APPENDICES

Appendix 1

COPD SURVEY – 1

Hospital MRN: □□□□□□

Date1: □□/□□/□□

Pub 1/Priv 2 □

Demographics

First name: _____Surname: _____Gender: (M/F)

Residential address: Suburb: Postcode:□□□□

Phone: (home) (□□)□□□□□□□□

(business) (□□)□□□□□□□□

(mobile) □□□□□□□□□□

Country of birth: _____Date of birth (age calculated): □□/□□/□□

Occupation(s): _____

Description of tasks:_____

Airborne exposures: _____

GP: Phone:(□□)□□□□□□□□

Contact person, First name: _____Surname:_____

Contact's address: Suburb: Postcode:□□□□

Phone:(□□)□□□□□□□□

Lung Function Testing Details

Race: _____□ Height □□□.□*cm* Weight □□□.□*kg*

(Caucasian=1, Asian=2, Other=3)

Make BMI calculated field in database or enter here **BMI** □□.□

Have you ever before performed breathing tests/lung function tests? (yes/no)

If yes give dates and place *(Most recent first)*

Lfdate1:□□/□□/□□ *lfplace1*_____

Lfdate2:□□/□□/□□ *lfplace2*_____

Lfdate3:□□/□□/□□ *lfplace3*_____

1. In the month preceding admission to hospital, have you smoked?

cigarettes (yes/no)
tobacco, e.g. pipe , roll your own, etc
(yes/no)
marijuana (yes/no)
other, state (yes/no)

2a. *A "regular Smoker" has smoked at least 7 cigarettes (or the equivalent in terms of tobacco smoked) per week for three months or more.*
Have you ever been a regular smoker? (yes/no)
If no, go to question 4
2b. In total, for how many years have you smoked/ for how many years did you smoke?

0-10[1]
11-20[2]
21-30[3]
31-40[4]
41-50[5]
greater than 50[6] □

3. During your period of heaviest smoking, (approximately) how many cigarettes per day would you smoke?

1-10[1]
11-25[2]
26-50[3]
greater than 50[4]
other[5] (specify other e.g. pipe etc_____) □

4. Do you regularly experience any of the following symptoms?

Cough, with or without sputum (phlegm) production (yes/no)
Wheeze (yes/no)
Shortness of breath (yes/no)

5a. Before you were admitted to hospital and when you were feeling relatively well, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough □□
Sputum production □□
Wheeze □□
Shortness of breath □□

5b. Before you were admitted to hospital this time and when you were relatively well) how many times per day would take an extra puffer or nebuliser dose (in addition to any normal daily inhaled medication) for relief of breathlessness or wheeze?

0[1]
1-2[2]
3-5[3]
>5[4] ☐

5c. At present, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough ☐☐
Sputum production ☐☐
Wheeze ☐☐
Shortness of breath ☐☐

5d. At present, how many times per day would you take an extra puffer or nebuliser dose (in addition to any regular daily inhaled medication) for relief of breathlessness or wheeze? *(this includes additional or "prn" medication prescribed by the medical team)*

0[1]
1-2[2]
3-5[3]
>5[4] ☐

6. Have you ever been told that you have

Asthma? (yes/no)
Emphysema? (yes/no)
Chronic bronchitis (yes/no)
Smoking-related lung disease? (yes/no)
COPD/COAD (yes/no)
Pulmonary or lung disease? (yes/no)

7. Do you take inhaled medications or "puffers"? (yes/no)

8. Which inhaled medications do you take?

Salbutamol (Ventolin, Asmol, Epaq) – grey body, blue cap, MDI	(yes/no)
(Airomir) – blue body, grey cap, MDI	(yes/no)
Nebulised?	(yes/no)
Terbutaline (Bricanyl) – white body, blue cap, TH	(yes/no)
(Bricanyl) –blue body, blue cap, MDI	(yes/no)
Salmeterol (Serevent) – turquoise body, green cap, MDI & ACH	(yes/no)
Eformoterol (Oxis) – turquoise base, white body, TH	(yes/no)
(Foradile) – white body, case & base baby blue, ATH	(yes/no)
Orciprenaline – (Alupent)	(yes/no)
Fenoterol – (Berotec)	(yes/no)
Ipratropium bromide (Atrovent) – transparent body, green cap, MDI	(yes/no)
Nebulised?	(yes/no)
(Apoven) Nebulised only	(yes/no)
(Ipratrin) Nebulised only	(yes/no)
(Ipravent) Nebulised only	(yes/no)
Tiatropium (Spiriva) – grey with green button, HH	(yes/no)
Cromoglycate (Intal) – white body, blue cap, MDI	(yes/no)
(Intal forte) – white body, red/pink cap, MDI	(yes/no)
(Tilade) – yellow body with blue button, MDI	(yes/no)
Nebulised (Intal, Cromese Sterinebs)?	(yes/no)
Budesonide (Pulmicort) – white body, brown base, TH	(yes/no)
Nebulised?	(yes/no)
Fluticasone (Flixotide) – orange/red shades body, red cap, MDI & ACH	(yes/no)
Beclomethasone (Qvar) – red/pink holder, MDI	(yes/no)
(Becotide) – brown body brown cap, MDI	(yes/no)
(Becloforte) – yellow body black cap, MDI	(yes/no)
(Seratide) – purple/mauve body, mauve cap, MDI &ACH	(yes/no)
(Combivent) – clear with grey button, MDI	(yes/no)
(Symbicort) – white body, red base, TH	(yes/no)
Other Inhaled Medication_____	(yes/no)

9a. Do you take beta blocker medication on a regular basis? *(include eye drops* (yes/no)
Ask specifically then tick

Atenolol brands	(yes/no)	*Noten*	(yes/no)
		Tenormin	(yes/no)
		Anselol	(yes/no)
		Atehexal	(yes/no)
		Tensig	(yes/no)
		Atenolol	(yes/no)
Metoprolol brands	(yes/no)	*Betaloc*	(yes/no)
		Lopresor	(yes/no)
		Minax	(yes/no)
		Metolol	(yes/no)
		Metohexal	(yes/no)
		Metoprolol	(yes/no)
Carvedilol brands	(yes/no)	*Dilatrend*	(yes/no)
		Kredex	(yes/no)

*Other please state*_____(yes/no)

9b. Duration of any regular beta blocker therapy ☐☐years ☐☐months ☐weeks

9c. What other medications do you take on a regular (at least 2nd daily) basis?

_____
_____
_____

10. In the last 12 months have you been admitted to hospital? (yes/no)

Details of Hospital Admissions

Admission	Date Admitted	Hospital	Reason	Respiratory Y/N	Cardiac Y/N
1					
2					
3					
4					
5					
6					

11. In the last twelve months how many times have you sought medical attention for your chest symptoms (includes hospital admissions)?
How many times have you been prescribed antibiotics or prednisone (prednisolone/ cortisone) for these increased symptoms?

Consultations	No Antibiotics or Steroids	Antibiotics only Tick if applicable	Steroids only Tick if applicable	Antibiotics & Steroids
1st				
2nd				
3rd				
4th				
5th				
6th				
7th				
8th				
9th				
10th				
Enter Totals				

Appendix 2

COPD SURVEY 2 **Name** _____ Hospital MRN: ☐☐☐☐☐

Date2 ☐☐/☐☐/☐☐

Please give full discharge diagnosis *(first cardiac)*

_____

_____ *Code later if ICD10 codes available*

Beta blocker indicated (Yes/No)

If Yes Beta blocker prescribed_____

If No reason why not_____

1. At present, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough	☐☐
Sputum production	☐☐
Wheeze	☐☐
Shortness of breath	☐☐

2. At present, how many times per day would you take an extra puffer or nebuliser dose (in addition to any regular daily inhaled medication) for relief of breathlessness or wheeze? *(this includes additional or "prn" medication prescribed by the medical team)*

0[1]
1-2[2]
3-5[3]
>5[4] ☐

3. While in hospital have you received extra treatment for your chest?

(Yes/No)

Does your extra treatment include antibiotics or prednisone (prednisolone/cortisone) given specifically for your chest problems?

(Yes/No)

Antibiotics ☐

Prednisone ☐

Antibiotic and prednisone ☐

4. Since you enrolled into the study, have you had any changes made to your medications? *Ask specifically about continuation of the beta blocker and newly introduced inhaled medications.*

_____

_____

_____

5. Have your smoking habits changed since enrolment to the study?

Increased [1]
No change [2]
Reduced [3]
Quit [4] ☐

Appendix 3

COPD SURVEY 3/4 **Name**_____Hospital MRN: □□□□□□

SURVEY No. □

Date3/4 □□/□□/□□

1. At present, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough □□

Sputum production □□

Wheeze □□

Shortness of breath □□

2. At present, how many times per day would you take an extra puffer or nebuliser dose (in addition to any regular daily inhaled medication) for relief of breathlessness or wheeze? *(this includes additional or "prn" medication prescribed by the medical team)*

0[1]
1-2[2]
3-5[3]
>5[4] □

3. Since you enrolled in the study on the □□/□□/□□ *pre-enter date*, have you been readmitted to hospital?

(yes/no)

Details of Hospital Admissions

Admission	Date Admitted	Hospital	Reason	Respiratory Y/N	Cardiac Y/N
1					
2					
3					
4					

4. Since you enrolled into the study
(a) how many times have you sought medical attention for your chest?
(b) how many times have you been given a course of antibiotics or prednisone (prednisolone/cortisone)?

Consultations	No Antibiotics or Steroids	Antibiotics only Tick if applicable	Steroids only Tick if applicable	Antibiotics & Steroids
1st				
2nd				
3rd				
4th				
Enter Totals				

5. Since you enrolled into the study, have you had any changes made to your medications? *Ask specifically about continuation of the beta blocker and newly introduced inhaled medications.*

_____

_____

6. Have your smoking habits changed since enrolment to the study?

Increased [1] No change [2] Reduced [3] Quit [4] ☐

Appendix 4

Table 1: Individual Subject Data – Demographics

Subject ID	Subject Category	Suburb	Insurance Status	Occupation	Gender	Age	BMI	Race
1	Full Protocol	St Peters	Medicare	Data Entry	Female	29.41	31.2213040	Caucasian
2	Full Protocol	Leichhardt	Ineligible	Travel Agent	Female	58.1	23.7386621	Caucasian
3	Full Protocol	Redfern	Medicare	Artist	Male	79.26	22.9590877	Caucasian
4	Full Protocol	Rozelle	Medicare	Manager Automotive Spare Parts, Carer	Male	54.03	23.7714286	Caucasian
5	Amended Protocol	Redfern	Medicare	Vet/Farrier's Assistant	Male	76.11	21.7554685	Caucasian
6	Full Protocol	Petersham	Medicare	Sales Assistant	Female	79.13	20.3125	Caucasian
7	Full Protocol	Darling Point	Medicare	House Wife	Female	84.19	25.4325260	Caucasian
8	Full Protocol	Glebe	Medicare	Company Sales Representative	Male	92.18	25.7439446	Caucasian
9	Full Protocol	Ermington	Medicare	Printer	Male	79.75	23.6712536	Caucasian
10	Full Protocol	Dulwich Hill	Medicare	Carpenter	Male	80.95	29.5157733	Caucasian
11	Amended Protocol	Concord West	Medicare	Builder	Male	72.78	33.2621407	Caucasian
12	Full Protocol	Concord	Medicare	Motor Mechanic	Male	67.55	25.9515571	Caucasian
13	Full Protocol	Stanmore	Medicare	Clerk	Male	62.16	40.7454649	Caucasian
14	Full Protocol	Waterloo	Medicare	Welder	Male	58	31.7417889	Caucasian
15	Full Protocol	Rozelle	Medicare	Receptionist	Female	76.22	25.8396814	Caucasian
16	Full Protocol	St Peters	Ineligible	Latex Manufacturer	Male	45.92	27.7322998	Caucasian
17	Amended Protocol	Waterloo	Medicare	Clerk	Male	64.61	24.0569348	Caucasian
18	Full Protocol	Dulwich Hill	Medicare	Cook	Female	68.41	34.6260388	Caucasian
19	Full Protocol	Glebe	Medicare	Restaurateur, Chef	Female	73.85	22.6912406	Caucasian
20	Full Protocol	Marrickville	Medicare	Clerk	Female	58.2	23.6652444	Caucasian
21	Full Protocol	Petersham	DVA	House Wife	Female	74.93	29.7441999	Caucasian
22	Full Protocol	Enfield	Private	Technical Aide	Female	60.69	29.7575846	Caucasian
23	Full Protocol	Marrickville	Private	Metal Polishing	Male	70.83	30.4779662	Caucasian
24	Full Protocol	Lilyfield	Private	Boat Builder	Male	50.26	24.5351240	Caucasian
25	Full Protocol	Glebe	Medicare	Taxi driver, Finance, IT	Male	45.81	23.9994592	Caucasian
26	Full Protocol	Dubbo	Medicare	Truck Driver	Male	44.28	30.7563678	Caucasian
27	Amended Protocol	Dubbo	Ineligible	Storeman	Male	44.41	46.7128028	Aboriginal
28	Full Protocol	Pyrmont	Medicare	Policeman	Male	68.59	29.6495116	Caucasian
29	Full Protocol	Drummoyne	Medicare	Carpenter	Male	65.84	35.4191263	Caucasian
30	Full Protocol	North Sydney	Medicare	Self Employed	Female	50.72	31.2025637	Caucasian
31	Full Protocol	Rozelle	Ineligible	Real Estate Agent	Male	68.31	31.5179326	Caucasian

