THE ORIGINALE STUDY (ORIGIN And Legacy Effects)

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Although no study drug is being administered during ORIGINALE, and no systematic collection of adverse events is required, sites and investigators must continue to report Adverse Drug Reactions according to local law. This reporting should occur to either the local Health Authority or to the manufacturer of the suspected product.

Approval Signatures for: The ORIGINALE Study

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Investigator approval signatures:

I have read the protocol and agree to conduct this trial in accordance with all stipulations of the protocol, with applicable laws and regulations in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Importance of Long-Term Follow-up of the ORIGIN Participants: The ORIGINALE (ORIGIN And Legacy Effects) Follow-up Study

1.0 Background and Rationale

Several studies of people with diabetes have now shown that long-term follow-up after large clinical outcomes trials have reported either: a) persistence of the cardiovascular effect of the intervention observed during the trial, or b) emergence of new cardiovascular effects that were not apparent during the trial. These effects were observed despite the absence of any systematic difference in exposure to the intervention during the post-trial follow-up period and have been described as a "legacy effects" of the intervention. A few relevant examples of such legacy effects are noted below.

a) The UKPDS compared the effect of more versus less intensive (i.e. standard) glucose lowering on diabetes-related clinical outcomes in newly diagnosed people with type 2 diabetes. At the end of the clinical trial (after a mean follow-up period of 10 years) there was a clear effect on clinically important eye or kidney disease (RR 0.75, 95%CI 0.60-0.93) but no effect on MI (RR 0.84, 95%CI 0.71-1.00) or death (RR 0.94; 95%CI 0.80, 1.10)[1]. Moreover after approximately 5 years of follow-up there was no clear effect on the "MACE" composite outcome of myocardial infarction, stroke or cardiovascular death (RR 0.80, 95%CI 0.62, 1.04)[2]. Participants were then passively followed for a mean of 8.5 years after the trial ended, during which there was no systematic difference in therapy and no difference in A1C between the 2 former treatment groups. Nevertheless, after a total follow-up period of approximately 18 years (10 active and 8 passive), people who had been in the intensive group had a significantly lower incidence of myocardial infarctions (RR 0.85; 95%CI 0.74, 0.97) and death (RR 0.87, 95% CI 0.79, 0.96)[3].

b) The ACCORD trial compared the effect of more versus less intensive (i.e. standard) glucose lowering on diabetes-related clinical outcomes in people with established type 2 diabetes of mean duration 10 years who had additional cardiovascular risk factors. The clinical trial was stopped after a mean follow-up period of 3.7 years due to a mortality signal on the recommendation of the DSMB. No explanation for this has yet been found and many explanations have been proposed including "chance" [4, 5]. At the end of the active phase of the trial there was a clear benefit on incident overt nephropathy (RR 0·68, 95%CI 0·54, 0·86), microalbuminuria (RR 0·79, 95%CI 0·69, 0·90) and worsened vision (RR 0·84, 95%CI0·73, 0·97) as well as retinopathy (RR 0.67, 95% CI 0.51, 0.87)[6]. There was no effect on the overall "MACE" outcome (RR 0.90, 95%CI 0.78-1.03) or on the stroke component, but there was a reduction in nonfatal MI (0.79, 95%CI 0.66, 0.95)[7]. After a further 1.3 years of passive follow-up during which both treatment groups were treated identically, a trend favoring reduced stroke began to emerge (Figure 1)[7]. Moreover, the effects of the intervention on overt nephropathy, microalbuminuria and reduced vision persisted. The importance of passive follow-up of this trial was most recently recognized by the US National Institutes of Health which recently funded a prolonged passive follow-up of the ACCORD participants for at least 3 years (the ACCORD International ONgoing study – ACCORDION)[13] which will determine the effect of 3.7 years of intensive versus standard glucose lowering on the long-term incidence of cardiovascular outcomes in this population.

c) The DCCT compared the effect of intensified versus conventional insulin therapy on retinal and renal disease in people with type 1 diabetes with a mean duration 5.5 years whose mean age was 28 and who did not have prior cardiovascular disease. At the end of the clinical trial (after a mean follow-up period of 6.5 years) there was a clear reduction in retinopathy and nephropathy[8] but no difference in the occurrence of the "MACE" composite outcome (Figure 2)[9]. However after a total follow-up of 17 years that included the active period and a subsequent passive follow-up period of approximately 11 years during which both treatment groups had similar A1C levels, there was a significant 57% reduction (95%CI 12, 79) in this "MACE" composite outcome (Figure 2)[9]. This trial is also notable since it showed that the effects of the intervention on atherosclerosis preceded effects on outcomes. Thus 6 years after the active period ended (and approximately 13 years after it began) there was clearly lower progression in carotid intima-media thickness in the intensive versus the conventional group[10].

d) The Coronary Drug Project (CDP) assessed the effect of niacin on mortality in 8341 men with a documented MI. No effect on the primary outcome of mortality was noted during the active 6 year treatment period (3.9% reduction, p=0.50) (CDP 1975). However, during a total follow-up period of 15 years (i.e. 9 years of passive follow-up) mortality in the niacin group was 11% lower than in the placebo group[12].

