To: Rob Watters, Chairman of the Technical Subcommittee (TSC)

From: The Expert Advisory Committee (EAC)

Re: CHAP C report (19 October 2004) prepared by the Ventana Clinical Research Corporation

Date: 24 January 2005

1. INTRODUCTION

The final draft of Ventana's Protocol C Report was presented to the Technical Sub Committee on October 19, 2004, as the first step in an agreed upon process requiring approval prior to public dissemination. It uses annual hospital discharge data collected from the Discharge Abstract Database (DAD) to compare discharge rates for 18 different health conditions [Appendix] between Port Colborne and three groups:

(a) The Province of Ontario

(b) 35 communities chosen to be similar to Port Colborne with respect to a number of socio demographic variables

(c) 11 communities in the Niagara peninsula chosen by their geographic proximity to Port Colborne.

2. AGE-SEX-YEAR STANDARDIZATION

Plots of the three-year moving averages of the annual age standardized hospital discharge rates over the period 1981 to 1999 for Port Colborne and the three comparison groups are given in exhibits E8 to E21 of the investigator's report. They make little comment on this analysis because it was not adjusted for differences between Port Colborne and Ontario in variables such as income and education level - variables that might explain differences in hospital discharge rates.

3. POISSON REGRESSION

The hospital discharge rates of Port Colborne were compared to a group of 35 comparison communities and then to a group of 11 Niagara communities using **Inpatient Discharge** data and **Poisson Regression** adjusted for over-dispersion in the data. The results were reported as a ratio of the hospital discharge rate in Port Colborne to the mean rate in the comparison communities. A ratio greater than 1.0 means that Port Colborne's discharge rate was greater than that in the comparison group(s).

Although mean income and proportion of adults completing high school were similar between the 35 comparison communities and Port Colborne, considerable variation remained and was adjusted for in the analysis along with two other potential confounders: access to health care and cigarette smoking. These variables were not measured on individuals but only across communities. Therefore residual confounding may exist.

For each of the 18 hospital discharge categories, nine Poisson regression analyses were conducted for all data and within categories defined by:

(a) age - (<20, 20-44, 45-64 and 65+ years)
(b) sex - (males, females)
(c) period - (1980 -1989, 1990-2000).

Only **four** of the 18 x 9 = **162** comparisons resulted in a significant elevation of the hospital discharge ratio:

(a) Ischemic heart disease for all data.
(b) Acute respiratory infection for all data.
(c) Chronic Obstructive Lung Disease for those < 20 years of age.
(d) Asthma for those < 20 years of age.

These four significant results are summarized in Table 1.

TABLE 1 FOUR SIGNIFICANT INPATIENT HOSPITAL DISCHARGE CATEGORIES USING 35 COMPARISON COMMUNITIES (CC)

	ONTARIO	COMPARISON COMMUNITIES	
	Adjusted* sex/age/year	Adjusted** sex/age/year	Fully *** Adjusted
Ischemic Heart Disease	1.40 E44**** (1.36,1.44)	1.24 E26 (1.15,1.33)	1.18 E26 (1.09,1.27)
Acute Respiratory Infections	1.78 E51 (1.68,1.88)	1.64 E33 (1.48,1.82)	1.38 E33 (1.24,1.52)
COPD < 20 yrs old	1.64 E54 (1.52,1.76)	1.54 E36 (1.40,1.70)	1.32 E36 (1.20,1.46)
Asthma < 20 yrs old	1.72 E55 (1.60,1.86)	1.72 E37 (1.58,1.87)	1.48 E37 (1.37,1.62)

* Not adjusted for over-dispersion. Not clear from Ventana report (P.41) but assume that rates were age/sex/year standardized.

** Adjusted for over dispersion and age/sex/year.

*** Adjusted for over dispersion, age/sex/year, and the four regional confounders: mean community income, proportion of residents without high school, regional prevalence of non-smoking, and population-to-physician ratio as a proxy for access to health care.