Subject ID	Subject Category	Suburb	Insurance Status	Occupation	Gender	Age	BMI	Race
32	Amended Protocol	Dunedoo	Medicare	House Wife	Female	73.11	30.8596074	Caucasian
33	Full Protocol	Dover Heights	Ineligible	Chartered Accountant	Male	76.07	24.0929705	Caucasian
34	Full Protocol	Elanora	Private	Director Media Company	Male	39.68	22.4087868	Caucasian
35	Full Protocol	Croyden	Medicare	Ship's Engineer, Garden Ctr Owner	Male	59.08	35.3218210	Caucasian
36	Amended Protocol	Lakes Entrance	Ineligible	Clothing Trade, Supervisor in Warehouse	Female	76.15	20.9041950	Caucasian
37	Full Protocol	Killara	Medicare	Secretary/ Receptionist, Air Hostess	Female	73.98	20.8299952	Caucasian
38	Full Protocol	Dulwich Hill	Medicare	Construction	Male	70.93	31.2394144	Caucasian
39	Full Protocol	Lewisham	Medicare	Boss General Textiles	Female	82.41	36.6285120	Caucasian
40	Amended Protocol	Redfern	Medicare	Cook, Fruit-Picking, Laundry	Female	73.48	17.8980229	Caucasian
41	Full Protocol	Rozelle	Medicare	Chartered Surveyor, Strata Inspector, Town Planning Consultant	Male	62.4	25.8166302	Caucasian
42	Full Protocol	Summer Hill	Ineligible	Timber Merchant, Glass Factory Worker, Dep't Store, Hospitality, Staffing Agency	Male	68.31	25.3086420	Caucasian
43	Full Protocol	Elizabeth Bay	Ineligible	Accountant, Clerk, Teacher	Female	81.82	22.6666667	Caucasian
44	Full Protocol	Glebe	Medicare	City Council Work, Sweeper Printer	Male	62.84	25.2092014	Caucasian
45	Full Protocol	Marrickville	Medicare	Cook, Shop Assistant, Store Worker	Female	55.7	31.2452370	Caucasian
46	Full Protocol	Redfern	Medicare	Cook, Labourer	Male	61.94	35.2010451	Caucasian
47	Full Protocol	Watsons Bay	Private	Electrical Engineer	Male	68.75	22.8395062	Caucasian
48	Full Protocol	Leichhardt	Medicare	Factory Worker, Electrician	Male	82.33	22.3093564	Caucasian
49	Amended Protocol	Drouin	Ineligible	Clerk, Financial Management, Gardener, Founder Toyworld	Male	75.11	32.0759130	Caucasian
50	Amended Protocol	Lismore	Medicare	Army, Hospital Work, Construction, Asbestos Removal, Merchant, Catering Officer	Male	59.62	32.4100371	Caucasian
51	Full Protocol	Newtown	Medicare	Fish Monger, Golf Club Manufacturer	Male	66.95	25.6895619	Aboriginal
52	Full Protocol	Erskineville	Medicare	Seaman, Cook, Factory Worker	Male	80.61	29.4887039	Asian
53	Full Protocol	Caringbah	Medicare	Mothercraft Nurse	Female	58.47	39.8961195	Caucasian
54	Full Protocol	Turella	Medicare	Fitter and Turner, Machinist, Tool-Maker	Male	65.02	33.5765087	Caucasian
55	Full Protocol	Faulconbridge	Medicare	Bookkeeper, Graphic Artist	Female	49.62	30.6361822	Caucasian
56	Full Protocol	Marrickville	Medicare	Construction Worker	Male	67.83	26.0789715	Caucasian
57	Full Protocol	Drummoyne	Private	Production Manager, News Media, Printing	Male	55.32	24.0493434	Caucasian
58	Amended Protocol	Sussex Inlet	Ineligible	Boilermaker, Timberyard Maintenance	Male	73.51	27.1314118	Caucasian
59	Full Protocol	Botobolar	Ineligible	Postal Clerk	Male	50.33	22.2222222	Caucasian
60	Full Protocol	Croyden	Medicare	Military Intelligence, Translator, Cook	Male	65.02	21.2009914	Caucasian
61	Full Protocol	Earlwood	Medicare	Bookkeeper	Female	54.71	29.9687825	Caucasian
62	Full Protocol	Rose Hill	DVA	Engineer, Maintenance, Seaman, Army	Male	72.02	21.0667433	Caucasian
63	Amended Protocol	Lithgow	Medicare	Bank Officer, Sewing Machinist	Female	52.97	55.078125	Caucasian
64	Full Protocol	Marrickville	Medicare	House Wife	Female	76.9	39.0625	Caucasian

Table 2: Individual Subject Data - Smoking and Respiratory Morbidity

Subject ID	Regular Smoker	Pack Years	Previous Asthma	Smoke-Related Lung Disease	Emphysema	COPD/ COAD	Chronic Bronchitis	Other Lung Disease
1	Yes	37.5	Yes					
2		0						Yes
3		0						Yes
4	Yes	82						
5	Yes	161.2		Yes				
6		0	Yes				Yes	
7	Yes	10						
8	Yes	63.75						
9		0						
10	Yes	65.55						
11	Yes	25.5						
12	Yes	22.5						
13	Yes	68	Yes				Yes	
14	Yes	50						
15		0						
16	Yes	7						
17		0						
18	Yes	42.5	Yes			Yes	Yes	
19	Yes	52.5						Yes
20	Yes	39.6					Yes	Yes
21	Yes	107.5	Yes			Yes		
22	Yes	7	Yes					Yes
23	Yes	10						Yes
24	Yes	3	Yes					
25		0						
26	Yes	26.25						
27	Yes	25						
28	Yes	96						
29	Yes	15						
30	Yes	18.75	Yes					
31	Yes	168					Yes	
32	Yes	21						
33	Yes	47						
34	Yes	0.6	Yes					
35		0						
36	Yes	5						
37	Yes	7.5						
38	Yes	37.5					Yes	
39		0						
40	Yes	123.75	Yes		Yes		Yes	
41	Yes	18.75						
42	Yes	21						
43		0	Yes					
44	Yes	118.25	Yes	Yes	Yes		Yes	Yes
45	Yes	1						
46	Yes	228	Yes				Yes	
47		0	Yes				Yes	
48	Yes	30						
49		0						
50	Yes	105	Yes					
51	Yes	51						
52	Yes	120						
53		0	Yes					
54	Yes	52.5						
55	Yes	6.5	Yes					
56	Yes	82.5						
57	Yes	1.95	Yes					
58	Yes	1.75			Yes	Yes		
59	Yes	49.5						
60		0						
61		0						
62	Yes	12.6						
63	Yes	7.8	Yes					
64		0						

Table 3: Individual Subject Data – Acute Cardiac Morbidity

Subject ID	Acute Coronary Syndrome	Valvular Heart Disease	Congestive Cardiac Failure	Arrhythmia	Pericardial Disease
1					
2				Yes	
3					
4	Yes				
5			Yes	Yes	
6	Yes				
7	Yes				
8	Yes				
9	Yes				
10					
11	Yes				
12	Yes				
13	Yes				
14	Yes				
15		Yes		Yes	
16				Yes	
17	Yes				
18					
19	Yes				
20				Yes	
21	Yes				
22					
23					
24	Yes				
25					
26	Yes				
27	Yes				
28	Yes				
29					
30	Yes				
31	Yes		Yes	Yes	
32	Yes			Yes	
33					
34				Yes	
35	Yes			Yes	
36					
37	Yes				Yes
38	Yes				
39					
40				Yes	
41					
42	Yes				
43					
44					
45				Yes	
46			Yes		
47	Yes				
48					Yes
49	Yes				
50	Yes				
51					
52	Yes				
53	Yes				
54				Yes	
55	Yes				
56	Yes				
57					
58	Yes				
59	Yes		Yes		
60					
61					
62	Yes				
63	Yes				
64	Yes				

Table 4: Individual Subject Data – Chronic Cardiovascular Morbidity and Risk Factors

Subject ID	IHD	Other Primary Cardiac Disease	Hypertension	Dyslipidaemia	Peripheral Vascular Disease	Cerebrovascular Disease	Diabetes Mellitus
1		Cardiomyopathy					
2		Valvular Heart Disease					
3	Yes						
4	Yes						
5	Yes				Yes		
6	Yes						
7	Yes						
8	Yes						
9	Yes						
10							Yes
11	Yes						Yes
12	Yes						
13	Yes						
14	Yes						
15						Yes	
16							
17	Yes						
18	Yes						
19	Yes						
20							
21	Yes						Yes
22							
23	Yes						Yes
24	Yes						
25							
26	Yes						Yes
27	Yes						
28	Yes				Yes		
29	Yes		Yes	Yes			Yes
30	Yes						
31	Yes						
32	Yes						
33			Yes			Yes	
34							
35	Yes						
36			Yes				
37	Yes		Yes	Yes			
38	Yes		Yes	Yes		Yes	
39			Yes			Yes	
40							
41	Yes		Yes				
42	Yes						
43							
44	Yes						Yes
45			Yes				
46							Yes
47	Yes						
48						Yes	
49	Yes				Yes	Yes	
50	Yes		Yes		Yes		
51	Yes						
52	Yes						Yes
53	Yes						Yes
54	Yes						
55	Yes		Yes	Yes			
56	Yes						
57	Yes						Yes
58	Yes						
59	Yes				Yes		Yes
60							
61							
62	Yes					Yes	
63	Yes		Yes	Yes			
64	Yes						

Table 5: Individual Subject Data – Medication Use

Subject ID	SABA	SAACh	ICS	LABA	LAACh	BB
1	Yes					
2						
3						Yes
4						
5						
6	Yes		Yes			
7						
8	Yes	Yes				
9						Yes
10						
11						Yes
12						Yes
13						
14						Yes
15	Yes		Yes			
16						
17						Yes
18			Yes			
19						Yes
20						
21	Yes					
22	Yes					
23						Yes
24	Yes					
25						
26						
27						
28						
29						Yes
30						
31						
32						Yes
33						
34	Yes					
35						Yes
36						
37						
38						Yes
39						
40	Yes	Yes				
41						
42						
43						
44	Yes	Yes	Yes			
45						Yes
46	Yes		Yes			
47						
48						
49						Yes
50	Yes					Yes
51						Yes
52						
53						
54						
55						
56						
57	Yes					
58						Yes
59						
60						
61						Yes
62	Yes	Yes				
63	Yes		Yes			
64						

SABA=short-acting beta-agonist SAACh=short-acting anticholinergic BB=beta-blocker
LABA=long-acting beta-agonist LAACh= long-acting anticholinergic ICS=inhaled corticosteroid

Appendix 5

Table 1: Individual Subject Data – Spirometry

Subject ID	%PFEV1	%PFVC	%PMMEF*	FEV1/FVC
1	98	95	113	0.88
2	43	49	26	0.67
3	45	48	28	0.71
4	79	85	41	0.68
6	49	63	22	0.57
7	101	97	112	0.72
9	85	82	67	0.72
10	46	63	13	0.58
11	89	106	43	0.65
12	85	89	64	0.74
13	49	58	24	0.66
14	80	85	68	0.75
15	74	81	41	0.68
16	88	89	81	0.8
17	80	80	77	0.78
18	62	68	36	0.69
19	55	68	29	0.61
20	84	84	77	0.79
21	38	49	22	0.58
22	83	85	83	0.77
23	74	71	47	0.67
24	78	76	75	0.82
25	101	102	89	0.81
26	94	105	64	0.72
28	88	99	42	0.65
29	81	84	69	0.78
30	95	103	70	0.77
31	31	42	14	0.55
32	100	96	97	0.78
33	92	99	60	0.71
34	81	97	50	0.67
35	76	73	80	0.82
36	72	71	66	0.92
37	92	95	73	0.69
38	82	89	52	0.69
39	55	70	60	0.68
40	45	54	26	0.59
41	84	101	94	0.75
42	66	70	48	0.72
43	102	98	74	0.72
44	42	62	18	0.52
45	115	115	117	0.81
46	44	60	23	0.59
49	103	119	77	0.68
50	74	83	49	0.71
51	68	86	35	0.62
52	66	77	22	0.61
53	63	67	49	0.75
54	24	44	10	0.39
55	94	97	91	0.75
56	58	64	36	0.72
57	71	80	48	0.7
58	74	73	69	0.77
59	57	58	34	0.7
60	33	38	17	0.78
61	89	102	48	0.72
62	90	95	74	0.72
63	102	113	91	0.74

*PMMEF= Predicted Maximum Mid-Expiratory Flow

Table 2a: Individual Subject Data - Obstructive Lung Function

Subject ID	FER1	FER2	FER3	FER4	Obstruction
1					
2	Obstructed	Obstructed			Obstructed
3		n/a	Obstructed	Obstructed	Obstructed
4	Obstructed		Obstructed	Obstructed	Obstructed
5	X	X	Deceased	Deceased	X
6	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
7				Obstructed	Obstructed
8	X	n/a	Deceased	Deceased	X
9					
10	X	Obstructed	Obstructed	n/a	Obstructed
11	Obstructed	a/p	a/p	a/p	Obstructed
12		n/a			
13	Obstructed	Obstructed		n/a	Obstructed
14			n/a	n/a	
15	Obstructed			Obstructed	Obstructed
16			n/a	n/a	
17		a/p	a/p	a/p	
18	Obstructed	Obstructed	Obstructed	n/a	Obstructed
19	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
20		n/a			
21	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
22					
23		X	n/a	Obstructed	Obstructed
24	X				
25		n/a			
26				n/a	
27	X	a/p	a/p	a/p	X
28	Obstructed		n/a	n/a	Obstructed
29		Obstructed			Obstructed
30		n/a			
31	Obstructed	Obstructed	n/a	n/a	Obstructed
32		a/p	a/p	a/p	
33		n/a			
34	Obstructed	X	Obstructed	Obstructed	Obstructed
35					
36		a/p	a/p	a/p	
37		Obstructed	Obstructed		Obstructed
38	Obstructed		n/a	n/a	Obstructed
39	Obstructed	X	Obstructed		Obstructed
40	Obstructed	a/p	a/p	a/p	Obstructed
41					
42					
43					
44	Obstructed	Obstructed	Deceased	Deceased	Obstructed
45		n/a	n/a		
46	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
47	X	n/a			
48	X	X	n/a	n/a	X
49	Obstructed	n/a	a/p	a/p	Obstructed
50		n/a	a/p	a/p	
51	X	Obstructed	Obstructed	Obstructed	Obstructed
52	Obstructed	Obstructed	Deceased	Deceased	Obstructed
53					
54	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
55					
56	X		Obstructed	n/a	Obstructed
57	Obstructed	n/a	Obstructed	Obstructed	Obstructed
58		a/p	a/p	a/p	
59	Obstructed		n/a	Deceased	Obstructed
60		n/a	Deceased	Deceased	
61					
62		n/a	n/a	n/a	
63		a/p	a/p	a/p	
64	n/a	n/a	Deceased	Deceased	n/a

n/a = not available a/p = amended protocol X=technically inadequate

Table 2b: Individual Subject Data - Bronchodilator Response

Subject ID	BDR1	BDR2	BDR3	BDR4	Overall BDR
1					
2	BDR				BDR
3		n/a			
4					
5	X	X	Deceased	Deceased	X
6	BDR				BDR
7					
8	X	n/a	Deceased	Deceased	X
9					
10			BDR		BDR
11		a/p	a/p	a/p	
12		n/a			
13				n/a	
14			n/a	n/a	
15					
16			n/a	n/a	
17		a/p	a/p	a/p	
18				n/a	
19		BDR			BDR
20		n/a			
21					
22					
23		X	n/a		
24					
25		n/a			
26				n/a	
27	X	a/p	a/p	a/p	X
28			n/a	n/a	
29		BDR			BDR
30		n/a			
31	BDR	BDR	n/a	n/a	BDR
32		a/p	a/p	a/p	
33		n/a			
34		X			
35					
36		a/p	a/p	a/p	
37					
38	BDR		n/a	n/a	BDR
39		X			
40	X	a/p	a/p	a/p	X
41					
42					
43					
44	BDR		Deceased	Deceased	BDR
45		n/a	n/a		
46	BDR	BDR	BDR	BDR	BDR
47	X	n/a			
48	X	X	n/a	n/a	X
49		a/p	a/p	a/p	
50		a/p	a/p	a/p	
51					
52			Deceased	Deceased	
53					
54	BDR	BDR	BDR	BDR	BDR
55					
56				n/a	
57		n/a			
58		a/p	a/p	a/p	
59			n/a	Deceased	
60		n/a	Deceased	Deceased	
61					
62		n/a	n/a	n/a	
63		a/p	a/p	a/p	
64	n/a	n/a	Deceased	Deceased	n/a

