difference with 80% power in a two-sided t-test is 100 per group. Allowing for 10% dropout rate, this gives a total requires sample size of 220.

On the basis of these calculations we aim to recruit 110 patients in each group for a total of 220 patients.

1.6.3 Study population

The population of interest is patients with severe uncontrolled asthma currently on GINA stage 3-4 therapy and prescribed an ICS/LABA inhaler. Precise inclusion and exclusion criteria are listed on the clinical trials registry and the protocol provided.

2 Statistical Analysis Plan (SAP)

2.1 Reporting of data

The first stage of analysis will be to use descriptive statistics to describe recruited individuals and to investigate comparability of the trial arms at baseline.

Continuous variables will be reported with mean and standard deviation for data which are approximately normally distributed, and median and interquartile range for skewed distributions.

Categorical variables will be reported as the number and percentage of total in each category.

All variables will be described for each study group separately, and for all participants together.

2.2 Study populations

The primary analyses will involve intention-to-treat comparisons between the two groups. A per-protocol analysis will also be conducted.

Intention-to-treat (ITT) population

All participants who were randomised and attended at least one study visit and for whom at least one month's adherence and PEFR data was available.

Per Protocol (PP) population

All participants from the ITT population excluding those who dropped out of the study prior to visit 6.

2.3 Analysis

2.3.1 General Principles

Data analysis and reporting will proceed according to CONSORT guidelines (2) for randomised controlled trials. Primary analysis will be performed according to the intention to treat principle. Additional per-protocol analysis will be performed to assess effects of differential dropout and sensitivity to missing data. No formal interim analysis will be undertaken.

All results and parameter estimates will be presented along with 95% confidence intervals. Unless otherwise stated a two-sided significance level of 0.05 will be used in all tests of statistical significance.

2.3.2 Software

All analysis and data-cleaning will be performed using Stata 15 software (StataCorp LLC, Texas, U.S.A.). Graphs and tables will be prepared using Stata and GraphPad Prism (GraphPad Software, Inc. California, U.S.A.).

2.3.3 Missing Data

A CONSORT diagram will be produced to describe study flow, including withdrawal of patients, post-randomisation exclusions and other causes of missing data (device failures, inability to complete questionnaires, etc.). Where possible reason for participant withdrawal will be recorded.

Data will be collected during clinic visits and entered through a purpose built electronic Case report Form (eCRF) system. The eCRF does not allow visits to conclude without entry of all necessary data, thus significantly reducing the likelihood of missing data due to non-entry. In the case of patients missing scheduled visits, visits will be re-scheduled at the earliest available opportunity.

For ITT analysis missing primary outcome data will be imputed using Multiple Imputation by Chained Equations (MICE) in Stata 15 (3, 4). Data missing due to device failures will be considered Missing Completely at Random (MCAR). Data missing due to subject withdrawal will be assumed Missing at Random (MAR) unless the reason given for withdrawal contradicts this assumption (e.g. withdrawal due to poor asthma control or adverse reaction to treatment).

2.3.4 Analysis of primary outcomes

The primary analyses will involve intention-to-treat comparisons between the two groups with transformation as appropriate after examination of distributions and adjustment for age, sex, FEV1 and stratification variables (i.e. site and day 7 FeNO (FeNO ≥45ppb or FeNO

<45ppb)). Secondary analyses will investigate the effects of further adjustment for any variables displaying marked imbalance between the groups at baseline.

The **first primary outcome** is the between-group difference in the proportion of patients prescribed guideline appropriate medication at the end of the study. The appropriateness of the prescribed therapy will be verified for each participant after study completion using all available adherence and PEFR data.

Further analyses will involve planned subgroup analyses

- Proportion of participants prescribed add-on therapy (e.g. Monoclonal antibody therapy, Maintenance Oral Corticosteroids)
- Proportion of participants whose ICS/LABA dose was increased
- Proportion of participants whose ICS/LABA dose was reduced

All analyses will use appropriate logistic regression models. Random or fixed effect models will be used as appropriate to control for study site effects. Results will be presented as odds ratios, 95% confidence intervals and p values.

The **second primary outcome** is the between-groups difference is the mean actual adherence rate over the final 12 weeks of the study. The actual adherence rate is the adherence rate corrected for technique and timing errors and is calculated using the method of Sulaiman et al. (5).

This outcome will be analysed in a similar way to the first but using linear regression models, with results presented as mean differences, 95% confidence intervals and p-values.

2.3.5 Analysis of secondary outcomes

Patient reported outcomes.