**** Ej refers to Exhibit number j in the Ventana report.

Plots of the 3-year moving averages of the annual age standardized hospital discharge rates for all data combined for the four health conditions are given in exhibits E8, E15, E18 and E19.

4. EXCESS ANNUAL DISCHARGES

The results could also have been reported as the excess or deficit number of hospital discharges in Port Colborne relative to that expected in a comparable group of communities.

Consider ischemic heart disease. First a quick analysis demonstrates the mutually consistent information presented in exhibits E8 and E44 of the Ventana report. Visual inspection of the 19 annual standardized rates in E8 suggests that Port Colborne has an annual standardized rate of about 950 per 100,000. Multiplying this by 18,500 gives 176 per year or 20 x 176 = 3,515 in total. This number, obtained from such a crude visual inspection, is very close to the 3,315 given in E44.

From E44 the observed number of hospital discharges over the 20 year period is 4,631. From E26 the rate ratio, adjusted for age, sex, calendar year and the four regional confounders is 1.18. Using this information the expected number of hospital discharges due to ischemic heart can be calculated

$$\frac{OBSERVED}{EXPECTED} = 1.18 = \frac{4631}{EXP}$$

Therefore 3925 discharges are expected. This means that each year there are **35** more discharges for ischemic heart disease [(4631 - 3925) /20 = 35] than would be expected from a comparable population. Similar calculations show, for example, that there are 17 excess discharges from acute respiratory infection per year and 11 excess asthma discharges per year among those less than 20 years of age.

Reporting the actual deficit or excess number of hospital discharges in Port Colborne relative to that expected in a group of comparable communities might be a more informative way for residents of Port Colborne to understand the negative or positive impact of the data.

5. NIAGARA CITIES AS COMPARISON GROUP

The Poisson Regression was repeated using a group of 11 cities located nearby in the Niagara peninsula as the comparison group. The results, reported in Table 2, were similar to those reported in Table 1.

TABLE 2 COMPARISONS BETWEEN PORT COLBORNE AND 11 NIAGARA CITIES FOR SAME FOUR HOSPITAL DISCHARGE CATEGORIES AS TABLE 1

		Adjusted ** sex, age & year	Fully *** Adjusted
Ischemic Heart Disease	E26	1.38 (1.28,1.49)	1.34 (1.24,1.44)
Acute Respiratory Infections	E33	1.40 (1.27,1.56)	1.19 (1.07,1.32)
Asthma <20 Years Old	E36	1.48 (1.34,1.63)	1.32 (1.20,1.45)
Asthma <20 Years Old	E37	1.52 (1.40,1.66)	1.38 (1.27,1.50)

** and *** Same meaning as in Table 1.

6. STUDENT T TESTS OF MEAN RATES

In section 2.5.2 of the Ventana Report the investigators explain how they obtained a rate ratio for Port Colborne and each of the 35 comparator communities using Poisson regression. This involved 36 separate analyses in which the rate of each city in turn was compared to the mean rate of the remaining 35 communities. Each analysis was adjusted for age, sex, calendar year and the four regionally defined confounding variables - mean income, proportion of adult residents without high school, smoking prevalence and population-to-physician ratio. A two-sample t test was used to compare the Port Colborne rate ratio to the mean of the rate ratios of the 35 other communities. This analysis resulted in p values much larger ($p>0.05$) than those obtained by the Poisson regression. The explanation of such a large difference might become clear if it were known whether, in the Poisson regressions, the sampling units were the 36 communities or the much larger number of age-sex-year categories. Box plots, used to graphically display the relative ranking of Port Colborne's hospital discharge rate ratio relative to the rate ratios of the other communities, are more difficult to interpret for communities of very different sizes.

