ONLINE SUPPLEMENT

Taking Care of Volunteers in a Stroke Trial: A New Assisted-Management Strategy

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Supplemental Figures

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Figure 1. Annual Report to Participants (Letter)

DATE

PATIENT NAME

IRIS **Insulin Resistance Intervention after Stroke Trial**

IRIS Site Name
Site Address
Site City, State Zip

PATIENT ADDRESS LINE 1
PATIENT ADDRESS LINE 2
CITY, STATE ZIP
IRIS ID#: XXX-XXX

Dear PATIENT NAME:

Thank you for participating in the IRIS trial. I am pleased to report that the trial is progressing very well. Over XXXX participants have been enrolled to date and all operations are running smoothly.

I am writing now with the results of your routine annual testing. We hope this information will help you and your health care provider to develop a plan to keep you healthy and reduce your risk for another stroke and heart disease.

The enclosed results were obtained at the time of your annual in-person interview. At that time, we asked you about risk factors for stroke, like cigarette smoking and heavy alcohol use. We also asked about your exercise habits and about any current treatments you were using to prevent another stroke. We measured your blood pressure and weight and tested your blood for evidence of high blood sugar, liver problems, high cholesterol and high triglycerides. The enclosed Annual Report shows your results, along with goals and recommendations to protect your health and help prevent another stroke or a heart attack.

At your request a copy of this letter has been sent to your personal health care provider. We encourage you to discuss this information with your health care provider, who can advise you if any additional action or testing is needed.

Thank you again for participating in this research. We are very grateful for your generous involvement in this international effort to improve the health of all patients after a stroke or transient ischemic attack (TIA). Your involvement will have a lasting impact on quality of care for thousands of other patients.

If you have any questions about the IRIS trial, please feel free to contact us.

Sincerely,

SITE PI NAME
IRIS Principal Investigator

SITE COORDINATOR NAME
Site Coordinator

CC: HCP NAME

Enc: 1) Annual Results, 2) “Staying Healthy after a Stroke or TIA”, 3) “Keeping your Bones Healthy”

Figure 2. Annual Report to Participants (Results)

IRIS Insulin Resistance Intervention after Stroke Trial

ANNUAL REPORT
DATE

PATIENT NAME

AGE: XX **GENDER:** X **ID#:** XXX-XXX **ANNUAL VISIT:** XX/XX/XXXX **BLOOD TEST:** XX/XX/XXXX

ITEM	GOAL	YOUR STATUS	GOAL MET?*
Physical Measures			
Blood pressure	Less than 140 / 90 mmHg	XXX/XX(X) mmHg	Yes/NO/Unk
Weight	XXX-XXX kgs	XXX kgs	Yes/NO/Unk
Body mass index**	18.0 to 25.0	XX	Yes/NO/Unk
Blood Results			
HDL ('good') cholesterol	At least 1.29 mmol/L (if male)*** At least 1.04 mmol/L (if female)***	XX mmol/L	Yes/NO/Unk
LDL ('bad') cholesterol	Less than 2.59 mmol/L	XX(X) mmol/L	Yes/NO/Unk
Total cholesterol	Less than 5.18 mmol/L	XXX mmol/L	Yes/NO/Unk
Triglycerides	Less than 1.69 mmol/L	XXX mmol/L	Yes/NO/Unk
ALT	0-0.92 ukat/L (if male) 0-0.67 ukat//L (if female)	XX	Yes/NO/Unk
Stroke Treatments			
Anticoagulant (Coumadin)	Should be taken by most stroke or TIA patients who have atrial fibrillation (an irregular heart rhythm)****	Taking/Not taking anticoagulant	Yes/NO/Unk OR --
Antiplatelet (Aspirin, Plavix, Aggrenox)	Taken if not on anticoagulants	Taking antiplatelets/Not taking antiplatelets	Yes/NO/Unk
Health Habits			
Cigarette smoking	No smoking	Current smoker/Non-smoker	Yes/NO/Unk
Alcohol use	Less than 3 drinks/day (if male) Less than 2 drinks/day (if female)	X.X drinks/day	Yes/NO/Unk
Aerobic exercise	3 days/week for total 20 minutes/day	Yes/No	Yes/NO/Unk
Strength training	2 days/week for 10 reps of 8 exercises	Yes/No	Yes/NO/Unk
Calcium intake	1200 mg/day from diet and/or supplements	Taking/Not taking supplement	?
Vitamin D intake	800 IUs/day from diet and/or supplements	Taking/Not taking supplement	?
Bone density testing	Measured within past 5 years	Yes/No	Yes/NO/Unk