In summary, these and other studies together highlight the value of post-trial long-term passive follow-up and ascertainment of important outcomes in participants who were studied in large clinical trials. They show that such follow-up can identify: a) persistence of effects on outcomes after a trial has ended; and b) emergence of new effects on outcomes that were not apparent during the trial.

The ORIGIN Trial is examining the effects of: a) insulin glargine vs. standard care; and 2) n-3 PUFA vs. placebo on cardiovascular outcomes and mortality among > 12,500 adults with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or early type 2 diabetes who have additional cardiovascular disease risk factors. Active follow-up was finished in 2011 after a median period of 6.2 years. In light of the above, ongoing simple follow-up of the ORIGIN participants for at least 2 years (until March 2014) has the potential to identify long-term effects of the interventions, regardless of the results observed at the end of the active treatment period. This follow-up will be accomplished within the ORIGINALE (ORIGIN And Legacy Effects) prospective passive follow-up study and will be conducted by the international network of ORIGIN investigators and led by PHRI. Indeed, a) the ORIGIN team has 10 years of experience working on ORIGIN, from original proposal development, protocol development, participant recruitment, treatment, and follow-up, to final trial close-out and manuscript preparation; b) participants have established ties with clinics and clinic staff; c) sites are familiar with ORIGIN methods and comfortable within the study group; d) investigators have forged a cohesive international research collaborative; and e) PHRI has established systems for data entry, dynamic monitoring reports, and tracking systems for all study outcomes. These facts, and the implementation of a simple follow-up schedule and protocol, highlight the feasibility and likelihood of success of ORIGINALE.

2.0 Research Questions

2.1 Primary Questions

a) Does targeting a fasting plasma glucose level $\leq$ 5.3 mmol/l with insulin glargine for a median duration of 6.2 years reduce cardiovascular morbidity and/or mortality after 8-9 years in people at high risk for vascular disease with either IFG, IGT, or early type 2 diabetes?
b) Do n-3 PUFA supplements for a median duration of 6.2 years reduce cardiovascular mortality after 8-9 years in people at high risk for vascular disease with either IFG, IGT, or early type 2 diabetes?

2.2 Secondary Questions

During a total of 8-9 years of follow-up in these people (6.2 years of active followed by 2 years of passive follow-up),

a) does targeting a fasting plasma glucose level $\leq$ 5.3 mmol/l with insulin glargine reduce 1) clinically important eye or kidney disease; 2) serious cancers; or 3) new diabetes, versus standard care?
b) do n-3 PUFA supplements reduce 1) major vascular events (cardiovascular death; myocardial infarction; or stroke); or 2) a composite of sudden unexpected death, non-sudden arrhythmic death, unwitnessed death, or resuscitated cardiac arrest, versus placebo?

3.0 Study Design

ORIGINALE is a simple observational follow-up study of consenting patients who participated in the ORIGIN Trial. ORIGINALE participants will be followed for major clinical events (including nonfatal myocardial infarctions and strokes), deaths, and other key measures of health. The major ORIGINALE-specific primary and secondary outcomes are defined in Section 3.7. Under ORIGINALE, participants will have a baseline visit, an optional interim phone call and a final visit in February or March 2014. A locally measured HbA1c and serum creatinine will be obtained at the final visit.

4.0 Timelines

New contracts and ethics submissions will be made by sites by November 2012. The last-participant-last-visit will be scheduled for January 2014. February and March 2014 will be devoted to site close-out and database close-out. During April, May and June 2014, study analyses, paper preparation, presentations, and final database preparation and documentation will be completed.

5.0 Participants

All surviving participants at sites consenting to participate will be approached for recruitment into ORIGINALE. We anticipate that approximately 8000 participants will be included in the ORIGINALE study.

