



The Auckland alcohol detoxification outcome study: Measuring changes in quality of life in individuals completing a medicated withdrawal from alcohol in a detoxification unit

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ABSTRACT

Aim: To measure outcomes in Quality of Life in alcohol dependent patients' following a medicated withdrawal from alcohol.

Methods: 79 patients that were admitted to a detoxification unit in Auckland, New Zealand between March 2016 and September 2016 were assessed for severity of alcohol dependence using the Alcohol Use Disorders Identification Test (AUDIT) and Severity of Alcohol Dependency Questionnaire (SADQ) and Quality of Life (QOL) using the World Health Organisation Quality of Life-abbreviated version of the WHOQOL 100 New Zealand version (WHOQOL-BREF NZ). Patients were followed up at three months and 12 months and an estimate of drinking behavior and the WHO-QOL BREF NZ were completed via telephone interview. QOL domain scores were assessed from baseline to three months and baseline to 12 months in both relapse and abstinent groups. At three months, a single question was asked in order to collect qualitative data.

Results: At baseline, the study population had statistically significantly lower mean QOL domain scores than scores reported from the general population. QOL improved in patients following detoxification at three months and 12 months in both the relapse and abstinent groups; however, the change in scores from baseline was greater in the abstinent group compared to the relapse group. The majority of patients reported that the admission had been a positive experience.

Conclusion: QOL improves in individuals following a medicated withdrawal from alcohol regardless of whether individual's relapse; however, those that remain abstinent have greater improvements in quality of life.

1. Introduction

Alcohol consumption is associated with an array of health, social and economic problems (Connor et al., 2015; WHO, 2014). Previous research has shown that 79% of New Zealanders report having consumed alcohol in the past year and 20% have consumed alcohol in a way that could cause harm to themselves or others (Lyons et al., 1997). The most recent estimate of the prevalence of alcohol dependence in New Zealand is 1.3% (Ministry of Health, 2016). Numerous studies have shown that only a small percentage of those patients with substance dependence including alcohol dependence will access treatment (Rehm et al., 2015; Scott et al., 2006; Wallhed et al., 2014). Patients in the Auckland region who access Community Alcohol and Drug Services (CADS) requesting support to stop drinking and who are assessed as being alcohol dependent and requiring a medically supervised

withdrawal from alcohol are admitted to the Medical Detoxification Service In-patient Unit (IPU). This is an 11 bed detoxification facility located in the community and it is the largest detoxification unit in New Zealand. There are approximately 500 admissions each year of which 70% are admissions for withdrawal from alcohol (Steenhuisen and Galea, 2014).

Measuring the outcomes of interventions is increasingly becoming an expectation of services delivering health care and to date there have been no studies of outcomes for this client group in New Zealand. Traditionally, the primary endpoints used in clinical trials following alcohol withdrawal were based on the quantity of alcohol consumed or percentage of days abstinent rather than patient reported outcomes such as quality of life (Luquiens et al., 2016). In recognition of the complexity of patients with alcohol dependence, over 20 years ago Babor et al. (1994) concluded that the evaluation of outcomes in the

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treatment of alcohol use disorders should consider three aspects: specific indicators of drinking behavior that measure frequency and quantity of drinking such that direct comparisons can be made pre and post treatment, areas of life functioning including medical problems, psychological and social functioning and global dimensions of relapse and outcomes. Life functioning and global dimensions can be assessed using a tool designed to measure Quality of Life (QOL) and increasingly studies of outcomes in treatment of alcohol dependence have measured changes in QOL (Daepfen et al., 2014; Donovan, 2005; Faller et al., 2015; Foster et al., 1998, 1998; Foster et al., 1999, 2000; Frischknecht et al., 2013; Lo Castro et al., 2009; Lyons et al., 1997; Picci et al., 2014; Srivastava and Bhatia, 2013; Ugochukwu et al., 2013; Vederhus et al., 2016). QOL is defined by the World Health Organization as “an individual’s perception of their position in life in the context of culture and value systems in which they live, and also in relation to their goals, expectations, standards, and concerns” (The WHOQOL Group, 1993). Published studies have consistently shown that the QOL of clients with alcohol dependence is lower than the general population and varies with the severity of dependence (Faller et al., 2015; Frischknecht et al., 2013; Lo Castro et al., 2009; Picci et al., 2014; Ugochukwu et al., 2013; Vederhus et al., 2016). QOL is determined by a range of parameters and studies have confirmed that QOL, particularly the mental aspect tends to improve after detoxification and treatment and worsen after relapse (Foster et al., 1998, 2000a; Foster et al., 2000b; Frischknecht et al., 2013; Lo Castro et al., 2009; Srivastava and Bhatia, 2013; Ugochukwu et al., 2013; Vederhus et al., 2016).