Between group differences in ACT, AQLQ and PEFR. As outlined for the primary outcome, comparisons between the two groups will be conducted with transformation as appropriate after examination of distributions, and adjustment for demographic and stratification. Secondary analyses will investigate the effects of further adjustment for any variables displaying marked imbalance between the groups at baseline. All analyses will use appropriate (that is, logistic or linear) regression models, with results presented as point estimates (odds ratios or difference in means), 95% confidence intervals and p values.

Clinical Outcomes

For most clinical outcomes, between-group differences will be investigated as described above for the primary outcomes and patient reported outcomes.

Time-to-event outcomes will be analysed with Cox-proportional hazards regression and corresponding Kaplan-Meier curves. Where the proportional hazards assumption is not met an appropriate parametric survival analysis method may be applied.

Economic outcomes

Cost utility analysis will be performed based on an Irish public healthcare perspective, comparing the INCA intervention to usual care. The primary effectiveness outcome will be Quality Adjusted Life Years (QALY), with number of exacerbations requiring treatment as a secondary outcome. The Incremental Cost Effectiveness Ratio (ICER) will be estimated over a 32 week time horizon. In addition established asthma Markov model may also be employed to assess cost effectiveness over a 10 year period. Further details of the cost-effectiveness analysis are given in Appendix B

Time lost to work will be reported as the mean difference between groups, and corrected for study site and covariates in the same manner as for the second primary outcome.

2.3.6 Further Subgroup Analyses

Primary analyses will be repeated separately for subgroups defined by clinical stratification variables, including baseline FeNO. FEV1 and Eosinophil count.

2.3.7 Sensitivity Analysis

Treatment management decisions made during the study rely on a cut-off value for good adherence (>=80%). Sensitivity analysis will be performed to determine the influence of this cut-off value on the primary outcome.

2.4 Safety Outcomes

2.4.1 Adverse Events

All adverse Events (AEs) and Severe Adverse Events (SAEs) as defined by European Medical Association (EMA) guidelines will be recorded in detail, and the number and percentage in each group reported.

Between-group difference in the number of AEs and SAEs will be analysed and reported as for other outcomes. SAEs causally linked to the study intervention will be reported in detail.

2.4.2 Withdrawals

The number and percentage of participants lost to follow-up will be reported for each group.Reasons for withdrawal will be recorded and included in the Consort diagram.

Loss of follow-up data due to device failures will also be reported.

3 References

1. Sulaiman I, Greene G, MacHale E, Seheult J, Mokoka M, D'Arcy S, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. Eur Respir J. 2018;51(1).

2. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.

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4. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. J Stat Softw. 2011;45(4):1-20.

5. Sulaiman I, Seheult J, MacHale E, Boland F, O'Dwyer SM, Rapcan V, et al. A Method to Calculate Adherence to Inhaled Therapy That Reflects the Changes in Clinical Features of Asthma. Ann Am Thorac Soc. 2016.

6. Zafari Z, Lynd LD, FitzGerald JM, Sadatsafavi M. Economic and health effect of full adherence to controller therapy in adults with uncontrolled asthma: A simulation study. Journal of Allergy and Clinical Immunology. 2014;134(4):908-U522.

7. Murphy C, Bennett K, Fahey T, Shelley E, Graham I, Kenny RA. Statin use in adults at high risk of cardiovascular disease mortality: cross-sectional analysis of baseline data from The Irish Longitudinal Study on Ageing (TILDA). BMJ Open. 2015;5(7):e008017.

Appendices

Appendix A – Additional Sample Size Calculations

Sample size for AQLQ difference

The INCA-1 dataset showed a pooled standard deviation of 1.49 in AQLQ at completion of the study. Assuming a standard deviation of 1.5, the sample size needed to detect a minimal clinically significant difference of 0.5 with 80% power and a 10% dropout rate is 148 per group for a total of 296.

Sample size for ACT difference

Seventy-four patients per treatment group provides an estimated 90% power to detect a minimal clinical important difference of 3 points, by using a two-sided t-test and assuming an SD of 5.3 as found in the INCA-1 dataset, and a dropout rate of 10%.

Sample size for cost

Assuming a cost of Severe Refractory asthma of €4,000 (SD 2000) per annum, and for others €2000 (SD 2000) and estimating to see a cost difference between active and control of €1000 per annum an estimated sample size of 80 in each group is required.

Sample size for PEF AUC difference

Eighty two patients per treatment group provides an estimated 80% power to detect a treatment difference of 8% in PEF by using a two-sided t test, assuming a SD of 17.3 and dropout rate of 10%.