6.0 Study Treatments

ORIGINALE is a post-intervention observational follow-up study. Therefore, there are no study treatments, and no medications or supplies will be provided to participants. Participants will be treated for any existing or developing conditions by their usual care physician throughout the duration of ORIGINALE. Any decision to begin, continue or discontinue use of insulin glargine or n-3 PUFA will be at the discretion of the participant and his or her usual physician.

7.0 Study Procedures & Visit Schedule

A Study Flowchart listing study visits and procedures performed at each visit appears as Table 1.

Baseline data for ORIGINALE will be obtained from the ORIGIN end-of-study data. All consenting participants will be contacted annually during ORIGINALE, either by phone or in clinic. A very short case report form will capture the relevant data. Those participants who are unwilling or unable to attend in-clinic visits, will be asked to complete phone visits and if unwilling or unable to complete phone visits, they will be asked if information can be obtained from a third party such as a family member or physician.

As ORIGINALE is a passive observational study and as no therapy is being provided or tested, AEs and SAEs will not be collected in ORIGINALE. Table 1 shows the schedule of visits.

Table 1: Schedule of Visits

Information Obtained	Baseline	**Interim Telephone Visit	Final Visit (February-March 2014)
Informed consent	X		
weight, vital signs	X		X
HbA1C*	X		X
Serum creatinine*	X		X
Concomitant medications	X		X
Check contact information	X	X	X
Ascertain outcomes#	X	X	X

*HbA1C and serum creatinine will be measured locally; #Outcomes to be ascertained are noted in Section 3.7; **Phone visit is optional to ensure adherence with the final visit and ascertainment of outcomes

8.0 Outcomes

All outcomes will be defined as they are for ORIGIN based on the available data. The 2 co-primary cardiovascular outcomes for the insulin glargine study are: 1) cardiovascular death or nonfatal myocardial infarction (MI) or nonfatal stroke; and 2) cardiovascular death; or nonfatal myocardial infarction; or nonfatal stroke; or revascularization procedure; or hospitalization for heart failure. The primary outcome for the n-3 PUFA study is cardiovascular death.

Other outcomes to be captured include: a) all deaths; b) need for renal replacement therapy, or renal death c) a rise in serum creatinine; d) the need for laser therapy or vitrectomy or anti-VEGF therapy for diabetic retinopathy; blindness (in either or both eyes) due to DR e) development of type 2 diabetes in participants with IGT or IFG at the original time of randomization; f) hospitalization for heart failure; g) revascularization procedures; h) cancers (except for basal and squamous cell skin cancer); i) amputations for ischemia; j) hospitalization for cardiovascular cause; k) unstable, new, or worsening angina; and k) chronic institutionalization. New diabetes will be defined differently during the 5 year passive follow-up period compared to ORIGIN because glucose testing and glucose tolerance tests will not be done. New diabetes will therefore

be defined as the first occurrence of a HbA1c level of 6.5% or higher or use of at least 1 glucose lowering drug in someone who was drug naïve at entry.

8.1 Adjudication of Outcomes

In ORIGIN, all deaths, cardiovascular events, renal and eye outcomes and diagnoses of diabetes are adjudicated centrally. Several trials have observed that while adjudication affects the absolute numbers of events, it does not affect hazard ratios or risk ratios and adjudication does not affect the conclusion of the trial [14-16]. Outcomes will therefore not be adjudicated in ORIGINALE.

9.0 Statistical Analysis

Analyses of the composite cardiovascular outcomes and other outcomes will be based on the time from randomization to the occurrence of the first event, with participants analyzed in the treatment group to which they were randomized. Participants who complete the study but do not experience an outcome will be censored on the last day of their follow-up. ORIGIN participants who do not participate in ORIGINALE will be censored at the time of their ORIGIN End of Usual Follow-up visit for cardiovascular outcomes and at the time of the last oral glucose tolerance test for incident diabetes.

Analyses of ORIGINALE outcomes will be by the same methods and using the same thresholds for determining statistical significance as in ORIGIN. In addition, analyses investigating whether the hazard ratios are similar during the active treatment phase and observational follow-up periods will be performed using Cox models with time-dependent covariates representing the phase of follow-up. These models allow a direct test of whether the hazard ratios comparing treatment groups are the same in the early periods of follow-up versus the later periods.

9.1 Sample Size and Statistical Power

ORIGIN initially enrolled 12,537 participants. At the time of the 2009 ORIGIN extension, at participating sites, 12,003 continued to be included. There have been approximately 2000 deaths, leaving approximately 10,000 surviving participants of whom 8000 are expected to participate in ORIGINALE.