2. Methodology

2.1. Study participants

The study followed 79 patients who met the criteria for DSM-IVR alcohol dependence (American Psychiatric Association, 1994) and who were admitted to the inpatient unit (IPU) for a medicated alcohol withdrawal between March 2016 and September 2016. Exclusion criteria for the study were: under 18 years of age, completing a withdrawal from other substances as well as a medicated withdrawal from alcohol and early discharge with failure to complete the medicated alcohol withdrawal. On admission, eligible patients were provided with written information regarding the aims, methods, risks and benefits of the study and, if they agreed to participate, they were asked to sign a consent form.

Patients received a medicated withdrawal with either diazepam or oxazepam over a seven-day period as per IPU unit guidelines (Waitemata District Health Board, 2014). Before discharge from the IPU, patients completed both the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993), the Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell et al., 1979) to determine severity of alcohol dependence and the WHOQOL-BREF NZ (Kirouac et al., 2017) to ascertain overall quality of life at the time of IPU admission.

An AUDIT score of 20 and above is indicative of alcohol dependence (Donovan et al., 2006). SADQ scores of 31 or higher indicate severe alcohol dependency and 30 or less mild to moderate alcohol dependence. The World Health Organization WHO-QOL (The WHOQOL Group, 1993) and the WHOQOL-BREF (The WHOQOL Group, 1998) have been used in previous studies of patients with alcohol use disorders including dependence to assess outcomes and in a recent review the WHOQOL was thought to have a slight advantage in measuring QOL in people with alcohol use disorders (Kirouac et al., 2017; Lo Castro et al., 2009; da Silva et al., 2005). The New Zealand version of the WHO-QOL BREF includes the 26 original questions and five additional questions that are specific to the New Zealand context and it has been validated for use in the New Zealand population (Krageloh et al., 2010; Krageloh et al., 2013).

At commencement of the study, demographic data and baseline

information were collected including age, sex, marital status, employment status, smoking status, physical health problems, ethnicity, mental health diagnoses and number of previous admissions to the IPU for alcohol withdrawal. During the admission patients had baseline blood testing of liver function and a full blood count.

Patients were followed up at three months and twelve months after the completion of their medicated withdrawal from alcohol. Follow up was by telephone interview and at both follow ups the interviewer completed the WHOQOL-BREF NZ as well as an assessment using the Timeline Follow Back Method of drinking behavior for both percentage of days abstinent and intensity of drinking as defined by the total amount of standard drinks consumed during the follow up period divided by the actual number of drinking days (Babor et al., 1994; Sobell and Sobell, 1992; Vakili et al., 2008). At the three month follow up, patients were asked a single question, “Did your detox have any impact on your quality of life?”

An individual was considered as abstinent at three months if they had a score of 100 for percentage of days abstinent at their three month follow up. An individual was considered abstinent any time if they had a score of 100 for percentage of days abstinent at both the three month and twelve month follow-up. Any individual that had relapsed at three months, but between three months and twelve months had a score of 100 for percentage of days abstinent; were still counted as having relapsed at any time.

The study was approved by the Northern B Health and Disability Ethics Committee, New Zealand [15/NTB/216].

2.2. Statistical analysis

Comparison of baseline to three month and baseline to twelve month quality of life domain scores of patients were compared using a paired *t*-test. A sub analysis was also undertaken assessing mean quality of life scores at baseline to three months and baseline to twelve months in relapse versus abstinent patients using Wilcoxon signed-rank test for dependent samples and Mann–Whitney U test for independent samples. Pearson correlation coefficients were used to examine the relationship between AUDIT scores and SADQ as well as severity of dependence and WHOQOL-NZ domain scores at baseline.