n/a = not available a/p = amended protocol X=technically inadequate

Table 3: Individual Subject Data - by Forced Expiratory Ratio

FER	ID	Age	Gender	BMI	Reg Smoker	PY	Asthma	COPD	Inh Med	Beta-Blocker	IHD
0.39	54	65.02	Male	33.58	Yes	42		Yes			Yes
0.52	44	62.84	Male	25.21	Yes	95	Yes	Yes	Yes		Yes
0.55	31	68.31	Male	31.52	Yes	134					Yes
0.57	6	79.13	Female	20.31		0	Yes		Yes		Yes
0.58	10	80.95	Male	29.52	Yes	52					
0.58	21	74.93	Female	29.74	Yes	86	Yes	Yes	Yes		Yes
0.59	40	73.48	Female	17.9	Yes	99	Yes	Yes	Yes		
0.59	56	61.94	Male	35.2	Yes	182	Yes	Yes	Yes	Yes	
0.61	19	73.85	Female	22.69	Yes	42				Yes	Yes
0.61	52	80.61	Male	29.49	Yes	96		Yes			Yes
0.62	51	66.95	Male	25.69	Yes	41				Yes	Yes
0.65	11	72.78	Male	33.26	Yes	20				Yes	Yes
0.65	28	68.59	Male	29.65	Yes	77				Yes	Yes
0.66	13	62.16	Male	40.75	Yes	54	Yes			Yes	Yes
0.67	2	58.1	Female	23.74		0				Yes	
0.67	34	39.68	Male	22.41	Yes	0	Yes		Yes		
0.68	4	54.03	Male	23.77	Yes	66				Yes	Yes
0.68	15	76.22	Female	25.84		0			Yes		
0.68	39	82.41	Female	36.63		0					
0.68	49	75.11	Male	32.08		0				Yes	Yes
0.69	18	68.41	Female	34.63	Yes	34	Yes	Yes	Yes		Yes
0.69	37	73.98	Female	20.83	Yes	6					Yes
0.69	38	70.93	Male	31.24	Yes	30		Yes		Yes	Yes
0.7	57	55.32	Male	24.05	Yes	2	Yes		Yes		Yes
0.7	59	50.33	Male	22.22	Yes	40					Yes
0.71	3	79.26	Male	22.96		0				Yes	Yes
0.71	33	76.07	Male	24.09	Yes	38					
0.71	50	59.62	Male	32.41	Yes	84	Yes		Yes	Yes	Yes
0.72	7	84.19	Female	25.43	Yes	8				Yes	Yes
0.72	9	79.75	Male	23.67		0				Yes	Yes
0.72	26	44.28	Male	30.76	Yes	21				Yes	Yes
0.72	42	68.31	Male	25.31	Yes	17				Yes	Yes
0.72	43	81.82	Female	22.67		0	Yes				
0.72	56	67.83	Male	26.08	Yes	66					Yes
0.72	61	54.71	Female	29.97		0				Yes	
0.72	62	72.02	Male	21.07	Yes	10			Yes		Yes
0.74	12	67.55	Male	25.95	Yes	18				Yes	Yes
0.74	63	52.97	Female	55.08	Yes	6	Yes		Yes		Yes
0.75	14	58	Male	31.74	Yes	40				Yes	Yes
0.75	23	70.83	Male	30.48	Yes	8				Yes	
0.75	41	62.4	Male	25.82	Yes	15				Yes	Yes
0.75	53	58.47	Female	39.9		0	Yes				Yes
0.75	55	49.62	Female	30.64	Yes	5	Yes			Yes	Yes
0.77	22	60.69	Female	29.76	Yes	6			Yes	Yes	
0.77	30	50.72	Female	31.2	Yes	15	Yes				Yes
0.77	58	73.51	Male	27.13	Yes	1		Yes		Yes	Yes
0.78	17	68.41	Male	24.06		0				Yes	Yes
0.78	29	65.84	Male	35.42	Yes	12				Yes	Yes
0.78	32	73.11	Female	30.86	Yes	17				Yes	Yes
0.78	48	65.02	Male	21.2		0					
0.79	20	58.2	Female	23.67	Yes	32					
0.8	16	45.92	Male	27.73	Yes	6					
0.81	25	45.81	Male	24		0					
0.81	45	55.7	Female	31.25	Yes	1				Yes	
0.82	24	50.26	Male	24.54	Yes	2	Yes		Yes	Yes	Yes
0.82	35	59.08	Male	35.32		0				Yes	Yes
0.88	1	29.41	Female	31.22	Yes	30	Yes		Yes		
0.92	36	76.15	Female	20.9	Yes	4					

Table 4: Individual Subject Data - Respiratory Symptoms by Forced Expiratory Ratio

FER	Subject ID	Dyspnoea	Cough	Wheeze
0.39	54	Yes	Yes	
0.52	44	Yes	Yes	
0.55	31	Yes		Yes
0.57	6	Yes	Yes	Yes
0.58	10	Yes	Yes	
0.58	21	Yes		Yes
0.59	40	Yes	Yes	Yes
0.59	56	Yes	Yes	Yes
0.61	19	Yes		
0.61	52	Yes		Yes
0.62	51			
0.65	11	Yes	Yes	Yes
0.65	28		Yes	Yes
0.66	13	Yes	Yes	Yes
0.67	2	Yes	Yes	
0.67	34	Yes		Yes
0.68	4		Yes	
0.68	15			Yes
0.68	39	Yes	Yes	Yes
0.68	49	Yes		
0.69	18	Yes	Yes	Yes
0.69	37	Yes		
0.69	38	Yes	Yes	
0.70	57			
0.70	59	Yes	Yes	
0.71	3	Yes	Yes	Yes
0.71	33	Yes		
0.71	50		Yes	Yes
0.72	7	Yes	Yes	
0.72	9	Yes	Yes	
0.72	26	Yes		
0.72	42			
0.72	43		Yes	
0.72	56	Yes		Yes
0.72	61		Yes	
0.72	62	Yes		
0.74	12	Yes		
0.74	63	Yes		Yes
0.75	14	Yes	Yes	Yes
0.75	23			
0.75	41			
0.75	53	Yes	Yes	Yes
0.75	55			
0.77	22	Yes	Yes	
0.77	30	Yes		
0.77	58	Yes		
0.78	17			
0.78	29	Yes		
0.78	32	Yes		
0.78	48	Yes	Yes	
0.79	20	Yes	Yes	Yes
0.80	16		Yes	Yes
0.81	25			
0.81	45	Yes		
0.82	24			
0.82	35	Yes		
0.88	1	Yes	Yes	
0.92	36	Yes		

Appendix 6

Table 1: Subjects with Cardiac Indications for Beta-Blocker Treatment

Subject ID	Age	Gender	Reg Smoker	Pack Year	BMI	IHD	BB Status
1	29.41	Female	Yes	37.5	31.2213039		
2	58.10	Female		0	23.7386621		Yes
3	79.26	Male		0	22.9590877	Yes	Yes
4	54.03	Male	Yes	82	23.7714286	Yes	Yes
5	76.11	Male	Yes	161.2	21.7554685	Yes	
6	79.13	Female		0	20.3125	Yes	
7	84.19	Female	Yes	10	25.432526	Yes	Yes
8	92.18	Male	Yes	63.75	25.7439446	Yes	
9	79.75	Male		0	23.6712536	Yes	Yes
11	72.78	Male	Yes	25.5	33.2621407	Yes	Yes
12	67.55	Male	Yes	22.5	25.9515571	Yes	Yes
13	62.16	Male	Yes	68	40.7454649	Yes	Yes
14	58.00	Male	Yes	50	31.7417889	Yes	Yes
15	76.22	Female		0	25.8396814		
17	64.61	Male		0	24.0569347	Yes	Yes
18	68.41	Female	Yes	42.5	34.6260388	Yes	
19	73.85	Female	Yes	52.5	22.6912406	Yes	Yes
20	58.20	Female	Yes	39.6	23.6652444		
21	74.93	Female	Yes	107.5	29.7441999	Yes	
23	70.83	Male	Yes	10	30.4779662	Yes	Yes
24	50.26	Male	Yes	3	24.535124	Yes	Yes
26	44.28	Male	Yes	26.25	30.7563678	Yes	Yes
27	44.41	Male	Yes	25	46.7128028	Yes	
28	68.59	Male	Yes	96	29.6495116	Yes	Yes
29	65.84	Male	Yes	15	35.4191263	Yes	Yes
31	68.31	Male	Yes	168	31.5179326	Yes	
32	73.11	Female	Yes	21	30.8596074	Yes	Yes
35	59.08	Male		0	35.321821	Yes	Yes
38	70.93	Male	Yes	37.5	31.2394144	Yes	Yes
40	73.48	Female	Yes	123.75	17.8980229		
41	62.40	Male	Yes	18.75	25.8166302	Yes	Yes
42	68.31	Male	Yes	21	25.308642	Yes	Yes
44	62.84	Male	Yes	118.25	25.2092014	Yes	
45	55.70	Female	Yes	1	31.245237		Yes
46	61.94	Male	Yes	228	35.2010451		Yes
49	75.11	Male		0	32.075913	Yes	Yes
50	59.62	Male	Yes	105	32.4100371	Yes	Yes
51	66.95	Male	Yes	51	25.6895619	Yes	Yes
52	80.61	Male	Yes	120	29.4887039	Yes	
53	58.47	Female		0	39.8961195	Yes	
54	65.02	Male	Yes	52.5	33.5765087	Yes	
55	49.62	Female	Yes	6.5	30.6361822	Yes	Yes
58	73.51	Male	Yes	1.75	27.1314118	Yes	Yes
59	50.33	Male	Yes	49.5	22.2222222	Yes	
60	65.02	Male		0	21.2009914		
62	72.02	Male	Yes	12.6	21.0667433	Yes	
63	52.97	Female	Yes	7.8	55.078125	Yes	
64	76.90	Female		0	39.0625	Yes	Yes

Table 2: Subjects with Cardiac Indications for Beta-Blocker Treatment – Respiratory Factors

Subject ID	Asthma	COPD	Inh Meds	BB Status	FER	Obstruction	BDR	Cough	Wheeze	Dyspnoea
1	Yes		Yes		0.88	No	No	Yes		Yes
2				Yes	0.69	Yes	Yes	Yes		Yes
3				Yes	0.71	No	No	Yes	Yes	Yes
4				Yes	0.68	Yes	No	Yes		
5		Yes						Yes		
6	Yes		Yes		0.57	Yes	Yes	Yes	Yes	Yes
7				Yes	0.74	No	No	Yes		Yes
8			Yes					Yes		Yes
9				Yes	0.72	No	No	Yes		Yes
11				Yes	0.65	Yes	No	Yes	Yes	Yes
12				Yes	0.74	No	No			Yes
13	Yes			Yes	0.66	Yes	No	Yes	Yes	Yes
14				Yes	0.75	No	No	Yes	Yes	
15			Yes		0.68	Yes	No		Yes	Yes
17				Yes	0.78	No	No			
18	Yes	Yes	Yes		0.69	Yes	No	Yes	Yes	Yes
19				Yes	0.61	Yes	Yes			Yes
20					0.79	No	No	Yes	Yes	Yes
21	Yes	Yes	Yes		0.61	Yes	No		Yes	Yes
23				Yes	0.75	No				Yes
24	Yes		Yes	Yes	0.82	No	No			
26				Yes	0.72	No	No			
27										Yes
28				Yes	0.65	Yes	No	Yes	Yes	
29				Yes	0.78	No	Yes			Yes
31					0.55	Yes	Yes		Yes	Yes
32				Yes	0.78	No	No			Yes
35				Yes	0.82	No	No			Yes
38				Yes	0.69	Yes	Yes			Yes
40	Yes		Yes		0.59	Yes	Yes	Yes	Yes	Yes
41				Yes	0.79	No	No			
42				Yes	0.72	No	No			
44	Yes	Yes	Yes		0.57	Yes	Yes	Yes		Yes
45				Yes	0.81	No	No			Yes
46	Yes		Yes	Yes	0.63	Yes	Yes	Yes	Yes	Yes
49				Yes	0.68	Yes	No			Yes
50	Yes		Yes	Yes	0.71	No	No	Yes	Yes	Yes
51				Yes	0.62	Yes	No			
52					0.61	Yes	No		Yes	Yes
53	Yes				0.75	No	No	Yes	Yes	Yes
54					0.45	Yes	Yes	Yes		Yes
55	Yes			Yes	0.79	No	No			
58		Yes		Yes	0.77	No	No			Yes
59					0.7	No	No	Yes		Yes
60					0.67	Yes	No	Yes		Yes
62			Yes		0.72	No	No			Yes
63	Yes		Yes		0.74	No	No		Yes	Yes
64				Yes						Yes

Appendix 7

FOLLOW-UP BETA-BLOCKERS, AIRWAYS DISEASE SURVEY: Part 5

Subject Number: ☐☐

Hospital MRN: ☐☐☐☐☐☐

SURVEY No. ☐

Date ☐☐/☐☐/☐☐

Please read the accompanying letter first and then answer the questions below by putting a number or tick ✓ in the appropriate box.

1. At present, do you use any puffer or nebuliser?

Yes ☐ No ☐

If yes, how many times per day would you use an extra puffer or nebuliser dose (in addition to any regular daily inhaled medication) for relief of breathlessness or wheeze? ***(Only tick one box for this question)***

No extra use of Puffer or Nebuliser	☐
1-2 extra Puffs or Nebuliser doses	☐
3-5 extra Puffs or Nebuliser doses	☐
More than 5 extra Puffs or Nebuliser doses	☐

2. ***Please tick or put a number in just one box for the number of times, and then (if applicable) record the number of hospitalisations for parts (a), (b) and (c).***

Since your last contact with the Study investigators, on __/__/2004,

(a) How many times have you sought medical attention for cough, breathing difficulty or wheeze? ***(include presentations to hospital)***

In 2004 None ☐ 1-2 ☐ 3-5 ☐ 6-10 ☐ 10+ ☐ estimated number ☐☐

Number of times that hospital admission was required _____

In 2005 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2006 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2007 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

(b) How many times have you sought medical attention for <u>chest pain, angina, palpitations or fluid retention</u>? ***(include presentations to hospital)***

In 2004, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2005, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2006, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2007, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

(c) How many times have you been given a course of antibiotics or prednisone (prednisolone/cortisone) because of difficulty breathing? ***(include presentations to hospital)***

In 2004 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2005 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2006 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2007 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

3 (a). Please provide a list of your current regular medications ***(don't forget inhaled medications!)****:*

_____
_____
_____
_____
_____
_____
_____

4. Please provide details of your current smoking status

(a) Never smoked ☐

(b) Former smoker ☐

(c) Current smoker ☐

5. Please supply your local doctor (or general practitioner)'s details. ***(If you don't have a regular GP, please provide the details of the medical practice that you most often frequent)***

(a) Name_____

(b) Practice address_____

(c) Practice telephone or email contact_____

If you wish to add more information please write in the space provided at the end of this survey (overleaf).

Thank you for your time, effort and ongoing participation in this research project.