***If 'NO'=item was not at goal when measured; 'Unk'=Unknown; '?'=Meeting goal depends on diet and/or supplement use.**

**Body mass index calculated as weight (kg) /height (m) ^{2}. It is a standard measure of weight adjusted for height.
*******For HDL, higher values are considered good and protect against vascular disease.
****Whether or not goal is met for anticoagulation depends on presence or absence of atrial fibrillation.

RECOMMENDATIONS ***(recommendation listed ONLY if applicable to patient)***

BLOOD PRESSURE: See your doctor within a few weeks for adjustment of your blood pressure medications. Your blood pressure was too high when we measured it.

LIPID RESULTS: Review the lipid results with your health care provider to consider changes in your cholesterol-lowering medication. Your LDL cholesterol may be too high (actual goals depend on your individual risk factors for heart disease and stroke).

ANTIPLATELET USE: Talk with your health care provider about taking aspirin or another antiplatelet medication. These medications may prevent future strokes in patients with a recent stroke or TIA.

CIGARETTE SMOKING: Do everything you can to stop smoking. You might ask your health care provider about medications to help you quit smoking. We have enclosed a brochure designed to help you stop smoking.

BONE HEALTH: Aim to get the recommended amounts of calcium & vitamin D through diet or supplements to reduce your risk of bone fracture. You can also strengthen your bones and protect blood vessels by regular exercise and avoiding excessive alcohol use.

The American Osteoporosis Foundation recommends bone mineral density testing for all men over age 69 and women over age 64.

Figure 3. Annual Cover Letter to HCPs

IRIS **Insulin Resistance Intervention after Stroke Trial**

RIS Site Name
Site Address
Site City, State Zip

DATE

HCP NAME
HCP ADDRESS1
HCP ADDRESS2
CITY, STATE ZIP

RE: PATIENT NAME
DOB: XX/XX/XXXX
IRIS ID#: XXX-XXX

Dear HCP NAME:

PATIENT NAME is enrolled in the Insulin Resistance Intervention after Stroke (IRIS) Trial, a randomized placebo-controlled clinical trial funded by the National Institutes of Health. The research objective for IRIS is to test the effectiveness of pioglitazone (Actos®) compared with placebo for prevention of recurrent stroke and myocardial infarction among non-diabetic patients with ischemic stroke or transient ischemic attack (TIA) and insulin resistance. The trial has enrolled XXXX participants from about 160 research centers throughout the world.

We are in frequent contact with each IRIS participant to monitor study endpoints, medication adherence and adverse events. Once a year, we complete a brief physical examination, repeat the ALT test, and measure vascular risk factors, including glucose and cholesterol.

We recently completed this testing for PATIENT NAME and have sent the participant a copy of the results. I am enclosing a copy of my letter. We have encouraged PATIENT NAME to contact you for any values that are indicated as not meeting the listed treatment goals. (In the IRIS protocol, patients remain under the care of their personal physician for all matters not directly related to the research intervention.)

If you have any questions, please call me.