Baseline scores of the four WHOQOL-NZ domains were compared to the domain scores in a reference group from the general New Zealand population (Krageloh et al., 2013). The comparison was made using unpaired *t*-test calculated with mean score and standard deviation of the two samples. All analysis was performed using STATA (Version 15.0, StataCorp, College Station, Texas).

3. Results

3.1. Sample characteristics

A total of 79 patients were recruited and baseline measurements assessed. The mean age of the study group was 47.8 years, the majority were European/Other ethnicity (84.8%), male (64.6%), unemployed (67.1%) and had previously received a detox (70.9%). Of the 79 that enrolled, 68 completed a follow-up at three months (follow-up rate 86.1%) and 60 completed a twelve month follow-up (follow-up rate 75.9%). Five patients that did not complete a follow-up at three months completed a twelve month follow-up. A comparison of baseline characteristics between all patients enrolled and those patients followed up at three and twelve months are presented in Table 1.

3.2. Quality of life – baseline to general population

A comparison was made between baseline quality of life domain scores of the study population and a sample of 808 New Zealanders from the general population (reference values) as reported by Krageloh et al. (2013) (Table 2). At baseline the study population had statistically

Table 1
Baseline variables of patients at enrolment, three months and twelve months follow-up.

	Enrolled (n = 79) n (%) or M (SD)	Followed up three months ^b n (%) or M (SD)	Followed up twelve months ^c n (%) or M (SD)
Age	47.8(11.4)		
Gender			
Female	28 (35.4%)	23 (33.8%)	21 (35.0%)
Male	51 (64.6%)	45 (66.2%)	39 (65.0%)
Ethnicity			
Maori	8 (10.1%)	7 (10.3%)	6 (10.0%)
Asian	3 (3.8%)	3 (4.4%)	3 (5.0%)
European/Other	67 (84.8%)	57 (83.8%)	51 (85.0%)
Pacific	1 (1.3%)	1 (1.5%)	0.0 (0.0%)
Marital status			
Married/defacto	17 (21.5%)	15 (22.1%)	13 (21.7%)
Single	56 (70.9%)	47 (69.1%)	41 (70.0%)
Widow/divorce	6 (7.6%)	6 (8.8%)	5 (8.3%)
Living situation			
Homeless/NFA ^a	7 (8.9%)	6 (8.8%)	3 (5.0%)
Renting/flatting	29 (36.7%)	25 (36.8%)	21 (35.0%)
Boarding	12 (15.2%)	9 (13.2%)	10 (16.7%)
Own home	26 (32.9%)	24 (35.3%)	21 (35.0%)
Unknown	5 (6.3%)	4 (5.9%)	5 (8.3%)
Employment status			
Employed	18 (22.8%)	16 (23.5%)	14 (23.3%)
Retired	8 (10.1%)	8 (11.8%)	6 (10.0%)
Unemployed	53 (67.1%)	44 (64.7%)	40 (66.7%)
Smoking status			
Ex-smoker	3 (3.8%)	3 (4.4%)	2 (3.3%)
Non-smoker	24 (30.4%)	20 (29.4%)	18 (30.0%)
Smoker	52 (65.8%)	45 (66.2%)	40 (66.7%)
First detox			
No	56 (70.9%)	47 (69.1%)	17 (28.3%)
Yes	23 (29.1%)	21 (30.9%)	43 (71.7%)
WHOQOL domain			
Physical	19.4 (5.3)	19.2 (5.2)	22.7 (6.3)
Psychological	22.6 (8.3)	22.3 (8.4)	29.9 (9.0)
Social	10.1 (3.8)	9.9 (3.8)	9.9 (3.8)
Environmental	25.3 (6.8)	25.1 (6.6)	28.4 (5.1)
SADQ baseline	38.5 (13.1)	–	–
AUDIT baseline	34.1 (5.5)	–	–

^a No Fixed Abode.^b 68 patient's followed up at 3-months.^c 60 patient's followed up at 12-months.**Table 2**
Comparison of baseline QOL scores to published scores from the general population.

	Study population baseline M (SD)	General population M (SD)	P-value
WHOQOL domain			
Physical	19.4 (5.3)	27.4 (4.8)	< .001
Psychological	22.6 (8.3)	22.5 (3.9)	.790
Social	10.1 (3.8)	11.6 (2.4)	< .001
Environmental	25.3 (6.8)	31.5 (4.8)	< .001

significantly lower mean quality of life domain scores in three of the four domains (physical, social and environmental).