Table 1: Long Term Beta-Blocker Exposure and Lung Function

ID[1]	Visit	Duration (Year)	Cum BB	Cum Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
1	1	0	1	0	0.6784	96	82	-10.82661	Male	-4.483396	82
1	2	0.008219	1	0	0.7405079	85	79	-10.82661	Male	-4.483396	82
1	3	0.5	2	0	0.6918892	88	83	-10.82661	Male	-4.483396	82
1	4	1	3	0	0.6699623	92	86	-10.82661	Male	-4.483396	82
2	1	0	0	0	0.8663793	114	110	-35.44661	Female	2.96648	37.5
2	2	0.008219	0	0	0.8783886	95	98	-35.44661	Female	2.96648	37.5
2	3	0.5	0	0	0.8735632	75	82	-35.44661	Female	2.96648	37.5
2	4	1	0	2	0.8346891	88	93	-35.44661	Female	2.96648	37.5
3	1	0	1	0	0.6905	49	43	-6.756612	Female	-4.516162	0
3	2	0.008219	1	0	0.6668527	52	44	-6.756612	Female	-4.516162	0
3	3	0.5	2	0	0.7244898	71	69	-6.756612	Female	-4.516162	0
3	4	1	3	0	0.7016976	72	68	-6.756612	Female	-4.516162	0
4	1	0	1	0	0.7071	48	45	14.40339	Male	-5.295737	0
4	2	0.008219	1	0				14.40339	Male	-5.295737	0
4	3	0.5	2	0	0.6917337	54	57	14.40339	Male	-5.295737	0
4	4	1	3	0	0.6360656	57	56	14.40339	Male	-5.295737	0
5	1	0	0	1	0.5701	63	49	14.27339	Female	-7.942325	0
5	2	0.008219	0	1	0.6126543	72	60	14.27339	Female	-7.942325	0
5	3	0.5	0	1	0.6223022	75	68	14.27339	Female	-7.942325	0
5	4	1	0	2	0.5624212	76	65	14.27339	Female	-7.942325	0
6	1	0	1	0	0.7355199	100	102	19.33339	Female	-2.822301	10
6	2	0.008219	1	0	0.7407278	101	97	19.33339	Female	-2.822301	10
6	3	0.5	2	0	0.7112181	95	99	19.33339	Female	-2.822301	10
6	4	1	3	0	0.677706	88	88	19.33339	Female	-2.822301	10
7	1	0	1	0	0.709637	82	85	14.89339	Male	-4.58357	0
7	2	0.008219	1	0	0.7007874	90	86	14.89339	Male	-4.58357	0
7	3	0.5	2	0	0.7090717	93	102	14.89339	Male	-4.58357	0
7	4	1	3	0	0.714031	95	107	14.89339	Male	-4.58357	0
8	1	0	1	0	0.7441	89	85	2.693393	Male	-2.303269	22.5
8	2	0.008219	1	0				2.693393	Male	-2.303269	22.5
8	3	0.5	2	0	0.7155101	91	95	2.693393	Male	-2.303269	22.5
8	4	1	3	0	0.7357143	92	101	2.693393	Male	-2.303269	22.5
9	1	0	1	0	0.663	58	49	-2.69661	Male	12.49064	68
9	2	0.008219	1	0	0.688067	66	66	-2.69661	Male	12.49064	68
9	3	0.5	2	0	0.7007199	73	72	-2.69661	Male	12.49064	68
9	4	1	3	0				-2.69661	Male	12.49064	68
10	1	0	1	0	0.7517	85	81	-6.85661	Male	3.486964	50
10	2	0.008219	1	0	0.7484904	58	80	-6.85661	Male	3.486964	50
10	3	0.5	2	0				-6.85661	Male	3.486964	50
10	4	1	3	0				-6.85661	Male	3.486964	50
11	1	0	0	0	0.6815	82	74	11.36339	Female	-2.415143	0
11	2	0.008219	0	0	0.7502756	82	90	11.36339	Female	-2.415143	0
11	3	0.5	0	0	0.7305136	74	80	11.36339	Female	-2.415143	0
11	4	1	0	1	0.677947	81	81	11.36339	Female	-2.415143	0
12	1	0	0	0	0.8027	89	88	-18.93661	Male	-0.5225247	7
12	2	0.008219	0	0	0.8072262	92	91	-18.93661	Male	-0.5225247	7
12	3	0.5	0	0				-18.93661	Male	-0.5225247	7
12	4	1	0	0				-18.93661	Male	-0.5225247	7
13	1	0	0	2	0.6917	72	64	3.553394	Female	6.371217	42.5
13	2	0.008219	0	4	0.6825476	68	69	3.553394	Female	6.371217	42.5
13	3	0.5	1	5	0.674175	67	66	3.553394	Female	6.371217	42.5
13	4	1	2	5				3.553394	Female	6.371217	42.5
14	1	0	1	0	0.5914832	73	63	8.993388	Female	-5.563586	52.5
14	2	0.008219	1	0	0.6089239	69	58	8.993388	Female	-5.563586	52.5
14	3	0.5	2	0	0.5965225	68	57	8.993388	Female	-5.563586	52.5
14	4	1	3	0	0.6086547	64	55	8.993388	Female	-5.563586	52.5
15	1	0	0	0	0.769419	84	90	-6.65661	Female	-4.58958	39.6
15	2	0.008219	0	0				-6.65661	Female	-4.58958	39.6
15	3	0.5	1	0	0.7074647	89	84	-6.65661	Female	-4.58958	39.6
15	4	1	2	0	0.709291	93	89	-6.65661	Female	-4.58958	39.6

ID[1]	Visit	Duration (Year)	Cum. BB	Cum. Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
16	1	0	0	0	0.6122	50	43	10.07339	Female	1.489375	107.5
16	2	0.008219	0	0	0.5818635	49	41	10.07339	Female	1.489375	107.5
16	3	0.5	0	0	0.6076002	58	67	10.07339	Female	1.489375	107.5
16	4	1	0	0	0.6705069	62	60	10.07339	Female	1.489375	107.5
17	1	0	1	0	0.766	88	91	-4.166612	Female	1.502761	7
17	2	0.008219	1	0	0.7761492	94	99	-4.166612	Female	1.502761	7
17	3	0.5	1	0	0.7409152	94	95	-4.166612	Female	1.502761	7
17	4	1	1	0	0.7700743	90	94	-4.166612	Female	1.502761	7
18	1	0	1	0	0.7465	76	83	5.973392	Male	2.223144	10
18	2	0.008219	1	0				5.973392	Male	2.223144	10
18	3	0.5	2	0				5.973392	Male	2.223144	10
18	4	1	3	1	0.6815227	86	87	5.973392	Male	2.223144	10
19	1	0	0	0	0.8104	102	109	-19.04661	Male	-4.255366	0
19	2	0.008219	0	0				-19.04661	Male	-4.255366	0
19	3	0.5	0	0	0.7134524	112	108	-19.04661	Male	-4.255366	0
19	4	1	0	0	0.7459283	111	111	-19.04661	Male	-4.255366	0
20	1	0	1	0	0.7551	111	113	-20.57661	Male	2.501542	26.25
20	2	0.008219	1	0	0.7157746	107	102	-20.57661	Male	2.501542	26.25
20	3	0.5	2	0	0.7387521	115	114	-20.57661	Male	2.501542	26.25
20	4	1	2	0				-20.57661	Male	2.501542	26.25
21	1	0	1	0	0.6525	108	104	3.733386	Male	1.394689	96
21	2	0.008219	1	0	0.740433	113	103	3.733386	Male	1.394689	96
21	3	0.5	2	0				3.733386	Male	1.394689	96
21	4	1	3	0				3.733386	Male	1.394689	96
22	1	0	1	0	0.7654406	91	97	0.9833862	Male	7.164304	15
22	2	0.008219	1	0	0.6980269	85	93	0.9833862	Male	7.164304	15
22	3	0.5	2	0	0.7779764	89	97	0.9833862	Male	7.164304	15
22	4	1	3	0	0.795128	94	105	0.9833862	Male	7.164304	15
23	1	0	0	0	0.7698	100	102	-14.13661	Female	2.947742	18.75
23	2	0.008219	0	0				-14.13661	Female	2.947742	18.75
23	3	0.5	0	2	0.7965162	86	91	-14.13661	Female	2.947742	18.75
23	4	1	0	2	0.849232	74	87	-14.13661	Female	2.947742	18.75
24	1	0	0	0	0.5708	43	36	3.453387	Male	3.263107	168
24	2	0.008219	0	0	0.5496838	47	38	3.453387	Male	3.263107	168
24	3	0.5	1	0				3.453387	Male	3.263107	168
24	4	1	2	0				3.453387	Male	3.263107	168
25	1	0	0	0	0.7069	104	112	11.21339	Male	-4.161853	47
25	2	0.008219	0	0				11.21339	Male	-4.161853	47
25	3	0.5	0	0	0.7292052	89	99	11.21339	Male	-4.161853	47
25	4	1	0	0	0.7304066	94	106	11.21339	Male	-4.161853	47
26	1	0	0	0	0.6735	98	87	-25.17661	Male	-5.846038	0.6
26	2	0.008219	0	0				-25.17661	Male	-5.846038	0.6
26	3	0.5	0	0	0.660835	98	85	-25.17661	Male	-5.846038	0.6
26	4	1	0	0	0.6872815	89	81	-25.17661	Male	-5.846038	0.6
27	1	0	1	0	0.8662198	69	85	-5.776608	Male	7.066995	0
27	2	0.008219	1	0	0.8209893	77	90	-5.776608	Male	7.066995	0
27	3	0.5	2	0	0.7785252	81	90	-5.776608	Male	7.066995	0
27	4	1	3	0	0.7830994	74	83	-5.776608	Male	7.066995	0
28	1	0	0	0	0.7319	96	101	9.123393	Female	-7.42483	7.5
28	2	0.008219	0	0	0.6934546	104	103	9.123393	Female	-7.42483	7.5
28	3	0.5	0	0	0.6630435	112	107	9.123393	Female	-7.42483	7.5
28	4	1	0	0	0.7492224	99	107	9.123393	Female	-7.42483	7.5
29	1	0	1	0	0.6888	98	99	6.07339	Male	2.98459	37.5
29	2	0.008219	1	0	0.7190769	93	98	6.07339	Male	2.98459	37.5
29	3	0.5	1	0				6.07339	Male	2.98459	37.5
29	4	1	1	0				6.07339	Male	2.98459	37.5
30	1	0	0	0	0.6838	71	73	17.55339	Female	8.373689	0
30	2	0.008219	0	0				17.55339	Female	8.373689	0
30	3	0.5	0	0	0.4394904	116	76	17.55339	Female	8.373689	0
30	4	1	0	0	0.709893	65	74	17.55339	Female	8.373689	0
31	1	0	1	0	0.7871323	105	116	-2.456609	Male	-2.438193	18.75
31	2	0.008219	1	0	0.7462977	104	109	-2.456609	Male	-2.438193	18.75
31	3	0.5	2	0	0.7096774	107	107	-2.456609	Male	-2.438193	18.75
31	4	1	3	0	0.7426013	102	107	-2.456609	Male	-2.438193	18.75

ID[1]	Visit	Duration (Year)	Cum. BB	Cum. Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
32	1	0	1	0	0.7243	72	77	3.453387	Male	-2.946181	21
32	2	0.008219	1	0	0.7071913	76	86	3.453387	Male	-2.946181	21
32	3	0.5	2	0	0.7174245	71	78	3.453387	Male	-2.946181	21
32	4	1	3	0	0.7219235	74	79	3.453387	Male	-2.946181	21
33	1	0	0	0	0.814741	101	127	16.96339	Female	-5.588159	0
33	2	0.008219	0	0	0.7191316	111	123	16.96339	Female	-5.588159	0
33	3	0.5	0	0	0.7765641	88	115	16.96339	Female	-5.588159	0
33	4	1	0	0	0.7289547	104	122	16.96339	Female	-5.588159	0
34	1	0	0	4	0.5681	64	51	-2.01661	Male	-3.045624	118.25
34	2	0.008219	0	4	0.5177278	66	48	-2.01661	Male	-3.045624	118.25
34	3	0.5	0	7				-2.01661	Male	-3.045624	118.25
34	4	1	0	8				-2.01661	Male	-3.045624	118.25
35	1	0	1	0	0.8067	115	123	-9.15661	Female	2.990413	1
35	2	0.008219	1	0				-9.15661	Female	2.990413	1
35	3	0.5	2	0				-9.15661	Female	2.990413	1
35	4	1	3	0	0.8019518	111	121	-9.15661	Female	2.990413	1
36	1	0	1	1	0.6284	63	55	-2.916611	Male	6.946221	228
36	2	0.008219	1	1	0.5854988	62	50	-2.916611	Male	6.946221	228
36	3	0.5	2	1	0.6864511	64	61	-2.916611	Male	6.946221	228
36	4	1	3	1	0.5882968	50	42	-2.916611	Male	6.946221	228
37	1	0	0	0	0.5966425	98	91	15.75339	Male	1.233878	120
37	2	0.008219	0	0	0.6060321	95	89	15.75339	Male	1.233878	120
37	3	0.5	0	0				15.75339	Male	1.233878	120
37	4	1	0	0				15.75339	Male	1.233878	120
38	1	0	0	0	0.7548	68	69	-6.386609	Female	11.64129	0
38	2	0.008219	0	0	0.7688194	78	81	-6.386609	Female	11.64129	0
38	3	0.5	0	0	0.7443946	72	72	-6.386609	Female	11.64129	0
38	4	1	0	0	0.7451254	70	70	-6.386609	Female	11.64129	0
39	1	0	0	0	0.45	45	30	0.1633865	Male	5.321687	52.5
39	2	0.008219	0	0	0.3927975	49	28	0.1633865	Male	5.321687	52.5
39	3	0.5	0	1	0.4411765	67	43	0.1633865	Male	5.321687	52.5
39	4	1	0	1	0.4282568	69	43	0.1633865	Male	5.321687	52.5
40	1	0	1	1	0.7947	96	100	-15.23661	Female	2.381356	6.5
40	2	0.008219	1	1	0.7459038	101	99	-15.23661	Female	2.381356	6.5
40	3	0.5	1	1	0.7991968	95	100	-15.23661	Female	2.381356	6.5
40	4	1	1	4	0.7793083	93	96	-15.23661	Female	2.381356	6.5
41	1	0	0	0	0.6988	82	80	-9.536611	Male	-4.205482	1.95
41	2	0.008219	0	0				-9.536611	Male	-4.205482	1.95
41	3	0.5	0	0	0.6831152	87	84	-9.536611	Male	-4.205482	1.95
41	4	1	0	0	0.6889797	87	85	-9.536611	Male	-4.205482	1.95
42	1	0	0	0	0.783587	39	38	0.1633865	Male	-7.053834	0
42	2	0.008219	0	0				0.1633865	Male	-7.053834	0
42	3	0.5	0	0				0.1633865	Male	-7.053834	0
42	4	1	0	0				0.1633865	Male	-7.053834	0
43	1	0	1	0	0.7151	102	97	-10.14661	Female	1.71396	0
43	2	0.008219	1	0	0.7705314	100	104	-10.14661	Female	1.71396	0
43	3	0.5	1	0	0.7592782	103	105	-10.14661	Female	1.71396	0
43	4	1	1	0	0.8047957	104	112	-10.14661	Female	1.71396	0
44	1	0	0	0	0.7208	97	106	7.163386	Male	-7.188081	12.6
44	2	0.008219	0	0				7.163386	Male	-7.188081	12.6
44	3	0.5	0	0				7.163386	Male	-7.188081	12.6
44	4	1	1	0				7.163386	Male	-7.188081	12.6
45	1	0	0	0	0.6964	66	63	-14.52661	Male	-6.032601	49.5
45	2	0.008219	0	0	0.7748567	59	63	-14.52661	Male	-6.032601	49.5
45	3	0.5	0	0				-14.52661	Male	-6.032601	49.5
45	4	1	0	0				-14.52661	Male	-6.032601	49.5
46	1	0	0	0				16.09339	Male	1.260947	65.55
46	2	0.008219	0	1	0.5789474	63	46	16.09339	Male	1.260947	65.55
46	3	0.5	0	1	0.6397694	51	53	16.09339	Male	1.260947	65.55
46	4	1	0	1				16.09339	Male	1.260947	65.55
47	1	0	1	0				-14.59661	Male	-3.719701	3
47	2	0.008219	1	0	0.8168686	78	87	-14.59661	Male	-3.719701	3
47	3	0.5	2	0	0.7612422	85	88	-14.59661	Male	-3.719701	3
47	4	1	2	0	0.7587903	87	89	-14.59661	Male	-3.719701	3