Sincerely,

SITE PI NAME
IRIS Principal Investigator

Enc. Letter to patient
IRIS Brochure

The IRIS Trial Secondary Prevention Goals

For lipid management, the IRIS goal for low-density lipoprotein (LDL) of less than 2.59 mmol/L was based on 2001 NCEP guidelines.[1] In 2008, the AHA revised its approach by recommending high-intensity statin therapy after atherosclerotic stroke or TIA in patients without known coronary heart disease (CHD).[2] Although statin therapy was not reported back to IRIS participants in their results letters, we describe statin use in this population in addition to achievement of LDL <2.59 mmol/L to reflect this revised approach.

For patients with ischemic stroke or TIA with atrial fibrillation, oral anticoagulation with vitamin K antagonists (VKA) was recommended at the time IRIS began enrolling[3] and remained the primary anticoagulation therapy for these patients until 2014 when the AHA allowed apixaban and dabigatran as Class I alternatives to VKA therapy.[4] IRIS participants were told that an anticoagulant is advisable for stroke or TIA patients with atrial fibrillation unless there is a contraindication.

In 2005 it was broadly recognized that all patients with non-cardioembolic stroke should receive aspirin monotherapy.[3,5] In 2008, the AHA revised its approach to allow clopidogrel monotherapy and the combination of aspirin and extended-release dipyridamole as Class I alternatives to aspirin monotherapy.[2] The IRIS trial anticipated these changes by advising any participant not taking an anticoagulant to take an antiplatelet agent such as aspirin, clopidogrel, or combined sustained-release dipyridamole-aspirin. IRIS participants were considered at goal for use of antithrombotic therapy if they were taking either an anticoagulant or an antiplatelet medication.

Guidelines for management of blood pressure, body weight, cigarette smoking, alcohol use, and aerobic exercise participation were unchanged during the trial. IRIS goals were defined as: blood pressure <140/90 mm Hg,[3,6] body mass index (BMI) 18-25 kg/m^2,[7] abstinence from cigarette smoking,[3] safe alcohol use ($\leq$2 drinks/day for men and $\leq$1 drink/day for women),[7] and aerobic exercise [large-muscle activities (e.g., walking, treadmill, stationary cycle, combined arm-leg ergometry, arm ergometry, seated stepper)] at least three days/week for a minimum total of 20 minutes/day.[8]

Table I. Baseline Characteristics of Study Cohort by Country*					
	United States n=2592	Canada n=543	United Kingdom n=256	Israel n=178	Germany n=151
Demographic Features (%)					
Age (years)	63.3±11	64.6±10	64.5±11	60.7±10	61.0±10
Male	63	70	68	74	72
Black race	16	2	2	0	1
Hispanic ethnicity	5	1	3	1	4
College education *(yrs>12)*	51	34	76	47	14
Married/living with partner	68	75	71	83	80
Clinical History (%)†					
Stroke at entry (vs. TIA)	89	83	79	90	88
Hypertension	74	64	61	58	86
Hyperlipidemia	70	63	56	71	71
Coronary artery disease	13	11	7	9	7
Atrial fibrillation	6	7	11	3	10
Carotid artery disease	20	20	16	8	13
Peripheral vascular disease	6	5	4	4	5
Current smoker	16	15	13	29	13
Physical Examination					
Body-mass index (kg/m^2)	30±6	29±4	30±5	28±4	29±4
Waist (cms)	104±15	102±13	104±15	102±13	107±10
Systolic blood pressure (mm Hg)	133±18	130±16	138±16	134±17	136±17
Diastolic blood pressure (mm Hg)	79±11	77±10	82±10	83±9	84±10
National Institutes of Health Stroke Scale (median [IQR])	0 (0,2)	0 (0,1)	0 (0,1)	0 (0,1)	0 (0,1)
Modified Rankin (median [IQR])	1 (0,2)	1 (0,2)	1 (0,1)	0 (0,1)	1 (0,1)
Modified mini-mental exam (median [IQR])	96 (92,99)	97 (93,99)	96 (94,99)	97 (93,99)	98 (95,100)
Laboratory Data					
Hemoglobin A_{1c} (proportion of total)	.058±.004	.058±.004	.057±.003	.058±.005	.056±.003
Homeostasis assessment model (median [IQR])‡	4.7 (3.7,6.3)	4.4 (3.7,5.8)	5.0 (3.9,6.7)	4.5 (3.8,5.8)	4.8 (4.0,6.2)
Low-density lipoprotein cholesterol (mmol/L)	2.33±0.80	1.99±0.83	2.15±0.78	2.51±0.75	2.38±0.73
High-density lipoprotein cholesterol (mmol/L)	1.22±0.34	1.19±0.28	1.32±0.34	1.17±0.31	1.29±0.31
Triglycerides (mmol/L)	1.64±0.87	1.54±0.64	1.49±0.80	1.55±0.80	1.47±0.79
Concomitant Medications (%)					
Statin therapy	80	88	91	76	86
Aspirin	78	71	40	64	82
Non-aspirin antiplatelet	42	37	77	39	22
Oral anticoagulants	11	11	11	7	15
Antithrombotics (any)	99	99	99	100	100