3.3. Quality of life – baseline and severity of dependence

Baseline AUDIT and SADQ scores of the 79 enrolled patients were negatively correlated with baseline physical, psychological, social and environmental domain scores (Table 3). As SADQ or AUDIT scores increased, quality of life scores decreased. The strongest correlation was seen with the psychological domain (AUDIT; $r = -.478$, $p = .001$, SADQ; $r = -.424$, $p = .001$). There was a moderate/strong positive correlation between SADQ score and AUDIT scores ($r = .661$,

Table 3
Correlations between AUDIT, SADQ and baseline domain scores.

	AUDIT (r)	p-value	SADQ (r)	p-value
WHOQOL domain				
Physical	-.386	.001	-.374	.001
Psychological	-.478	.001	-.424	.001
Social	-.322	.004	-.330	.003
Environmental	-.293	.009	-.384	.001

$p = .001$).

3.4. Quality of life – follow-up

Quality of life scores within the four domains were compared from baseline to three months within the 68 patients that completed follow-up at three months and from baseline to twelve months in the 60 patients that had both baseline and twelve month measurements. The mean scores in all four domains were statistically significantly higher at three months and at twelve months when compared with the mean baseline scores (Table 4). In addition to completing the WHOQOL, patients were asked the question “Did your detox have any impact on your quality of life?” Sixty-six patient responses were positive and there were four main themes: the medicated alcohol withdrawal helped the patient to become abstinent, it gave the opportunity for planning future supports, it broke the cycle and it helped the patient to feel better physically and mentally.

3.5. Quality of life – relapse vs abstinent

A total of 49 out of 68 patients had relapsed at their three month follow-up (three month relapse rate 72.1%). Of those who were followed up at twelve months, 51 out of 60 had relapsed since baseline (twelve month relapse rate 85.0%). A comparison between the relapse group and abstinent groups identified no statistically significant differences in mean baseline quality of life domain scores in the patients followed up at three months (Table 5) or twelve months (Table 6). Of note, at the three month follow up 34 out of the 68 patients had between 80 and 100 per cent drinking days abstinent (50%) and at twelve months 22 out of the 60 patients had between 80 and 100 per cent drinking days abstinent (37%).

At both three and twelve months, the abstinent group had statistically significantly higher quality of life domain scores across all domains when compared with the follow-up scores in the relapse group, with the exception of environmental domain at three months. A comparison of mean quality of life scores at baseline versus the three and twelve month follow-up scores within both the relapse and abstinent groups (Table 7) showed scores were statistically significantly higher in the abstinent groups across all domains at three months and in psychological, social and environmental domains at twelve months compared with baseline. Within the relapse group, quality of life scores at both follow up points and compared with baseline, were statistically significantly higher in the physical and psychological domains. In addition, at three months the social domain was statistically significantly higher and at twelve months the environmental domain compared with baseline scores were higher. Although the scores increased in three of the four domains in the relapse group, the degree of change was much larger in the abstinent group at both follow up points.

3.6. Percentage of drinking days abstinent and quality of life

Percentage of drinking days abstinent from baseline to three months of the 68 patients and 60 patients to twelve months follow-up were positively correlated with baseline physical, psychological, social and environmental domain scores. As percentage of days abstinent increased, quality of life scores increased, with the correlation varying in

Table 4
Baseline domain scores compared with three month and twelve month.

	Baseline M (SD) ^a	3-month M (SD) ^a	p-value	Baseline M (SD) ^b	12-month M (SD) ^b	p-value
WHOQOL domain						
Physical	19.1 (5.2)	22.8 (6.1)	< .001	19.7 (5.3)	22.7 (6.3)	< .001
Psychological	22.3 (8.4)	30.3 (8.6)	< .001	22.5 (8.2)	29.9 (9.0)	< .001
Social	9.9 (3.8)	12.1 (4.0)	< .001	9.9 (3.8)	11.4 (4.4)	.008
Environmental	25.1 (6.6)	27.8 (6.0)	< .001	25.6 (6.3)	28.5 (5.1)	< .001

^a Only includes those with baseline and three month measurements (n = 68).

^b Only includes those with baseline and twelve month measurements (n = 60).

Table 5
Domain scores at baseline and three months comparing relapse vs abstinent.