ID[1]	Visit	Duration (Year)	Cum. BB	Cum. Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
48	1	0	1	0				2.093387	Male	-2.565263	51
48	2	0.008219	1	0	0.6213115	88	79	2.093387	Male	-2.565263	51
48	3	0.5	2	0	0.6395953	83	79	2.093387	Male	-2.565263	51
48	4	1	3	0	0.6137648	85	78	2.093387	Male	-2.565263	51
49	1	0	0	0				2.973392	Male	-2.175853	82.5
49	2	0.008219	0	0	0.7155664	66	68	2.973392	Male	-2.175853	82.5
49	3	0.5	0	0	0.6665434	67	73	2.973392	Male	-2.175853	82.5
49	4	1	0	0				2.973392	Male	-2.175853	82.5
50	1	0	0	0				3.89339	Male	-5.415317	0
50	2	0.008219	0	0				3.89339	Male	-5.415317	0
50	3	0.5	0	0	0.7574204	82	92	3.89339	Male	-5.415317	0
50	4	1	0	0	0.686618	91	84	3.89339	Male	-5.415317	0
51	1	0	1	0	0.6478	106	89	7.923388	Male	5.007314	25.5
51	2	0.008219	1	0				7.923388	Male	5.007314	25.5
51	3	0.5	2	0				7.923388	Male	5.007314	25.5
51	4	1	3	0				7.923388	Male	5.007314	25.5
52	1	0	1	0	0.7809	83	93	-0.2466095	Male	-4.19789	0
52	2	0.008219	1	0				-0.2466095	Male	-4.19789	0
52	3	0.5	2	0				-0.2466095	Male	-4.19789	0
52	4	1	3	0				-0.2466095	Male	-4.19789	0
53	1	0	1	0	0.7814	96	107	8.25339	Female	2.604783	21
53	2	0.008219	1	0				8.25339	Female	2.604783	21
53	3	0.5	2	0				8.25339	Female	2.604783	21
53	4	1	3	0				8.25339	Female	2.604783	21
54	1	0	0	0	0.9239905	65	77	11.29339	Female	-7.350629	5
54	2	0.008219	0	0				11.29339	Female	-7.350629	5
54	3	0.5	0	0				11.29339	Female	-7.350629	5
54	4	1	0	0				11.29339	Female	-7.350629	5
55	1	0	0	1	0.5882353	54	46	8.623393	Female	-10.3568	123.75
55	2	0.008219	0	1				8.623393	Female	-10.3568	123.75
55	3	0.5	0	1				8.623393	Female	-10.3568	123.75
55	4	1	0	1				8.623393	Female	-10.3568	123.75
56	1	0	1	0	0.6825067	122	127	10.25339	Male	3.821088	0
56	2	0.008219	1	0				10.25339	Male	3.821088	0
56	3	0.5	1	0				10.25339	Male	3.821088	0
56	4	1	1	0				10.25339	Male	3.821088	0
57	1	0	1	0	0.7079	85	84	-5.236611	Male	4.155213	105
57	2	0.008219	1	0				-5.236611	Male	4.155213	105
57	3	0.5	2	0				-5.236611	Male	4.155213	105
57	4	1	3	0				-5.236611	Male	4.155213	105
58	1	0	1	0	0.7415105	75	87	8.653392	Male	-1.123412	1.75
58	2	0.008219	1	0				8.653392	Male	-1.123412	1.75
58	3	0.5	2	0				8.653392	Male	-1.123412	1.75
58	4	1	3	0				8.653392	Male	-1.123412	1.75
59	1	0	0	0	0.7399	113	111	-11.88661	Female	26.8233	7.8
59	2	0.008219	0	0				-11.88661	Female	26.8233	7.8
59	3	0.5	0	0				-11.88661	Female	26.8233	7.8
59	4	1	0	0				-11.88661	Female	26.8233	7.8

[1] Subject ID matched on medical record number, unique to Appendix 7: Tables 1 and 2

[2] Expressed as subject population mean subtracted from individual subject value

Table 2: Long Term Beta-Blocker Exposure and Respiratory Symptoms

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
1	1	0	1	0	-10.82661	Male	-4.483396	82	1	5	3	0
1	2	0.008219	1	0	-10.82661	Male	-4.483396	82	1	5	3	0
1	3	0.5	2	0	-10.82661	Male	-4.483396	82	1	5	2	0
1	4	1	3	0	-10.82661	Male	-4.483396	82	1	5	3	0
2	1	0	0	0	-35.44661	Female	2.96648	37.5	1	5	2	8
2	2	0.008219	0	0	-35.44661	Female	2.96648	37.5	1	1	1	5
2	3	0.5	0	0	-35.44661	Female	2.96648	37.5	0	1	0	1
2	4	1	0	2	-35.44661	Female	2.96648	37.5	1	1	0	1
3	1	0	1	0	-6.756612	Female	-4.516162	0	0	8	0	9
3	2	0.008219	1	0	-6.756612	Female	-4.516162	0	0	5	0	7
3	3	0.5	2	0	-6.756612	Female	-4.516162	0	0	5	0	3
3	4	1	3	0	-6.756612	Female	-4.516162	0	0	0	0	7
4	1	0	1	0	14.40339	Male	-5.295737	0	0	7	3	5
4	2	0.008219	1	0	14.40339	Male	-5.295737	0	0	7	5	5
4	3	0.5	2	0	14.40339	Male	-5.295737	0	0	7	3	5
4	4	1	3	0	14.40339	Male	-5.295737	0	0	4	9	5
5	1	0	0	1	14.27339	Female	-7.942325	0	1	2	1	2
5	2	0.008219	0	1	14.27339	Female	-7.942325	0	1	2	1	2
5	3	0.5	0	1	14.27339	Female	-7.942325	0	1	2	1	2
5	4	1	0	2	14.27339	Female	-7.942325	0	1	2	1	2
6	1	0	1	0	19.33339	Female	-2.822301	10	0	5	3	7
6	2	0.008219	1	0	19.33339	Female	-2.822301	10	0	5	3	7
6	3	0.5	2	0	19.33339	Female	-2.822301	10	0	2	2	3
6	4	1	3	0	19.33339	Female	-2.822301	10	0	2	3	3
7	1	0	1	0	14.89339	Male	-4.58357	0	0	5	0	7
7	2	0.008219	1	0	14.89339	Male	-4.58357	0	0	1	0	3
7	3	0.5	2	0	14.89339	Male	-4.58357	0	0	2	0	3
7	4	1	3	0	14.89339	Male	-4.58357	0	0	3	0	3
8	1	0	1	0	2.693393	Male	-2.303269	22.5	0	1	1	9
8	2	0.008219	1	0	2.693393	Male	-2.303269	22.5	0	8	5	9
8	3	0.5	2	0	2.693393	Male	-2.303269	22.5	0	1	1	5
8	4	1	3	0	2.693393	Male	-2.303269	22.5	0	1	2	0
9	1	0	1	0	-2.69661	Male	12.49064	68	3	1	1	5
9	2	0.008219	1	0	-2.69661	Male	12.49064	68	3	1	1	5
9	3	0.5	2	0	-2.69661	Male	12.49064	68	5	1	4	5
9	4	1	3	0	-2.69661	Male	12.49064	68				
10	1	0	1	0	-6.85661	Male	3.486964	50	7	3	3	2
10	2	0.008219	1	0	-6.85661	Male	3.486964	50	7	3	3	2
10	3	0.5	2	0	-6.85661	Male	3.486964	50				
10	4	1	3	0	-6.85661	Male	3.486964	50				
11	1	0	0	0	11.36339	Female	-2.415143	0	6	2	1	8
11	2	0.008219	0	0	11.36339	Female	-2.415143	0	5	2	1	7
11	3	0.5	0	0	11.36339	Female	-2.415143	0	3	2	1	6
11	4	1	0	1	11.36339	Female	-2.415143	0	2	2	0	5
12	1	0	0	0	-18.93661	Male	-0.5225247	7	1	2	2	1
12	2	0.008219	0	0	-18.93661	Male	-0.5225247	7	1	2	2	1
12	3	0.5	0	0	-18.93661	Male	-0.5225247	7				
12	4	1	0	0	-18.93661	Male	-0.5225247	7				
13	1	0	0	2	3.553394	Female	6.371217	42.5	10	10	1	8
13	2	0.008219	0	4	3.553394	Female	6.371217	42.5	7	10	1	8
13	3	0.5	1	5	3.553394	Female	6.371217	42.5	7	8	1	8
13	4	1	2	5	3.553394	Female	6.371217	42.5				
14	1	0	1	0	8.993388	Female	-5.563586	52.5	0	0	0	2
14	2	0.008219	1	0	8.993388	Female	-5.563586	52.5	0	0	0	1
14	3	0.5	2	0	8.993388	Female	-5.563586	52.5	0	0	1	2
14	4	1	3	0	8.993388	Female	-5.563586	52.5	0	0	1	1
15	1	0	0	0	-6.65661	Female	-4.58958	39.6	3	5	2	1
15	2	0.008219	0	0	-6.65661	Female	-4.58958	39.6				
15	3	0.5	1	0	-6.65661	Female	-4.58958	39.6	3	5	2	1
15	4	1	2	0	-6.65661	Female	-4.58958	39.6	3	5	2	1

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
16	1	0	0	0	10.07339	Female	1.489375	107.5	8	3	1	10
16	2	0.008219	0	0	10.07339	Female	1.489375	107.5	5	2	0	5
16	3	0.5	0	0	10.07339	Female	1.489375	107.5	1	1	0	0
16	4	1	0	0	10.07339	Female	1.489375	107.5	5	3	1	5
17	1	0	1	0	-4.166612	Female	1.502761	7	0	6	1	7
17	2	0.008219	1	0	-4.166612	Female	1.502761	7	0	4	1	8
17	3	0.5	1	0	-4.166612	Female	1.502761	7	0	0	0	2
17	4	1	1	0	-4.166612	Female	1.502761	7	0	0	0	0
18	1	0	1	0	5.973392	Male	2.223144	10	2	2	0	2
18	2	0.008219	1	0	5.973392	Male	2.223144	10	2	2	0	6
18	3	0.5	2	0	5.973392	Male	2.223144	10				
18	4	1	3	1	5.973392	Male	2.223144	10	0	5	5	4
19	1	0	0	0	-19.04661	Male	-4.255366	0	0	3	2	1
19	2	0.008219	0	0	-19.04661	Male	-4.255366	0				
19	3	0.5	0	0	-19.04661	Male	-4.255366	0	1	5	3	2
19	4	1	0	0	-19.04661	Male	-4.255366	0	0	1	7	1
20	1	0	1	0	-20.57661	Male	2.501542	26.25	1	3	3	1
20	2	0.008219	1	0	-20.57661	Male	2.501542	26.25	1	3	3	1
20	3	0.5	2	0	-20.57661	Male	2.501542	26.25	1	3	2	1
20	4	1	2	0	-20.57661	Male	2.501542	26.25				
21	1	0	1	0	3.733386	Male	1.394689	96	2	3	2	0
21	2	0.008219	1	0	3.733386	Male	1.394689	96	2	3	2	0
21	3	0.5	2	0	3.733386	Male	1.394689	96				
21	4	1	3	0	3.733386	Male	1.394689	96				
22	1	0	1	0	0.9833862	Male	7.164304	15	5	1	5	6
22	2	0.008219	1	0	0.9833862	Male	7.164304	15	5	1	5	6
22	3	0.5	2	0	0.9833862	Male	7.164304	15	5	1	3	6
22	4	1	3	0	0.9833862	Male	7.164304	15	8	6	8	6
23	1	0	0	0	-14.13661	Female	2.947742	18.75	3	1	1	5
23	2	0.008219	0	0	-14.13661	Female	2.947742	18.75	0	1	1	4
23	3	0.5	0	2	-14.13661	Female	2.947742	18.75	1	1	1	0
23	4	1	0	2	-14.13661	Female	2.947742	18.75	3	1	1	3
24	1	0	0	0	3.453387	Male	3.263107	168	0	4	0	10
24	2	0.008219	0	0	3.453387	Male	3.263107	168	0	1	0	6
24	3	0.5	1	0	3.453387	Male	3.263107	168				
24	4	1	2	0	3.453387	Male	3.263107	168				
25	1	0	0	0	11.21339	Male	-4.161853	47	0	1	2	0
25	2	0.008219	0	0	11.21339	Male	-4.161853	47				
25	3	0.5	0	0	11.21339	Male	-4.161853	47	0	2	3	0
25	4	1	0	0	11.21339	Male	-4.161853	47	0	1	2	0
26	1	0	0	0	-25.17661	Male	-5.846038	0.6	3	2	1	5
26	2	0.008219	0	0	-25.17661	Male	-5.846038	0.6	3	2	1	2
26	3	0.5	0	0	-25.17661	Male	-5.846038	0.6	3	6	2	2
26	4	1	0	0	-25.17661	Male	-5.846038	0.6	4	4	3	2
27	1	0	1	0	-5.776608	Male	7.066995	0	10	7	3	10
27	2	0.008219	1	0	-5.776608	Male	7.066995	0	1	1	2	7
27	3	0.5	2	0	-5.776608	Male	7.066995	0	1	1	1	5
27	4	1	3	0	-5.776608	Male	7.066995	0	1	1	1	7
28	1	0	0	0	9.123393	Female	-7.42483	7.5	0	1	0	1
28	2	0.008219	0	0	9.123393	Female	-7.42483	7.5	0	1	0	1
28	3	0.5	0	0	9.123393	Female	-7.42483	7.5	0	3	0	1
28	4	1	0	0	9.123393	Female	-7.42483	7.5	0	5	0	1
29	1	0	1	0	6.07339	Male	2.98459	37.5	0	2	2	8
29	2	0.008219	1	0	6.07339	Male	2.98459	37.5	0	2	2	0
29	3	0.5	1	0	6.07339	Male	2.98459	37.5				
29	4	1	1	0	6.07339	Male	2.98459	37.5	0	1	1	0
30	1	0	0	0	17.55339	Female	8.373689	0	2	5	2	6
30	2	0.008219	0	0	17.55339	Female	8.373689	0	1	0	0	4
30	3	0.5	0	0	17.55339	Female	8.373689	0	1	3	0	3
30	4	1	0	0	17.55339	Female	8.373689	0	0	4	0	3
31	1	0	1	0	-2.456609	Male	-2.438193	18.75	0	0	0	0
31	2	0.008219	1	0	-2.456609	Male	-2.438193	18.75	0	0	0	0
31	3	0.5	2	0	-2.456609	Male	-2.438193	18.75	0	1	0	0
31	4	1	3	0	-2.456609	Male	-2.438193	18.75	0	0	0	0