*****Plus–minus values means ± SD. Features are presented as median values when distributions are highly skewed; medians are shown with values to describe dispersion (IQR=25th percentile, 75th percentile).
†Clinical history variables were defined as follows: stroke or TIA, see entry criteria; hypertension, self-report; hyperlipidemia, self-report; coronary artery disease, self-report history of myocardial infarction, coronary-artery bypass graft, or coronary stent insertion; congestive heart failure, self-report; atrial fibrillation, history of AF on baseline electrocardiogram as determined by site investigator; peripheral vascular disease, self-report; current smoking, self-report. (Uncertain self-report ='no'.)
‡The homeostasis model assessment (HOMA) is an index of insulin resistance based on fasting insulin and glucose values. A HOMA over 3.0 was used to identify patients with insulin resistance in the IRIS trial.[9]

Table II. Number of Participants Known Alive with Missing Data – Overall and by Country

Time Point		Pt. Alive	All Prevention Goals	All Priority Prevention Goals*	Physiological Goals			Drug Use Goals		Behavioral Goals		
					BP <140/90 mm Hg	LDL-c <2.59 mmol/L	BMI 18-25 kg/m^2	Statin Therapy	Antithrombotic Therapy†	Cigarette Smoking Abstinence	Safe Alcohol Use‡	Aerobic Exercise§
UNITED STATES	Baseline	2592	87	41	10	31	10	8	0	0	20	19
	Year 1	2529	343	322	261	298	206	190	189	176	184	188
	Year 2	2455	532	501	422	448	263	256	250	249	256	258
	Year 3	2260	578	552	476	481	291	277	281	265	275	283
CANADA	Baseline	543	8	5	2	2	2	2	1	0	2	0
	Year 1	537	55	53	32	51	25	20	20	22	23	24
	Year 2	527	62	59	43	53	27	20	20	20	22	20
	Year 3	495	74	72	54	67	31	27	27	27	29	31
UNITED KINGDOM	Baseline	256	14	3	0	3	0	0	0	0	11	0
	Year 1	252	35	21	16	20	13	14	14	11	21	16
	Year 2	243	34	28	21	28	19	15	15	14	21	14
	Year 3	211	41	33	18	31	15	12	12	13	16	14
ISRAEL	Baseline	178	3	0	0	0	0	0	0	0	2	1
	Year 1	175	13	8	7	8	6	8	5	5	7	5
	Year 2	174	13	11	10	11	9	9	8	8	9	8
	Year 3	166	23	19	17	19	14	13	13	13	15	14
GERMANY	Baseline	151	14	2	0	2	0	0	0	0	8	4
	Year 1	146	14	10	6	10	3	3	3	3	5	5
	Year 2	144	16	13	10	13	4	3	2	2	5	2
	Year 3	123	26	19	14	18	9	6	6	5	12	5
ALL	Baseline	3718	126	51	12	38	12	10	1	0	43	24
	Year 1	3639	460	414	322	387	253	235	231	217	240	238
	Year 2	3543	657	612	506	553	322	303	295	293	313	302
	Year 3	3255	742	695	579	616	360	335	339	323	347	347

Abbreviations: BP, blood pressure; LDL-c, low-density lipoprotein cholesterol; BMI, body mass index.