Sample size for difference in exacerbation rate (time-to-event analysis)

The sample size required to detect a reduction in exacerbation hazard rate of 30% (Hazard ratio 0.7) with 80% power based on an exponential test is 128 per group, for a total of 256.

Longitudinal disease modelling.

Employing multi-level survival analysis on the course of asthma over time we can assess the interaction of predictors including adherence, FeNO, blood biomarkers (peripheral blood

eosinophils, periostin), symptoms and lung function and events (dependents) such as exacerbations in a continuous time domain.

Appendix B: Economic evaluation

Type of evaluation

Cost-utility analysis with quality adjusted life years gained (QALYs) as effectiveness outcome (to allow for across disease comparisons) supplemented by a secondary cost-effectiveness analysis with all treated exacerbations as effectiveness outcome (to allow for asthma specific comparisons).

Perspective

The proposed economic evaluation will adopt an Irish publicly-funded health perspective (including all substantial direct medical costs incurred in the treatment of the participants as recommended by the Irish Health Information and Quality Authority (HIQA)) as well as a societal perspective (also including indirect costs such as work productivity losses).

Time horizon

A 32 week time horizon will be used, corresponding to the trial length. However, we anticipate that the time horizon is limited since it is less than one year and hence the impact of seasonal influences will not be assessed. As such, costs and effects may be impacted beyond the 32- week time horizon. Therefore in addition, economic modelling, based on an established asthma Markov model, may be used to assess the cost-effectiveness over a 10 year time horizon (6).

Comparator

The INCA device intervention will be compared to routine care as described in this protocol.

Target population

Severe uncontrolled asthma patients as specified in the study protocol.

Resource-use measurement, valuation and costs

The main areas of resource use to be collected are: (i) health care utilisation, (ii) medication costs and (iii) costs associated with the INCA intervention. Health care utilisation data will be collected on (i) numbers of GP visits, (ii) number and duration of Emergency department attendance and (iii) number, duration and reason for hospital admissions (if any).

Medication costs will be collected including details of dose, frequency and type of medications use and the duration of medication use. Information on concomitant medications will also be recorded, but information on costs, unless directly related, will not be included. The time for delivering the intervention and device cost will be recorded as part of the study protocol. The differential costs associated with managing patients in the two arms of the trial will be estimated from data from the trial and from unit costs available from the participating hospitals. GP visits cost between approximately €50 and €70 per visit (7). Days in hospital will be costed using average cost per patient per day based on Drug Related Group (DRG) case-mix costs. These costs include all resources used during the hospital stay. Drug costs will be available via the Monthly Index of Medical Specialities (MIMS) or costs for reimbursable items under the community drug schemes. Time for delivering the intervention will be costed using the Health Sector Executive (HSE) salary scales at the time of the study, including pay related social insurance (PRSI).

Sensitivity analyses

Probabilistic (to assess parameter uncertainty) and deterministic (to assess key parameters that impact the ICER most) sensitivity analyses will be performed to assess the robustness of the ICER obtained via the model. Results of the deterministic analyses will be depicted using a tornado diagram. Scatter plots and cost-effectiveness acceptability curves (CEACs) will be used for the results of the PSA.

Budget impact analysis

To inform the payer regarding the affordability, a budget impact analysis will be presented along with the economic evaluation.

Outcomes

Asthma specific and general quality of life will be assessed using the AQLQ and EQ-5D-3L respectively. Utility will be derived from the EQ-5D scores using Irish valuation tariffs. It is anticipated that Irish valuation tariffs will be available by the end of the trial. In the absence of Irish public preference data, UK tariffs will be considered. Regarding the exacerbation outcome measure, statistical modelling will be used to assess the risk of exacerbations based on factors, including adherence rates, lung function and patient identified risks during the intervention, bearing in mind the duration of the interview.

Appendix C: Figures and Tables

Table 1: Recruitment

		N
Screened		**XXX**
Eligible for trial (% of all referrals)		**XXX (YY%)**
Reasons for non-eligibility	>20PY Smoking History	X
	No exacerbations requiring oral corticosteroids in past year	X
	Prescribed or awaiting biologic therapy	X
	No confirmed asthma diagnosis	X
	ACT >19	X
	<18 years old	X
	etc	X
	etc	X
Eligible but declined (of all eligible)		**XXX (YY%)**
Reasons for decline	Refused	X
	Sensitivity to fluticasone or salbutamol	X
	etc	x
Recruited to trial (% of all eligible)		**XX (XX%)**