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
32	1	0	1	0	3.453387	Male	-2.946181	21	4	0	2	8
32	2	0.008219	1	0	3.453387	Male	-2.946181	21	0	0	2	2
32	3	0.5	2	0	3.453387	Male	-2.946181	21	0	0	2	2
32	4	1	3	0	3.453387	Male	-2.946181	21	0	0	0	2
33	1	0	0	0	16.96339	Female	-5.588159	0	0	5	0	7
33	2	0.008219	0	0	16.96339	Female	-5.588159	0	0	8	0	8
33	3	0.5	0	0	16.96339	Female	-5.588159	0	0	1	0	3
33	4	1	0	0	16.96339	Female	-5.588159	0	0	1	0	3
34	1	0	0	4	-2.01661	Male	-3.045624	118.25	2	3	2	9
34	2	0.008219	0	4	-2.01661	Male	-3.045624	118.25	0	0	0	7
34	3	0.5	0	7	-2.01661	Male	-3.045624	118.25				
34	4	1	0	8	-2.01661	Male	-3.045624	118.25				
35	1	0	1	0	-9.15661	Female	2.990413	1	0	0	0	9
35	2	0.008219	1	0	-9.15661	Female	2.990413	1				
35	3	0.5	2	0	-9.15661	Female	2.990413	1				
35	4	1	3	0	-9.15661	Female	2.990413	1	0	0	0	2
36	1	0	1	1	-2.916611	Male	6.946221	228	2	5	6	5
36	2	0.008219	1	1	-2.916611	Male	6.946221	228	2	6	6	2
36	3	0.5	2	1	-2.916611	Male	6.946221	228	5	5	7	5
36	4	1	3	1	-2.916611	Male	6.946221	228	7	8	5	9
37	1	0	0	0	15.75339	Male	1.233878	120	4	8	10	4
37	2	0.008219	0	0	15.75339	Male	1.233878	120	2	1	1	1
37	3	0.5	0	0	15.75339	Male	1.233878	120				
37	4	1	0	0	15.75339	Male	1.233878	120				
38	1	0	0	0	-6.386609	Female	11.64129	0	6	6	3	5
38	2	0.008219	0	0	-6.386609	Female	11.64129	0	6	4	0	5
38	3	0.5	0	0	-6.386609	Female	11.64129	0	6	6	3	5
38	4	1	0	0	-6.386609	Female	11.64129	0	4	4	0	5
39	1	0	0	0	0.1633865	Male	5.321687	52.5	1	1	1	10
39	2	0.008219	0	0	0.1633865	Male	5.321687	52.5	1	1	1	5
39	3	0.5	0	1	0.1633865	Male	5.321687	52.5	2	7	5	5
39	4	1	0	1	0.1633865	Male	5.321687	52.5	2	1	2	4
40	1	0	1	1	-15.23661	Female	2.381356	6.5	0	0	0	1
40	2	0.008219	1	1	-15.23661	Female	2.381356	6.5	0	1	1	0
40	3	0.5	1	1	-15.23661	Female	2.381356	6.5	0	2	2	0
40	4	1	1	4	-15.23661	Female	2.381356	6.5	0	5	10	1
41	1	0	0	0	-9.536611	Male	-4.205482	1.95	0	2	0	0
41	2	0.008219	0	0	-9.536611	Male	-4.205482	1.95				
41	3	0.5	0	0	-9.536611	Male	-4.205482	1.95	0	1	0	2
41	4	1	0	0	-9.536611	Male	-4.205482	1.95	1	3	0	2
42	1	0	0	0	0.1633865	Male	-7.053834	0	0	6	1	6
42	2	0.008219	0	0	0.1633865	Male	-7.053834	0	0	6	1	6
42	3	0.5	0	0	0.1633865	Male	-7.053834	0				
42	4	1	0	0	0.1633865	Male	-7.053834	0				
43	1	0	1	0	-10.14661	Female	1.71396	0	0	1	0	4
43	2	0.008219	1	0	-10.14661	Female	1.71396	0	0	1	1	1
43	3	0.5	1	0	-10.14661	Female	1.71396	0	0	1	1	1
43	4	1	1	0	-10.14661	Female	1.71396	0	0	1	0	1
44	1	0	0	0	7.163386	Male	-7.188081	12.6	0	1	1	10
44	2	0.008219	0	0	7.163386	Male	-7.188081	12.6				
44	3	0.5	0	0	7.163386	Male	-7.188081	12.6				
44	4	1	1	0	7.163386	Male	-7.188081	12.6				
45	1	0	0	0	-14.52661	Male	-6.032601	49.5	0	3	1	5
45	2	0.008219	0	0	-14.52661	Male	-6.032601	49.5	0	2	0	5
45	3	0.5	0	0	-14.52661	Male	-6.032601	49.5				
45	4	1	0	0	-14.52661	Male	-6.032601	49.5				
46	1	0	0	0	16.09339	Male	1.260947	65.55	0	5	3	5
46	2	0.008219	0	1	16.09339	Male	1.260947	65.55	0	4	2	3
46	3	0.5	0	1	16.09339	Male	1.260947	65.55	0	0	0	1
46	4	1	0	1	16.09339	Male	1.260947	65.55				
47	1	0	1	0	-14.59661	Male	-3.719701	3	2	1	1	6
47	2	0.008219	1	0	-14.59661	Male	-3.719701	3	2	1	1	6
47	3	0.5	2	0	-14.59661	Male	-3.719701	3	2	1	1	0
47	4	1	2	0	-14.59661	Male	-3.719701	3	2	1	1	0

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
48	1	0	1	0	2.093387	Male	-2.565263	51	0	0	3	0
48	2	0.008219	1	0	2.093387	Male	-2.565263	51	0	0	3	0
48	3	0.5	2	0	2.093387	Male	-2.565263	51	0	0	3	0
48	4	1	3	0	2.093387	Male	-2.565263	51	0	0	3	0
49	1	0	0	0	2.973392	Male	-2.175853	82.5	1	2	5	7
49	2	0.008219	0	0	2.973392	Male	-2.175853	82.5	1	2	3	2
49	3	0.5	0	0	2.973392	Male	-2.175853	82.5	1	2	3	2
49	4	1	0	0	2.973392	Male	-2.175853	82.5				
50	1	0	0	0	3.89339	Male	-5.415317	0	0	1	1	0
50	2	0.008219	0	0	3.89339	Male	-5.415317	0	0	1	1	0
50	3	0.5	0	0	3.89339	Male	-5.415317	0	0	0	1	0
50	4	1	0	0	3.89339	Male	-5.415317	0	0	0	0	0
51	1	0	1	0	7.923388	Male	5.007314	25.5	3	5	1	3
51	2	0.008219	1	0	7.923388	Male	5.007314	25.5				
51	3	0.5	2	0	7.923388	Male	5.007314	25.5				
51	4	1	3	0	7.923388	Male	5.007314	25.5				
52	1	0	1	0	-0.2466095	Male	-4.19789	0	1	1	1	1
52	2	0.008219	1	0	-0.2466095	Male	-4.19789	0				
52	3	0.5	2	0	-0.2466095	Male	-4.19789	0				
52	4	1	3	0	-0.2466095	Male	-4.19789	0				
53	1	0	1	0	8.25339	Female	2.604783	21	0	2	0	5
53	2	0.008219	1	0	8.25339	Female	2.604783	21				
53	3	0.5	2	0	8.25339	Female	2.604783	21				
53	4	1	3	0	8.25339	Female	2.604783	21				
54	1	0	0	0	11.29339	Female	-7.350629	5	0	0	0	3
54	2	0.008219	0	0	11.29339	Female	-7.350629	5				
54	3	0.5	0	0	11.29339	Female	-7.350629	5				
54	4	1	0	0	11.29339	Female	-7.350629	5				
55	1	0	0	1	8.623393	Female	-10.3568	123.75	7	7	7	7
55	2	0.008219	0	1	8.623393	Female	-10.3568	123.75				
55	3	0.5	0	1	8.623393	Female	-10.3568	123.75				
55	4	1	0	1	8.623393	Female	-10.3568	123.75				
56	1	0	1	0	10.25339	Male	3.821088	0	0	0	1	1
56	2	0.008219	1	0	10.25339	Male	3.821088	0				
56	3	0.5	1	0	10.25339	Male	3.821088	0				
56	4	1	1	0	10.25339	Male	3.821088	0				
57	1	0	1	0	-5.236611	Male	4.155213	105	2	0	0	9
57	2	0.008219	1	0	-5.236611	Male	4.155213	105				
57	3	0.5	2	0	-5.236611	Male	4.155213	105				
57	4	1	3	0	-5.236611	Male	4.155213	105				
58	1	0	1	0	8.653392	Male	-1.123412	1.75	0	0	0	5
58	2	0.008219	1	0	8.653392	Male	-1.123412	1.75				
58	3	0.5	2	0	8.653392	Male	-1.123412	1.75				
58	4	1	3	0	8.653392	Male	-1.123412	1.75				
59	1	0	0	0	-11.88661	Female	26.8233	7.8	5	1	0	4
59	2	0.008219	0	0	-11.88661	Female	26.8233	7.8				
59	3	0.5	0	0	-11.88661	Female	26.8233	7.8				
59	4	1	0	0	-11.88661	Female	26.8233	7.8				

[1] Subject ID matched on medical record number, unique to Appendix 7: Tables 1 and 2

[2]Expressed as subject population mean subtracted from individual subject value

Table 3a: Long Term Beta-Blocker Exposure and Cardiac Events

ID	Duration	BB Status	BB Ceased	BB Started	Heart 04	Heart 05	Heart 06	Heart 07	Heart 08
1	1813	0			2	0	0	0	0
2	1731	1			0	0	0	4	0
3	1744	1			0	0	0	0	0
4	1764	1			0	0	1	0	0
5	3	0							
6	1730	0			0	0	0	0	0
7	427	1							
8	1	0							
9	1736	1			0	0	0	0	0
10	211	0							
11	1746	1			0	0	0	0	0
12	1731	1			0	0	0	0	0
13	412	1							
14	1807	1	May-04		1	1	1	0	1
15	1757	0			2	0	0	1	0
16	2	0							
17	1761	1			0	0	2	1	0
18	1762	0		Jul-03	1	1	0	3	0
19	407	1							
20	1716	0		Mar-04	0	0	0	0	0
21	1714	0			0	0	0	0	0
22	1750	1	Aug-03		0	1	4	8	0
23	406	1							
24	1762	1	Apr-04		0	0	0	0	0
25	405	0							
26	1736	1	Mar-04		1	0	0	0	0
27	1750	0			0	0	0	0	0
28	390	1							
29	1743	1			0	0	2	0	0
30	1772	0			4	4	8	0	0
31	1704	0		Jun-03	1	0	0	1	1
32	390	1							
33	406	0							
34	1701	0			0	0	0	0	0
35	1743	1			0	0	1	0	0
36	1697	0			0	0	1	0	0
37	1697	0			0	0	0	0	0
38	387	1	Jan-04						
39	389	0							
40	1	0							
41	1687	1			0	0	0	0	0
42	383	1							
43	1688	0			0	0	0	0	0
44	5	0							
45	1687	1			0	0	0	1	0
46	1685	1			1	2	1	0	0
47	1759	0			0	0	0	0	0
48	8	0							
49	1	1							
50	1763	1			1	1	1	1	1
51	1705	1	Mar-06		1	0	0	2	0
52	3	0							
53	1708	0			2	7	5	5	1
54	1679	0		Sep-04	4	4	4	4	0
55	1746	1	Oct-03		0	2	1	0	1
56	1670	0			0	0	0	4	0
57	1683	0			0	0	0	0	0
58	1667	1			2	4	0	4	0
59	348	0							
60	2	0							
61	1706	1	Oct-03		0	0	0	0	0
62	1667	0	Apr-06	Jun-04	0	0	0	0	0
63	1665	0			0	0	1	0	0
64	1	0							

Table 3b: Long Term Beta-Blocker Exposure - Type 1 Respiratory Exacerbations

ID	Duration	BB Status	BB Ceased	BB Started	CAL 02	CAL 03	CAL 04	CAL 05	CAL 06	CAL 07	CAL 08
1	1813	0			0	1	4	1	0	0	0
2	1731	1			0	2	1	0	0	4	0
3	1744	1			2	2	3	2	2	2	0
4	1764	1			0	2	2	0	2	0	0
5	3	0			7	0					
6	1730	0			1	0	1	0	0	0	0
7	427	1			0	1	0				
8	1	0			2	0					
9	1736	1			0	0	0	0	0	0	0
10	211	0			1	1					
11	1746	1			1	0	0	0	0	0	0
12	1731	1			0	1	0	0	0	0	1
13	412	1			0	0	0				
14	1807	1	May-04		0	0	0	0	1	0	0
15	1757	0			2	1	8	2	2	4	0
16	2	0			0	0					
17	1761	1			0	0	0	0	0	0	0
18	1762	0		Jul-03	4	2	3	0	1	0	0
19	407	1			1	0	1				
20	1716	0		Mar-04	1	0	1	0	0	0	0
21	1714	0			0	0	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	4	0	0
23	406	1			0	0	1				
24	1762	1	Apr-04		1	0	0	0	0	1	0
25	405	0			0	0	0				
26	1736	1	Mar-04		0	0	0	0	0	0	0
27	1750	0			0	0	0	0	0	0	0
28	390	1			0	0	0				
29	1743	1			0	0	2	4	4	4	0
30	1772	0			2	2	0	0	0	0	0
31	1704	0		Jun-03	0	0	1	0	0	1	1
32	390	1			0	1	1				
33	406	0			0	0	0				
34	1701	0			2	0	0	0	0	0	0
35	1743	1			1	0	1	0	0	2	0
36	1697	0			0	0	0	0	0	0	0
37	1697	0			2	0	0	0	0	0	0
38	387	1	Jan-04		1	0	0				
39	389	0			8	0	1				
40	1	0			5	0					
41	1687	1			0	0	0	0	0	0	0
42	383	1			0	0	0				
43	1688	0			1	1	0	0	0	0	0
44	5	0			4	2					
45	1687	1			2	0	2	2	2	2	0
46	1685	1			10	0	11	1	1	0	0
47	1759	0			1	0	1	0	0	1	0
48	8	0			1	0					
49	1	1			0	0					
50	1763	1			1	0	0	0	0	0	0
51	1705	1	Mar-06		0	0	0	0	0	0	0
52	3	0			2	3					
53	1708	0			9	3	2	1	0	0	0
54	1679	0		Sep-04	0	1	7	4	4	4	0
55	1746	1	Oct-03		2	1	4	1	0	2	1
56	1670	0			3	0	0	4	4	4	0
57	1683	0			0	2	1	0	0	0	0
58	1667	1			12	0	1	4	4	4	1
59	348	0			17	1	1				
60	2	0			0	0					
61	1706	1	Oct-03		0	0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	5	1	5	0	1	1	0
63	1665	0			2	0	0	0	0	0	0
64	1	0			0	0					