ORIGIN had an estimated 80% power to detect a 16% RRR in the primary composite outcome of the first occurrence of nonfatal myocardial infarction, or nonfatal stroke, or CV death during the active follow-up period. Assuming a type 1 error rate of 5%, the enrolment of 8000 participants in the passive follow-up study, and a median follow-up period of approximately 8 years and a growing effect size with time, ORIGINALE will provide 80% power to detect a 15%-25% difference in this outcome (depending on the size of the legacy effect).

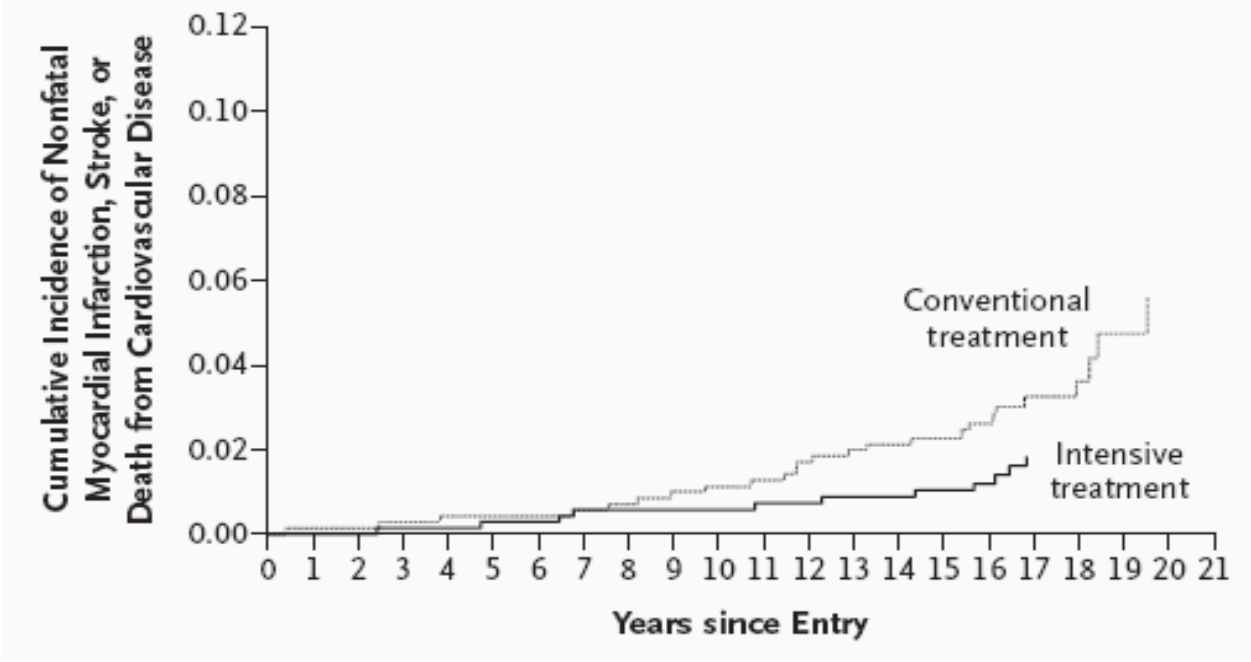
10.0 Summary

ORIGINALE is a highly feasible long-term observational follow-up study. It will determine the 8-9 year effects of more than 6 years of treatment with insulin glargine and/or n-3 PUFA on cardiovascular and other outcomes among people at risk for cardiovascular disease who have IFG/IGT or type 2 diabetes at baseline. Most importantly, it may discover persistent or new effects of insulin glargine or n-3 PUFA that require long-term follow-up to be detected.

Figure 1 ACCORD

Outcome	Intensive	Standard	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events (%)			
Primary outcome				
Before transition	380 (2.0)	414 (2.2)	0.90 (0.78–1.03)	0.13
Until end of study	503 (2.1)	543 (2.2)	0.91 (0.81–1.03)	0.12
Nonfatal myocardial infarction				
Before transition	207 (1.1)	257 (1.4)	0.79 (0.66–0.95)	0.01
Until end of study	287 (1.2)	344 (1.4)	0.82 (0.70–0.96)	0.01
Nonfatal stroke				
Before transition	72 (0.4)	72 (0.4)	0.99 (0.72–1.38)	0.98
Until end of study	82 (0.3)	94 (0.4)	0.87 (0.65–1.17)	0.35
Death from cardiovascular causes				
Before transition	140 (0.7)	109 (0.6)	1.27 (0.99–1.63)	0.07
Until end of study	187 (0.7)	144 (0.6)	1.29 (1.04–1.60)	0.02

Figure 2



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