*See text for justification of priority prevention goals: BP <140/90 mm Hg, LDL-c <2.59 mmol/L, and use of antithrombotic therapy.

†Antithrombotic therapy includes antiplatelet or anticoagulation therapies.

‡Safe alcohol use was defined as ≤2 drinks/day for males and ≤1 drink/day for females.[7]

§Aerobic exercise was defined as large-muscle activities at least 3 days/week for a total of 20 minutes/day.[8]

Table III. Achievement of Secondary Stroke Prevention Goals by Year – Overall and by Country

Time Point		Pts. Alive	% Meeting All Goals	% Meeting Priority Prevention Goals*	% Meeting Physiological Goals			% Meeting Drug Use Goals		% Meeting Behavioral Goals		
					BP <140/90 mm Hg	LDL-c <2.59 mmol/L	BMI 18-25 kg/m^2	Statin Therapy	Antithrombotic Therapy†	Cigarette Smoking Abstinence	Safe Alcohol Use‡	Aerobic Exercise§
UNITED STATES	Baseline	2592	3	46	66	68	18	81	99	84	94	48
	Year 1	2529	4	48	71	66	16	77	96	83	95	49
	Year 2	2455	3	49	72	68	17	77	96	84	95	47
	Year 3	2260	3	50	72	67	17	77	96	84	95	48
CANADA	Baseline	543	4	63	75	81	18	88	100	85	91	51
	Year 1	537	5	64	77	83	19	86	98	85	94	54
	Year 2	527	6	68	78	85	18	87	98	85	93	48
	Year 3	495	7	65	77	83	19	84	98	85	94	49
UNITED KINGDOM	Baseline	256	3	42	53	77	21	91	99	87	88	46
	Year 1	252	3	47	62	71	21	88	100	89	90	38
	Year 2	243	5	51	69	74	19	88	98	90	91	47
	Year 3	211	4	53	74	74	23	84	96	92	90	46
ISRAEL	Baseline	178	3	37	61	54	26	76	100	72	99	52
	Year 1	175	2	37	65	55	25	77	98	72	100	47
	Year 2	174	2	40	64	60	22	81	97	68	100	43
	Year 3	166	3	45	68	61	20	78	97	70	98	44
GERMANY	Baseline	151	2	39	61	67	17	86	100	87	94	43
	Year 1	146	0	35	56	61	13	83	99	87	92	34
	Year 2	144	1	36	59	58	18	81	99	87	94	31
	Year 3	123	2	38	61	60	13	75	98	86	97	30
ALL	Baseline	3720	3	47	66	70	18	83	99	84	93	48
	Year 1	3639	4	49	70	68	17	79	97	84	94	48
	Year 2	3543	4	51	71	70	18	80	97	84	95	46
	Year 3	3255	4	52	72	70	18	78	96	84	95	47

Abbreviations: BP, blood pressure; LDL-c, low-density lipoprotein cholesterol; BMI, body mass index.

*****See text for justification of priority prevention goals: BP <140/90 mm Hg, LDL-c <2.59 mmol/L, and use of antithrombotic therapy.