Table 3c: Long Term Beta-Blocker Exposure - Type 2 Respiratory Exacerbations

ID	Duration	BB Status	BB Ceased	BB Started	CAL 02	CAL 03	CAL 05	CAL 06	CAL 07	CAL 08
1	1813	0			0	1	1	0	0	0
2	1731	1			0	0	0	0	0	0
3	1744	1			2	1	0	0	1	0
4	1764	1			0	0	0	1	0	0
5	3	0			0	0				
6	1730	0			1	0	0	0	0	0
7	427	1			0	0				
8	1	0			2	0				
9	1736	1			0	0	0	0	0	0
10	211	0			0	1				
11	1746	1			1	0	0	0	0	0
12	1731	1			0	0	0	0	0	1
13	412	1			0	0				
14	1807	1	May-04		0	0	0	0	1	0
15	1757	0			2	0	0	0	4	0
16	2	0			0	0				
17	1761	1			0	0	0	0	0	0
18	1762	0		Jul-03	1	2	1	1	1	0
19	407	1			0	0				
20	1716	0		Mar-04	1	0	0	0	0	0
21	1714	0			0	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	0	0
23	406	1			0	0				
24	1762	1	Apr-04		0	0	0	0	1	0
25	405	0			0	0				
26	1736	1	Mar-04		0	0	0	0	0	0
27	1750	0			0	0	0	0	0	0
28	390	1			0	0				
29	1743	1			0	0	4	4	4	0
30	1772	0			0	2	0	0	0	0
31	1704	0		Jun-03	0	0	0	0	3	0
32	390	1			0	0				
33	406	0			0	0				
34	1701	0			0	0	0	0	0	0
35	1743	1			1	0	0	0	0	0
36	1697	0			0	0	0	0	0	0
37	1697	0			0	0	0	0	0	0
38	387	1	Jan-04		0	0				
39	389	0			2	0				
40	1	0			5	0				
41	1687	1			0	0	0	0	0	0
42	383	1			0	0				
43	1688	0			1	1	0	0	0	0
44	5	0			3	2				
45	1687	1			0	0	1	1	1	0
46	1685	1			4	0	0	0	0	0
47	1759	0			1	0	0	0	1	0
48	8	0			0	0				
49	1	1			0	0				
50	1763	1			1	0	0	0	0	0
51	1705	1	Mar-06		0	0	0	0	0	0
52	3	0			2	3				
53	1708	0			3	3	1	0	0	0
54	1679	0		Sep-04	0	1	0	0	1	0
55	1746	1	Oct-03		1	3	1	0	1	1
56	1670	0			3	0	0	0	1	0
57	1683	0			0	0	0	0	0	0
58	1667	1			3	0	0	1	4	0
59	348	0			0	0				
60	2	0			0	0				
61	1706	1	Oct-03		0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	2	1	1	1	1	0
63	1665	0			1	0	0	0	0	0
64	1	0			0	0				

Table 3d: Long Term Beta-Blocker Exposure – Cardiac Admissions

ID	Duration	BB Status	BB Ceased	BB Started	2002	2003	2004	2005	2006	2007	2008
1	1813	0			1	1	2	0	0	0	0
2	1731	1			0	3	0	0	0	2	0
3	1744	1			1	1	0	0	0	0	0
4	1764	1			0	3	0	0	1	0	0
5	3	0			1						
6	1730	0			0	0	0	0	0	0	0
7	427	1			0	5	0				
8	1	0			2	1					
9	1736	1			0	1	0	0	0	0	0
10	211	0			0	0					
11	1746	1			0	1	0	0	0	0	0
12	1731	1			0	1	0	0	0	0	0
13	412	1			0	1	0				
14	1807	1	May-04		0	0	0	0	1	0	1
15	1757	0			4	2	2	0	0	1	0
16	2	0			0	1					
17	1761	1			0	2	0	0	2	1	0
18	1762	0		Jul-03	1	1	1	1	0	1	0
19	407	1			0	2	0				
20	1716	0		Apr-04	0	1	0	0	0	0	0
21	1714	0			0	2	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	1	0	0
23	406	1			2	1	0				
24	1762	1	Apr-04		1	0	0	0	0	0	0
25	405	0			0	0	0				
26	1736	1	Mar-04		0	1	1	0	0	0	0
27	1750	0			0	1	0	0	0	0	0
28	390	1			0	1	0				
29	1743	1			0	1	0	0	2	0	0
30	1772	0			0	0	0	0	1	0	0
31	1704	0		Jun-03	0	1	0	0	0	1	1
32	390	1			0	1	0				
33	406	0			0	0	0				
34	1701	0			0	1	0	0	0	0	0
35	1743	1			0	1	0	0	1	0	0
36	1697	0			0	0	0	0	0	0	0
37	1697	0			1	2	0	0	0	0	0
38	387	1	Jan-04		0	2	1				
39	389	0			0	0	0				
40	1	0			0	1					
41	1687	1			0	1	1	0	0	0	0
42	383	1			0	1	0				
43	1688	0			0	0	0	0	0	0	0
44	5	0			3	2					
45	1687	1			1	2	0	0	0	1	0
46	1685	1			1	1	1	1	0	0	0
47	1759	0			0	1	0	0	0	0	0
48	8	0			0	1					
49	1	1			1						
50	1763	1			0	0	0	1	0	0	0
51	1705	1	Mar-06		1	1	0	0	0	0	0
52	3	0			1	2					
53	1708	0			2	1	0	1	0	0	0
54	1679	0		Sep-04	0	2	0	0	0	0	0
55	1746	1	Oct-03		0	1	0	0	0	0	0
56	1670	0			0	1	0	0	0	1	0
57	1683	0			0	1	0	0	0	0	0
58	1667	1			0	2	0	2	1	0	1
59	348	0			0	2	1				
60	2	0			0	1					
61	1706	1	Oct-03		0	0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	0	0	0	0	0	0	0
63	1665	0			0	3	0	0	1	0	0
64	1	0			0	1					

Table 3e: Long Term Beta-Blocker Exposure – Respiratory Admissions

ID	Duration	BB Status	BB Ceased	BB Started	2002	2003	2004	2005	2006	2007	2008
1	1813	0			0	0	2	1	0	0	0
2	1731	1			0	0	0	0	0	2	0
3	1744	1			0	0	0	0	0	0	0
4	1764	1			0	0	0	0	1	0	0
5	3	0			0	0					
6	1730	0			0	0	0	0	0	0	0
7	427	1			0	0	0				
8	1	0			1	0					
9	1736	1			0	0	0	0	0	0	0
10	211	0			0	1					
11	1746	1			0	0	0	0	0	0	0
12	1731	1			0	0	0	0	0	0	0
13	412	1			0	0	0				
14	1807	1	May-04		0	0	0	0	0	0	0
15	1757	0			1	0	2	0	0	1	0
16	2	0			0	0					
17	1761	1			0	0	0	0	0	0	0
18	1762	0		Jul-03	1	2	2	0	1	0	0
19	407	1			0	0	0				
20	1716	0		Apr-04	0	0	0	0	0	0	0
21	1714	0			0	0	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	0	0	0
23	406	1			0	0	0				
24	1762	1	Apr-04		0	0	0	0	0	0	0
25	405	0			0	0	0				
26	1736	1	Mar-04		0	0	0	0	0	0	0
27	1750	0			0	0	0	0	0	0	0
28	390	1			0	0	0				
29	1743	1			0	0	0	0	1	0	0
30	1772	0			0	0	0	0	0	0	0
31	1704	0		Jun-03	0	0	0	0	0	1	1
32	390	1			0	0	0				
33	406	0			0	0	0				
34	1701	0			0	0	0	0	0	0	0
35	1743	1			0	0	0	0	0	0	0
36	1697	0			0	0	0	0	0	0	0
37	1697	0			0	0	0	0	0	0	0
38	387	1	Jan-04		0	0	0				
39	389	0			0	0	0				
40	1	0			0	0					
41	1687	1			0	0	0	0	0	0	0
42	383	1			0	0	0				
43	1688	0			0	0	0	0	0	0	0
44	5	0			4	2					
45	1687	1			0	0	0	0	0	0	0
46	1685	1			1	0	1	1	0	0	0
47	1759	0			0	0	0	0	0	0	0
48	8	0			0	0					
49	1	1			0	0					
50	1763	1			0	0	0	0	0	0	0
51	1705	1	Mar-06		0	0	0	0	0	0	0
52	3	0			1	2					
53	1708	0			0	0	0	0	0	0	0
54	1679	0		Sep-04	0	1	0	0	0	1	0
55	1746	1	Oct-03		0	0	0	0	0	0	0
56	1670	0			0	0	0	1	0	1	0
57	1683	0			0	0	0	0	0	0	0
58	1667	1			0	0	0	0	1	1	0
59	348	0			0	0	0				
60	2	0			0	0					
61	1706	1	Oct-03		0	0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	0	1	1	0	0	1	0
63	1665	0			0	0	0	0	0	0	0
64	1	0			0	0					

Table 4: Long Term Beta-Blocker Exposure and Survival

ID	DOB	Gender	Pack Years	HospResp	BB	Status	Death
1	28/11/69	Female	37.5	0		Living	
2	20/3/41	Female	0	0	Yes	Living	
3	23/1/20	Male	0	0	Yes	Living	
4	15/4/45	Male	82	0	Yes	Living	
5	18/3/23	Male	161.2	1		Deceased	15/08/2003
6	11/3/20	Female	0	0		Living	
7	18/2/15	Female	10	0	Yes	Deceased	16/11/2005
8	22/2/07	Male	63.75	2		Deceased	02/05/2003
9	26/7/19	Male	0	0	Yes	Living	
10	14/5/18	Male	65.55	0		Deceased	21/06/2006
11	17/7/26	Male	25.5	0	Yes	Living	
12	8/10/31	Male	22.5	0	Yes	Living	
13	1/3/37	Male	68	0	Yes	Lost	
14	29/4/41	Male	50	0	Yes	Living	
15	7/2/23	Female	0	2		Living	
16	29/5/53	Male	7	0		Living	
17	21/9/34	Male	0	0	Yes	Living	
18	1/12/30	Female	42.5	1		Living	
19	9/7/25	Female	52.5	0	Yes	Deceased	04/11/2007
20	6/3/41	Female	39.6	0		Living	
21	12/6/24	Female	107.5	0		Living	
22	8/9/38	Female	7	0	Yes	Living	
23	19/7/28	Male	10	0	Yes	Living	
24	13/2/49	Male	3	0	Yes	Living	
25	26/7/53	Male	0	0		Living	
26	7/2/55	Male	26.25	0	Yes	Living	
27	22/10/54	Male	25	0		Living	
28	16/10/30	Male	96	0	Yes	Deceased	01/09/2005
29	18/7/33	Male	15	0	Yes	Living	
30	29/8/48	Female	18.75	0		Living	
31	28/1/31	Male	168	0		Living	
32	8/4/26	Female	21	0	Yes	Living	
33	26/4/23	Male	47	0		Living	
34	14/9/59	Male	0.6	0		Living	
35	20/4/40	Male	0	0	Yes	Living	
36	12/4/23	Female	5	0		Living	
37	15/6/25	Female	7.5	0		Living	
38	2/7/28	Male	37.5	0	Yes	Lost	
39	9/1/17	Female	0	0		Deceased	17/07/2006
40	13/12/25	Female	123.75	0		Deceased	26/03/2004
41	12/1/37	Male	18.75	0	Yes	Living	
42	15/2/31	Male	21	0	Yes	Lost	
43	12/8/17	Female	0	0		Living	
44	6/8/36	Male	118.25	5		Deceased	05/01/2004
45	27/9/43	Female	1	0	Yes	Living	
46	30/6/37	Male	228	0	Yes	Living	
47	8/9/30	Male	0	0		Living	
48	8/2/17	Male	30	0		Deceased	29/01/2007
49	2/5/24	Male	0	0	Yes	Living	
50	28/10/39	Male	105	0	Yes	Living	
51	14/7/32	Male	51	0	Yes	Living	
52	19/11/18	Male	120	2		Deceased	17/09/2003
53	7/1/41	Female	0	0		Living	
54	21/6/34	Male	52.5	0		Living	
55	13/11/49	Female	6.5	0	Yes	Living	
56	29/8/31	Male	82.5	0		Living	
57	5/3/44	Male	1.95	0		Living	
58	26/12/25	Male	1.75	0	Yes	Living	
59	1/3/49	Male	49.5	0		Deceased	25/07/2004
60	24/6/34	Male	0	0		Deceased	17/10/2003
61	16/10/44	Female	0	0	Yes	Living	
62	23/6/27	Male	12.6	0		Living	
63	14/7/46	Female	7.8	0		Living	
64	14/7/22	Female	0	0		Deceased	10/12/2004

Appendix 8
Response to Examiners

Examiner 1

General comments

The examiner notes that the results show an increase in cardiac events associated with beta-blocker use, and no statistically significant survival advantage, despite the fact that beta-blockers are known to substantially reduce cardiac events and mortality in randomised trials. The implication put forward is that potential confounding variables have been omitted in the analysis and the examiner suggests that severity of cardiac disease might be one of these. The examiner also mentions survival bias as a potential source of confounding.

The examiner has valid concerns about two factors which potentially confound the results, and which are acknowledged in the thesis discussion. In the beta-blocker group, the analysis of adverse cardiac events shows an increased risk of cardiac events and hospital admissions at study baseline, and a reduced annual risk of cardiac events over the study duration, although by the conclusion of the study the final risk of adverse cardiac events is still greater in the beta-blocker group than in the reference group. Except for the baseline risk of hospital admissions, none of these results achieve statistical significance for a difference between the two groups. The survival results are as the examiner has described; beta-blockers are protective, but statistical significance is lost after adjustment for potential confounding covariates. The results reported here do not appear to contradict the general body of medical literature. The study lacked sufficient power to demonstrate a statistically significant reduction in cardiac events or hospital admissions over time, or to demonstrate improved survival, since the studies which have reported such findings have described them in subject populations of far greater magnitude.

Cardiac disease severity is indeed likely to be greater in the beta-blocker group compared to the controls. However, it is difficult to precisely quantify and adjust for this increased cardiovascular disease (CVD) severity, particularly in a subject group with heterogeneous cardiac disease. One potential choice is to adjust for left ventricular function (a measure which is subjective and anyway was not available for most of the subjects). It was considered that prior cardiac-related hospital admission probably gave some measure of disease severity, but had not generally been used for this purpose in the medical literature. The analyses were adjusted for mean FEV1, which is traditionally a marker of severity and prognosis in respiratory disease. However, FEV1 also has a strong correlation with adverse cardiovascular events, in particular fatal events, and is equivalent to conventional cardiovascular risk factors, including serum cholesterol and hypertension, in predicting adverse cardiac events. Moreover, in this analysis, FEV1 was a predictor for both cardiac and respiratory events. While it is acknowledged that FEV1 may not be the ideal marker of cardiac severity in this study, because of its inherent links with respiratory disease, and because of missing FEV1 data for some subjects, its

inclusion as a covariate does afford some adjustment for CVD severity. Similar arguments hold for the inclusion of pack years' smoking and age as covariates.