	Abstinent (n = 19) M (SD) ^a	Re-lapse (n = 49) M (SD) ^a	p-value
WHOQOL domain			
Baseline			
Physical	20.2 (6.6)	18.8 (4.6)	.502
Psychological	24.5 (7.9)	21.0 (7.2)	.156
Social	10.7 (3.6)	9.5 (3.9)	.227
Environmental	25.3 (7.7)	25.0 (6.2)	.617
Three month			
Physical	25.9 (3.9)	21.6 (6.4)	.017
Psychological	35.7 (6.2)	28.2 (8.5)	.001
Social	15.1 (2.5)	11 (3.9)	< .001
Environmental	29.9 (5.7)	26.9 (5.9)	.064

^a Only includes those with baseline and three month measurements.

Table 6
Domain scores at baseline and twelve months comparing relapse vs abstinent groups.

	Abstinent (n = 9) M (SD) ^a	Re-lapse (n = 51) M (SD) ^a	p-value
WHOQOL domain			
Baseline			
Physical	21.7 (7.3)	19.3 (4.9)	.449
Psychological	26.4 (11.0)	21.8 (7.6)	.329
Social	10.3 (3.4)	9.9 (3.9)	.835
Environmental	24.7 (8.1)	25.7 (6.1)	.732
Twelve month			
Physical	28.2 (4.4)	21.7 (6.1)	.005
Psychological	38.1 (5.6)	28.4 (8.7)	.002
Social	15.6 (2.9)	10.7 (4.1)	.002
Environmental	32.8 (3.6)	27.7 (5.9)	.007

^a Only includes those with baseline and twelve month measurements.

strength across domains. Although the correlation was only moderate, the strongest correlation at three months was within the physical domain ($r = .607$, $p = .001$) followed by the social domain ($r = .585$,

Table 7
Baseline domain scores compared with three month and twelve month within relapse and abstinent groups.

	Baseline Mean (SD) ^a	3-month Mean (SD) ^a	p-value	Baseline Mean (SD) ^b	12-month Mean (SD) ^b	p-value
WHOQOL domain						
Abstinent						
Physical	20.2 (6.6)	25.9 (3.9)	.003	21.7 (7.3)	28.2 (4.4)	.066
Psychological	24.5 (7.9)	35.7 (6.2)	.001	26.4 (11.0)	38.1 (5.6)	.013
Social	10.7 (3.6)	15.1 (2.5)	.001	10.3 (3.4)	15.6 (2.9)	.011
Environmental	25.3 (7.7)	29.9 (5.7)	.013	24.7 (8.1)	32.8 (3.6)	.018
Relapse						
Physical	18.8 (4.6)	21.6 (6.4)	.002	19.3 (4.9)	21.7 (6.1)	.007
Psychological	21.0 (7.2)	28.2 (8.5)	< .001	21.8 (7.6)	28.4 (8.7)	< .001
Social	9.5 (3.9)	11 (3.9)	.012	9.9 (3.9)	10.7 (4.1)	.090
Environmental	25.0 (6.2)	26.9 (5.9)	.085	25.7 (6.1)	27.7 (5.9)	.031

^a Only includes those with baseline and three month measurements.

^b Only includes those with baseline and twelve month measurements.

$p = .001$), the psychological domain ($r = .511$, $p = .001$) and the environmental domain ($r = .388$, $p = .001$). At twelve months the correlations were weaker, with the strongest being within the psychological domain ($r = .562$, $p = .001$) followed by the environmental domain ($r = .528$, $p < .001$), the social domain ($r = .502$, $p = .001$) and the physical domain ($r = .459$, $p = .001$). The strength of the correlations was limited by the small sample size.