†Antithrombotic therapy includes antiplatelet or anticoagulation therapies

‡Safe alcohol use was defined as ≤2 drinks/day for males and ≤1 drink/day for females.[7]

§Aerobic exercise was defined as large-muscle activities at least 3 days/week for a total of 20 minutes/day.[8]

Table IV. Associations between Baseline Features and Achievement of Priority Prevention Goals from Baseline to Year 3*

Baseline Feature	Bivariate Analysis						Adjusted Analysis†	
	Feature Present		Feature Not Present		OR‖	P	OR	P
	Pts.	At Goal	Pts.	At Goal				
Male sex	678	56%	307	46%	1.54	0.002	1.40	0.02
White race	846	56%	131	36%	2.26	<0.0001	1.71	0.01
Hispanic ethnicity	25	56%	956	53%	1.13	0.76		
Married/with partner	738	57%	244	42%	1.79	<0.0001	1.47	0.02
High school graduate	768	56%	200	45%	1.53	0.007		
Index stroke (vs TIA)	848	53%	137	53%	1.02	0.91		
CAD history‡	133	59%	852	52%	1.30	0.16		
Atrial fibrillation history§	59	61%	926	52%	1.42	0.2		
PVD history	54	41%	931	54%	0.59	0.06		
Non-smoker	844	55%	141	42%	1.69	0.004	1.62	0.01
Obese	442	51%	543	55%	0.84	0.19		
Abdominal obesity	605	53%	377	54%	0.94	0.64		
	At Goal		Not At Goal					
	Mean (SD)							
Age, years	63.0	(10.4)	63.6	(10.3)	0.94	0.37		
3MS score	95.6	(5.0)	94.0	(6.7)	1.61	<0.0001	1.55	0.0003
Rankin score	1.0	(1.0)	0.9	(0.9)	1.06	0.38		
NIH stroke scale	1.0	(1.6)	0.9	(1.5)	1.03	0.45		

Abbreviations: OR, odds ratio; CAD, coronary artery disease; PVD, peripheral vascular disease.
*See text for justification of priority prevention goals: BP <140/90 mm Hg, LDL-c <2.59 mmol/L, and use of antithrombotic therapy. Comparison group is participants not at goal at any time from baseline to year 3.
†Logistic model selected in stepwise procedure considering only significant features in bivariate analysis.
‡CAD history was defined as self-reported history of myocardial infarction, CABG, or coronary stent insertion.
§Considered uncertain atrial fibrillation history as absent.
‖OR for being at goal if feature present vs. absent for categorical features; OR for 10 unit change in age, 3MS score, and for 1 unit change in Rankin, NIHSS.

Table V. Treatment Effect According to Achievement of Priority Prevention Goals at Baseline*

Achievement Status	Stroke or Myocardial Infarction *No. Participants (%)*				Hazard Ratio (95% CI)	P Value†
	N	Pioglitazone	N	Placebo		
At goal	846	67 (7.9)	884	96 (10.9)	0.71 (0.52, 0.97)	0.02
Not at goal	989	103 (10.4)	948	120 (12.7)	0.82 (0.63, 1.07)	0.15

Abbreviations: CI, confidence interval.

*See text for justification of priority prevention goals: BP <140/90 mm Hg, LDL-c <2.59 mmol/L, and use of antithrombotic therapy.

†P value from log-rank statistic using a type I error of 0.05 (2-sided), not adjusted for interim looks. P=0.49 for interaction.

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Table VI. Associations Between Enrollment Country and Achievement of Priority Prevention Goals from Baseline to year 3*

			Bivariate Analysis		Adjusted Analysis‡	
Enrollment Country	N	At Goal	OR†	P value	OR†	P value
Canada	197	75%	3.45	<0.0001	3.05	<0.0001
Germany	49	31%	0.37	0.002	0.34	0.0001
Israel	60	35%	0.46	0.005	0.41	0.002
UK	51	39%	0.56	0.05	0.49	0.02
US	628	50%	0.76	0.04	0.89	0.39

Abbreviations: OR, odds ratio.

*See text for justification of priority prevention goals: BP <140/90 mm Hg, LDL-c <100 mg/dL, and use of antithrombotic therapy. Comparison group is participants not at goal at any time from baseline to year 3.

†OR for being at goal if enrolled from specified country vs enrolled from another country.

‡Logistic model adjusted for male sex, white race, marital status (married/with partner vs not), smoking status (non-smoker vs smoker) and baseline 3MS score.

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