Table 2: Attrition

		N	% of target N=220
Recruited and Randomised		**XXX**	**YY%**
Completed randomised treatment protocol		x	y%
Withdrawn or lost		X	x% of randomised
Reason for withdrawal	Family or Work Commitments	x	yy%
	Did not wish to continue	X	y%
	Withdrawn on recommendation of PI	X	y%
	Sensitivity to fluticasone/salmeterol	x	y%
Data loss			% of total
INCA device failures		xx	y%

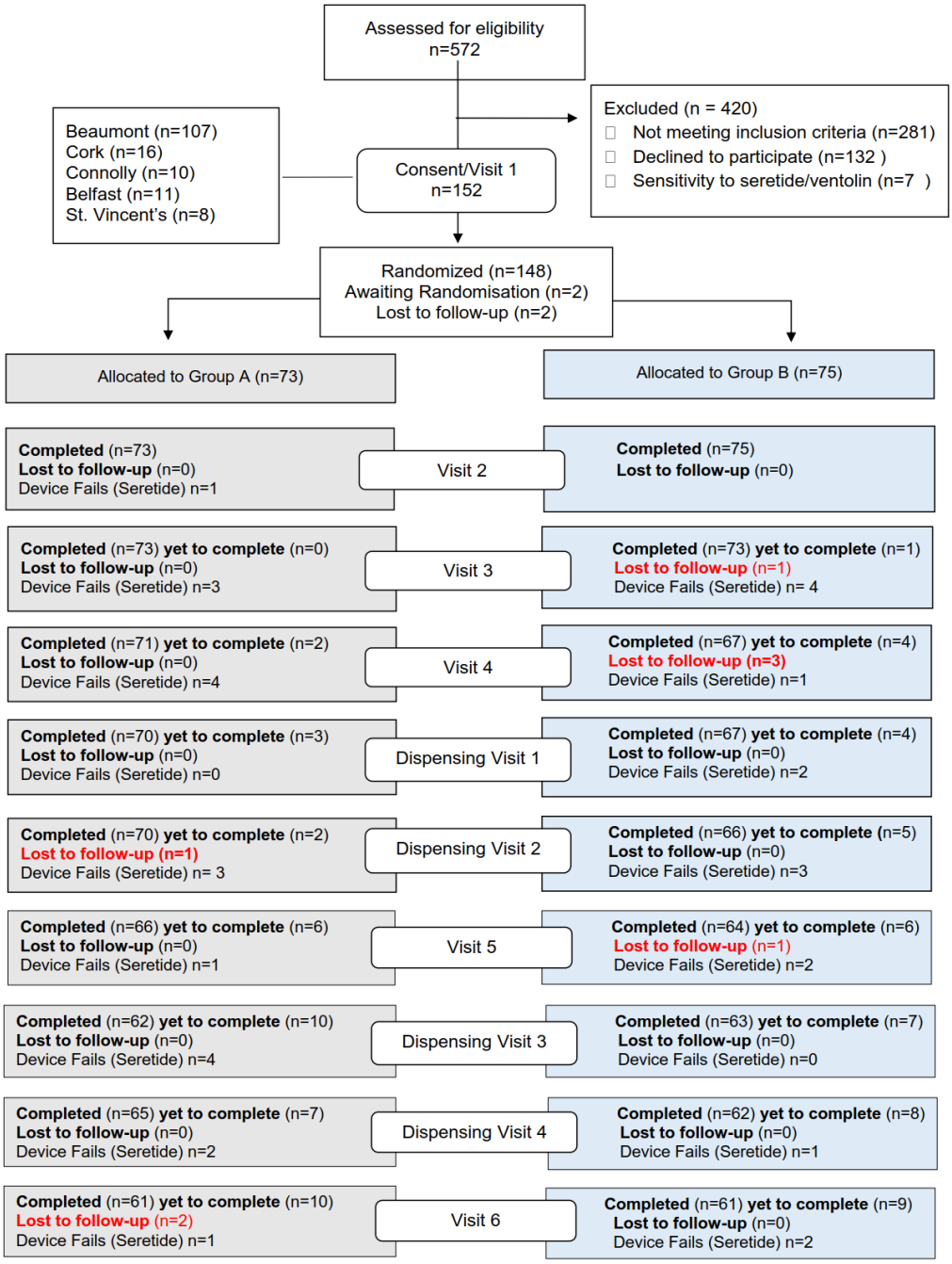

Figure 1: Consort

Table 3: Baseline demographics

		Active (n=xx)	**Control (n=xx)**
Characteristic		**Mean (SD)** **N(%)** **Median (IQR)**	**Mean (SD)** **N(%)** **Median (IQR)**
Age (years)			
Sex • Male • Female			
BMI			
FEV1 (L)			
FEV1 % predicted			
FEV1<60% predicted			
Eosinophils (10^9/L)			
FeNO (ppb)			
FeNO > 45ppb			
No. of exacerbations in past year			
No. of hospitalisations in past year			
No. of courses of oral steroids in past year			
Years since asthma diagnosis			
AQLQ			
ACT			
Smoking Status	Never		
	Former		
	Current		
Fluticasone/Salmeterol Dose	250		
	500		