4. Discussion

This is the first study assessing quality of life outcomes after a medicated alcohol withdrawal in Australasia. The main finding of the study was that patients entering a detoxification unit for a medicated alcohol withdrawal have a quality of life that is poor compared to the general population and that QOL improves following admission in all patients, but improves most in those patients that remain completely abstinent. Improvement in QOL was seen at three months and maintained at twelve months. The percentage of patients who were 100% abstinent was low, but was consistent with other studies (Foster et al., 1999, 2000c). At three and twelve months, there was a moderate correlation between percentage of days abstinent and increased QOL especially in the physical domain. The finding that patients entering a detoxification unit have lower QOL confirms the findings of previous studies although in our study patients had scores in the psychological domain at baseline which were the same as the general population (Daeppen et al., 2014; Faller et al., 2015; Foster et al., 1998, 1999; Foster et al., 2000a,b; Frischknecht et al., 2013; Lo Castro et al., 2009; Picci et al., 2014; Vederhus et al., 2016). The association of an improvement in QOL with abstinence is also consistent with the findings of other studies, although most other studies have shown an improvement predominantly in mental health this study shows improvements in all domains, especially physical health (Foster et al., 1998, 1999; Foster et al., 2000a; Frischknecht et al., 2013; Lo Castro et al., 2009; Srivastava and Bhatia, 2013; Ugochukwu et al., 2013; Vederhus et al., 2016). Although complete abstinence resulted in the greatest improvement in QOL there was some indication of a correlation between the percentage of days abstinent and QOL, suggesting that any

reduction in drinking following a medicated withdrawal may lead to an improved QOL. The improvements in QOL were seen in all domains, but were most marked in the psychological and social domains. These findings lend weight to the use of recovery capital and implementation of models of care that assist patients with psychological, environmental and social aspects of their life following a medicated withdrawal from alcohol (Babor et al., 1987; Best et al., 2012, 2010; Best et al., 2016). Follow up after discharge was variable and those patients who maintained abstinence were not found to have engaged in any particular follow up although the study was not designed to assess this. Most patients reported that the admission had a positive impact on their quality of life. All the patients were assessed as being severely dependent with an average AUDIT score of 34 and SADQ score of 38. The initial baseline assessment of severity of dependence showed that there was a direct correlation between the AUDIT and SADQ suggesting that the AUDIT only could be used to assess severity of alcohol dependence in future studies.

This study has important strengths, but also certain limitations. The high relapse rates at three and twelve months resulted in a small sample for comparison between the abstinent and relapse groups at each follow-up point. Future research with a larger sample that accounted for the high relapse rate would add validity to the findings. A larger sample size could also have allowed us to explore predictors of alcohol abstinence and possibly identify a statistically significant increase in quality of life at twelve months. It must be noted that many of the patients were transient and thus often proved difficult to contact. In addition, understanding the relationship between the admission for a medicated alcohol withdrawal and changes in QOL is complex. This is especially so if there are other changes occurring at the same time and as in any naturalistic study various confounding factors are present limiting causal inferences. Another limitation was that follow up was by telephone interview instead of face to face and verbal reports of alcohol use can be unreliable and inaccurate (Simons et al., 2015; Sobell and Sobell, 1992; Vakili et al., 2008). There was evidence of this on several occasions where study investigators had access to patients' clinical notes, which showed discrepancies between what was disclosed to the investigator compared to what was recorded in the clinical file. The investigators did send out forms for patients to have blood tests to check liver function at three months however no patients had the blood tests done and therefore there was no objective measure available to assess alcohol use.

Strengths of the study were its prospective nature and the reasonably low attrition rate (25%) in what is often a difficult population to research. This low attrition rate allowed the study to still show statistically significant changes in QOL within particular domains and follow-up points. A further strength was the use of validated measures of alcohol dependence and quality of life. All interviews were also undertaken by only two researchers, which limited interviewer bias due to variation in interviewing technique.

5. Conclusion

In conclusion, our study found poor quality of life in alcohol dependent patients before treatment initiation and suggests that quality of life improves after a medicated detoxification. This study can help guide treatment recommendations for patients and suggests that promoting abstinence over controlled use for those patients with severe alcohol dependence could be an appropriate intervention although from a harm reduction perspective any reduction in drinking is likely to lead to an improvement in QOL. It also advocates for incorporating quality of life measures into the evaluation of treatment outcomes. This study has provided evidence supporting the ongoing provision of medically supervised alcohol withdrawal in the Auckland region.

Role of the funding source

Nothing declared.

Contributors

David Prentice and Dr. Vicki Macfarlane were the only investigators who obtained consent and completed the initial interviews of patients and the telephone interviews at three and 12 months. Michael Walsh provided statistical advice prior to commencement of the study and completed the statistical analysis of the results and the tables. All contributors have been involved with writing the final manuscript and have approved the final version.

Declaration of Competing Interest

No conflict declared.

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