7. SUMMARY

The following is a summary of the significant positive (+), significant negative (-) and not significant (0) findings for the Poisson regression analyses using the two comparison groups

	FINDINGS			
	-	0	+	Totals
USING 35 COMPARATOR COMMUNITIES	12	4	2	18
USING 11 NIAGARA COMMUNITIES	4	12	2	18

The large number of significant negative findings is surprising. All of the analyses reported in the Appendix table were repeated using the sum of Inpatient and Day Surgery discharges. The results (not reported here) for the four significantly positive findings, i.e. those for Ischemia, Acute Respiratory, and COPD < 20 years of age, and Asthma < 20 years of age are nearly identical to those derived using only inpatient data. This is not surprising because these four conditions would involve almost no day surgery.

8. CONCLUSIONS

Although an elevation in hospital discharge rates for Port Colborne was found for four conditions, the statistical evidence supporting a hypothesis of a local exposure affecting the health of community members of Port Colborne is weak because:

(a) The end point of the analysis is a hospital discharge not a death or an incident disease event. Hospital discharges can vary among communities due to differences in access to health care as well as differences in rates and severity of disease.

(b) The number of annual hospital discharges that represent repeat visits for people is unknown and could affect variation across communities in the total discharge rate, caused by variation in hospital utilization patterns and access to alternative care.

(c) It is unknown what proportion of the hospital discharges are for workers in metal-related industries, including INCO, where exposures to COCs may be much higher than those in the community.

(d) The probability that a significant finding, discovered among 162 comparisons, is due to chance is likely much higher than the 5% nominal significance level. Although hospital discharge ratios for asthma and COPD were significant for those less than 20 years of age, the ratios for all ages combined were not. Elevated results found only by inspection of sub-categories are more prone to the Type I Error inflation caused by the multiple comparisons.

(e) Adjustments for the four important confounding variables, (mean income, smoking prevalence, proportion of adults without high school and population-to-physician ratio) is sub-optimal because they could not be based on measurements associated with each individual discharge but instead involved regional summaries.

(f) No adjustment was made for air pollution, known to be associated with conditions such as asthma and heart ischemia.

(g) The hospital discharge ratio for all 18 conditions combined is significantly lower in Port Colborne relative to the 35 comparison communities (0.88) and almost identical to that in the Niagara communities (1.02). Does this suggest residents of Port Colborne are healthier or have lower hospital utilization?

(h) The large discrepancies between the p values obtained from the Poisson and Student's t test analyses are difficult to explain without knowing more details of the analysis.

In support of the hypothesis are that the

(a) Four significant associations may have biological plausibility

(b) First analysis was corroborated with a second comparison group

The investigators were aware of these issues and clearly identified many of them in their report. Protocol C was designed to study associations using the hospital discharge as the end-point. This end-point enjoys wide acceptance in the scientific community. Unlike measurements in a survey, hospital discharges are readily available in a convenient form for most of the population. With information obtained from the results of their survey (Protocol A) an argument for further research might be established.

Considering all of these issues together we agree with the investigators who correctly caution against drawing conclusions about causal relationships from their analysis.

APPENDIX

Statistically significant positive (+), negative (-) and not significant (0) findings for 18 Discharge Categories using all data combined over period 1980 to 2000

		Significant Finding	
		CC	Niagara
1.	All Causes	-	0
2.	Malignant neoplasms of respiratory & intrathoracic organs	-	0
3.	Nervous system	-	-
4.	Circulatory system	-	0
5.	Ischemic heart disease	+	+
6.	Acute myocardial infarction	0	0
7.	Heart failure	0	0
8.	Cerebrovascular disease	-	0
9.	Digestive system	-	0
10.	Genitourinary system	-	-
11.	Non-malignant disease of the respiratory system	-	0
12.	Acute respiratory system	+	+
13.	Respiratory tract	-	-
14.	Pneumonia and influenza	0	0
15.	Chronic obstructive pulmonary disease (COPD)**	-	0
16.	Asthma**	0	0
17.	Skin and subcutaneous tissue	-	-
18.	Injury and poisoning	-	0

CC: 35 comparison communities. Niagara: 11 Niagara communities.
** Only analyses using < 20 years of age were significant.

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