Table 4: First Primary Outcome

	Active (n=XX)	**Control (n=XX)**	
Outcome	**N(%)**	**N(%)**	**Odds ratio (95% C.I.)**
Prescribed guideline appropriate therapy			
Prescribed monoclonal antibody therapy			
Prescribed maintenance oral corticosteroids			
Fluticasone/Salmeterol dose increased			
Fluticasone/Salmeterol dose reduced			

Table 5: Second Primary Outcome

	Active (n=XX)	**Control (n=XX)**	
Outcome	**Mean (SD)**	**Mean (SD)**	**Mean Difference (95% C.I.)**
Actual Adherence Rate (Weeks 20 -32)			
Actual Adherence Rate (Weeks 1-4)			
Actual Adherence Rate (Weeks 4-20)			

Table 6: Secondary Outcomes

	Active (n=xx)	**Control (n=xx)**	
Characteristic	**Mean (SD)** **N(%)**	**Mean (SD)** **N(%)**	**Mean Difference (95% C.I.)** **Odds Ratio (95% C.I.)**

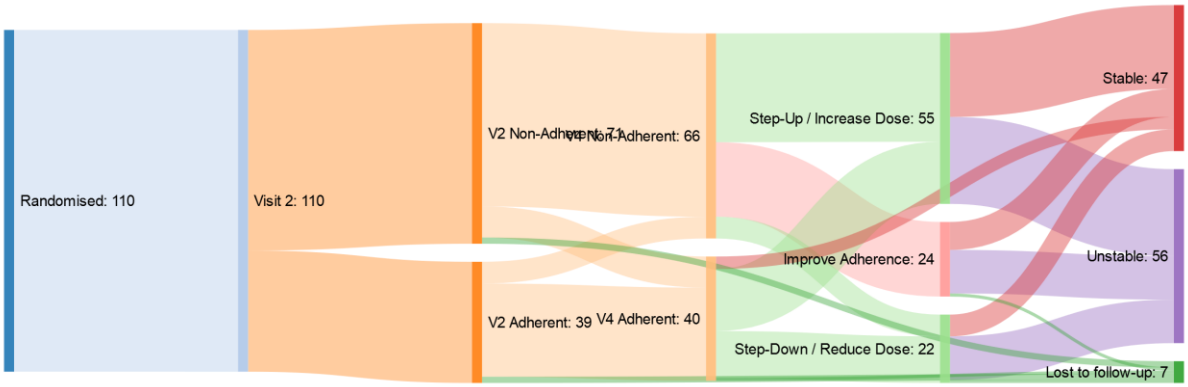

Figure 2a: Control group Sankey Chart

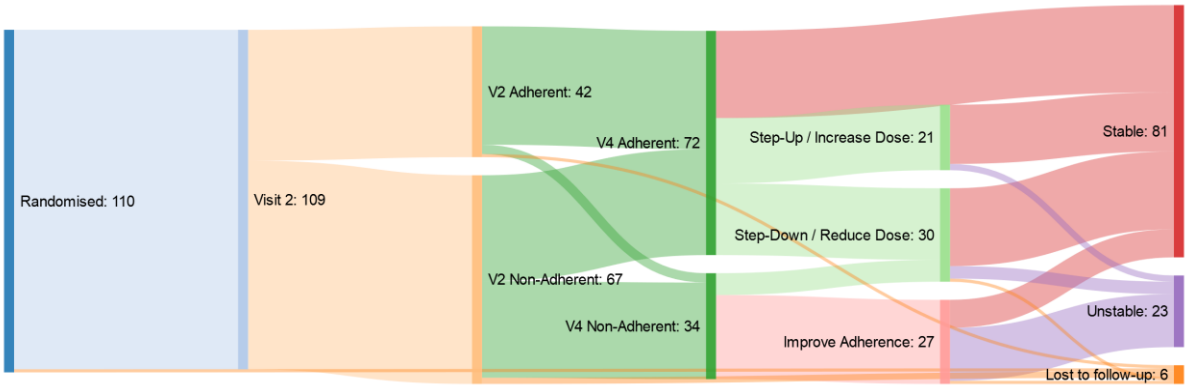

Figure 2b: Active Group