The examiner is understandably concerned about the potential for survival bias and has recommended a ***sensitivity analysis***. Obviously, the deceased subjects are likely to represent a group of patients with more severe disease than the survivors. This may also apply to subjects who fail to attend follow up. Since FEV1 is strongly related to survival in both respiratory and cardiac disease, we looked for a correlation between FEV1 and leaving the study. None was present and hence this analysis did not suggest the presence of significant survival bias (6.5 Discussion, page 130).

It is difficult to correct for survival bias in a study of this size, because it is not possible to accurately predict the likelihood of exacerbation events in the deceased, had they survived. For the sensitivity analysis, we allocated one extra exacerbation to each of the deceased subjects, as suggested by the examiner. Allocating extra exacerbations to the deceased subjects would be expected to lessen the magnitude and significance of the effect of beta-blockers on exacerbation risk, since only a minority of the deceased subjects (three of 14) received beta-blocker treatment. However, the selected sensitivity analysis did not substantially change the results. For symptoms-based respiratory exacerbations, the effect sizes for beta-blocker exposure were marginally reduced and statistical significance was maintained at the same level. For treated exacerbations, the effect sizes were marginally reduced, and although the annual risk of exacerbations remained significantly increased in the beta-blocker group, the increased risk at study conclusion then fell short of statistical significance. Because the number of exacerbations allotted to the deceased group is an arbitrary decision, the sensitivity analysis is not expected to demonstrate the "true result", but the analysis does demonstrate that survival bias could potentially impact on the results, and hence is included in the results section for Chapter 6 (6.4.3.4 Respiratory Exacerbations – Supplementary Analyses, page 120).

Chapter 1: Literature review

The examiner states that the side effects attributed to beta-blockers (1.2 Beta-blocker Medications, page 18) have not been confirmed as being increased in pooled data from randomised placebo-controlled trials.

To be accepted as a "side effect", an adverse effect may be increased in the population of patients taking the drug, or may be reported in association with a small number of cases and be attributed to the medication in question. The side effects specified in the thesis are those detailed in the product information for most beta-blocker drugs.

A reference is requested for the statement: cardioselective beta-blockers have caused respiratory symptoms and deterioration of lung function in selected cases (1.2.3 Potential Adverse Respiratory Effects, page 28).

The author is able to report this from clinical experience. However, the literature also contains many references. One exemplar has been inserted (reference 49).

The examiner comments that the Norwegian Timolol Trial (reference 56) is the only trial of many which has found an association with a beta-blocker drug and respiratory infections. The examiner goes on to mention that a meta-analysis of cardioselective beta-blockers in patients with reactive airways disease (reference 58) found no effect on respiratory symptoms or respiratory exacerbations.

The examiner's comment refers to a section of the literature review in which the author reviewed the beta-blocker trials in the treatment of cardiac disease and employed this strategy to seek evidence of reported adverse events, or dosage reduction or subject withdrawals due to adverse respiratory events (1.2.4 Evidence for Adverse Respiratory Effects, page 31). There was very little evidence of dose reductions, subject withdrawals or adverse affects, and the Norwegian Timolol Trial (reference 56) is the only one to report adverse events. That was the reason for mentioning it. However, it should be remembered that many of these trials excluded patients with known obstructive airways disease. Discussion about reference 58, including its weaknesses, is deferred until a subsequent paragraph, because the subject group in this case is different; the meta-analysis subjects had reactive airways disease by definition.

The examiner requests the basis of the statement claiming that there has been a hesitance to embrace the conclusions of the two meta-analyses investigating beta-blocker use in patients with chronic obstructive pulmonary disease (COPD) and reactive airways disease (references 57 and 58, respectively).
1.2.4 Evidence for Adverse Respiratory Effects, page 35.

The statement and reasons proffered were intended to reflect opinion and they are presented for the purpose of delineating the author's main criticisms of the two meta-analyses. However, there is some basis in the medical literature for the author's comments. Although the situation has improved, even very recent studies of beta-blocker prescription, after myocardial infarction and in heart failure, describe underprescription in patients with obstructive airways disease (reference 48). Hence, although there is evidence that prescribing practice has changed, it remains suboptimal.

The examiner requests evidence that acute beta-blockade in congestive heart failure causes an immediate worsening of haemodynamics, before the improvement seen with longer term treatment (1.2.4 Evidence for Adverse Respiratory Effects, page 38).

The author agrees that the trials investigating the introduction of beta-blocker treatment for congestive heart failure have shown little evidence of acute haemodynamic worsening in comparison with placebo. Cardiology guidelines for the implementation of beta-blockade in heart failure suggest that this should occur in a stable state; bradycardia, hypotension and pulmonary oedema or significant fluid overload are considered relative contraindications. The guidelines recommend commencement with very small doses, and gradual upward titration to the optimal therapeutic dose over a period of several weeks. It is likely that these strategies temper the effects of bradycardia and reduced myocardial contractility that are associated with beta blockade, so that haemodynamic stability is preserved. The author would point out that previous reports of worsening of symptoms or haemodynamic parameters associated with beta-blocker

treatment in congestive heart failure may reflect characteristics of the older generation drugs or higher initiation doses. In fact, when Eichhorn and Bristow (1) compared the acute haemodynamic effects of beta-blockade in heart failure reported in 3 studies, greater adverse haemodynamic effects were seen with older generation, non-vasodilatory agents, with significant reduction in cardiac index after single dose propranolol or metoprolol, but not following single dose bucindolol or carvedilol.

However, the author's statement about acute haemodynamic worsening is really related to cardiogenic shock, rather than to congestive heart failure (1.2.4 Evidence for Adverse Respiratory Effects, page 38). By definition, in shock haemodynamics are compromised and so this actually represents a different situation. Even today beta-blockers remain contraindicated in this group, except in very exceptional circumstances.

The examiner notes that updated 2007 asthma guidelines from the National Heart Lung and Blood Institute address the issue of beta-blocker treatment in asthma patients with comorbid CVD.

This reference has been added to the section of the literature review which discusses beta-blocker prescribing (reference 116).

Chapter 2: The study protocol

Discussion of statistical analysis has been amalgamated in Chapter 2.

Chapter 3: The study population

Textual references to tables and diagrams have been inserted.

Chapter 4: The prevalence of coexistent airways obstruction in patients with cardiac disease

The examiner enquires about the subjects with a previous diagnosis of asthma, but normal spirometry.

Asthma is an episodic disease and spirometry is expected to be normal if measured during periods of good asthma control. A measure of asthma was required in the subject population, and a choice between self-reported asthma and objectively measured lung function was considered.

The subject group contained 19 self-reported asthmatics. Only three of these demonstrated a positive bronchodilator response (BDR). In fact, BDR was more frequently observed in subjects who had not previously been diagnosed with asthma. It was considered that the self-reported asthmatics probably did not well represent the type of asthmatic typically reported in the medical literature and also that the diagnosis may have been overestimated in this group. For a small number of those reporting asthma,

the history was limited to asthma in childhood, and these were not differentiated from the group as a whole. More concerning was that 15 of 19 also reported being "regular smokers" (Chapter 2, 2.5 Definitions, page 70, and reference 130), eight of the 19 had accumulated more than 20 pack years' smoking history, five of the19 self-reported additional COPD or emphysema and only one was taking standard first line treatment for asthma, according to international asthma guidelines (2), namely inhaled corticosteroids.

Of the options for diagnosis of asthma with lung function testing, bronchial hyperresponsiveness testing would have provided more sensitive and specific diagnostic information, but was not appropriate in the setting of acute cardiac disease. However, by choosing the presence of BDR to represent asthma in the subject population, there was risk that asthma prevalence would be underestimated. This is especially the case considering that bronchodilator medications could not be withheld prior to testing. The BDR testing demonstrates an unarguable asthmatic presence within the subject population, but the results should be interpreted in the context of likely underestimation. For the reasons stated above, and to maintain consistency, BDR was used as the covariate to represent asthma in some of the statistical analyses performed.

The examiner enquires as to whether prevalence of previously diagnosed cardiac disease or obstructive lung disease was similar in the patients who refused consent in comparison with the study participants.

Prevalence data for the presence of previously diagnosed cardiac and obstructive lung disease in the patients who refused consent are not available.

The examiner questions the author's recommendations for screening cardiac patients with spirometry (4.4 Discussion, page 96), fearing confusion about treatment decisions.

The author's suggestions about spirometry screening are not intended to change treatment decisions in cardiac disease. Treatment decisions should be based on the entire clinical context and not solely on the results of spirometry. The purpose of such screening would be to identify early, patients with cardiac disease and comorbid obstructive airways disease, to prospectively gather information about the characteristics of their lung disease and then to document disease progression or course. It is anticipated that such screening would contribute to the knowledge base for beta-blocker prescribing in this group.

The potential utility of screening spirometry and bronchial provocation testing has also been discussed in Chapter 7 (7.4 Screening and Monitoring, page 142). The author concurs that there is currently insufficient scientific evidence to mandate the use of lung function testing as part of the assessment and treatment of cardiac disease. The purpose of this chapter was to explore the potential implications of the high degree of overlap between cardiac and obstructive airways disease and how we might better understand their interactions, particularly in the context of beta-blocker therapy. Hence, the suggestions proffered with regard to lung function testing. For now, given the extent of

coexisting cardiac and obstructive lung disease, the author would suggest that it is best clinical practice to confirm the presence of one or both diseases, and if possible, to quantify the severity. There is a risk that comorbid lung disease will remain undiagnosed if not specifically sought in patients with cardiac disease because of frequent coexistence and symptom overlap. The same holds true for cardiac disease in patients with known obstructive airways disease. The main relevance for this last point is that without diagnosis, patients may miss out on disease-modifying therapeutic intervention.

The examiner comments about lacking evidence for utility of the conventional investigation tools, such as the electrocardiogram (ECG) and chest x-ray for risk stratification (4.4 Discussion, page 96).

The intentions of the author were not to recommend that the conventional investigation tools here-mentioned be used for risk stratification, although the ECG is still used for this purpose in coronary artery disease (CAD), in combination with other factors. The point being made in this section was that the cause for deterioration of respiratory symptoms is often difficult to elucidate in patients with combined cardiac and obstructive airways disease. The author was suggesting that clinical assessment; that is, history, careful physical examination and simple, minimally invasive investigations, might help to clarify the cause.

Chapter 5: Beta-blocker prescription in patients with coexisting cardiac and obstructive airways disease

The examiner enquires about beta-blocker prescription data for subjects with cardiac failure and arrhythmia.

The author presented data for the prevalence of CAD in the subset of the subject population in whom beta-blockers were considered treatment of choice, comparing the group prescribed beta-blockers and those who were not. CAD outcomes were reported because this was by far the most common cardiac diagnosis in the subjects, either as the cause of acute presentation or as a previously confirmed diagnosis. The numbers of subjects with heart failure and arrhythmia were rather a small proportion of the subject population, totalling five and twelve, respectively. In addition, two of the subjects diagnosed with arrhythmia had bradyarrhythmia, and hence beta-blockers were inappropriate. Two of five subjects with heart failure and four of ten subjects with tachyarrhythmia had comorbid CAD, and so had been represented in the CAD comparison.

Beta-blockers were prescribed in one of five patients with heart failure, meaning that the proportion with heart failure was 3.4% in the group treated with beta-blockers and 21.1% in the group who were not. For subjects with tachyarrhythmia, beta-blockers were prescribed in 4 of 10 patients; the proportion with tachyarrhythmia being 13.8% in the group receiving beta-blockers and 31.6% in the group who were not. These data show that those given beta-blockers had a lower prevalence of heart failure and tachyarrhythmia.

Chapter 5, Chapter 6: The longer term effects of beta-blocker medications on lung function, respiratory exacerbations and survival in patients with cardiac disease

The examiner suggests that the Cochrane meta-analyses of beta-blocker trials in patients with obstructive airways disease (reference 57 and 58) may have already addressed the question of whether beta-blockers cause airflow obstruction and respiratory exacerbations.

The author believes that the meta-analyses only partly address the question of airflow obstruction and beta-blocker use. The data contained in the meta-analyses are likely sufficient to address this question in the setting of single dose effect, but are insufficient to answer the question of the long term effects, which is relevant to the substantial number of subjects in this current study who entered the study already using beta-blockers over the longer term. In the meta-analysis focussing on reactive airways disease (reference 58), the range of durations of longer term trials was 3 – 28 days, the total number of included subjects was 121 and half of the included trials reported no lung function data. In the meta-analysis for COPD (reference 57), the duration range was 2 – 84 days (mean 1.1 month), included subjects totalled 126 and again half of the included trials reported no lung function data. From preliminary research in a murine asthma model, it has been suggested that beta-blocker effects on the airways may differ between the settings of acute and chronic dosing, and one proposed mechanism is beta-receptor upregulation. Obviously, to capture a difference between single dose and longer term effect on lung function, lung function parameters must be measured and sufficient study duration must be allocated.

For the reasons mentioned above, the author feels that the Cochrane meta-analyses also do not adequately address the issue of beta-blocker effects on respiratory exacerbations. Since exacerbations are infrequent events occurring over time, even the maximal trial duration of 84 days in the meta-analysis for COPD (reference 57) is not adequate to answer this question. The only caveat to this might be if the subject population has frequent exacerbations associated with advanced disease. In the meta-analysis for COPD, exacerbations were not quantified, although all included trials claimed to report them. The prevalence of symptoms was surprisingly low for a COPD population, with only one patient in each of the treatment and placebo groups reporting any symptoms. This, together with the use of clinical COPD diagnosis in more than half of the trials does raise the question of whether the included subjects truly had COPD, and whether the spectrum of COPD severity was adequately represented by the subject population.

The examiner requests that hazard ratios be reported for the survival analyses.

Inadvertent omission of the first paragraph of the section 6.4.3.5 Death (page 121) was the reason for the missing hazards ratios. The omitted paragraph also explains that cause of death was unknown for most of the deceased subjects. The paragraph has been reinstated within the thesis text.

The significant benefit of beta-blockers on survival seen in the univariable analysis was not present in the adjusted analysis. Of necessity, the comparative survival profiles are presented unadjusted, although they suggest that beta-blockers do not have an adverse

effect on survival, even in those with more severe lung disease, that is, FEV1 50%, previous respiratory-related hospital admission and a 50 pack years' smoking history. However, the author had decided against reporting hazard ratios for the comparative survival profiles in order to prevent the reader from placing undue weight on the results. Although all of the comparisons are statistically significant, it must be remembered that such profiles require data extrapolation and remain unadjusted for the covariates which converted the overall survival analysis from significant to non-significant.

The examiner requests further explanation of the sequential measures of BDR proportion in the subject population (6.4.1 Spirometry, page 111).

For these results, which are represented graphically, potential for statistical analysis and interpretation was severely limited, due to small numbers and missing spirometry data. Overall, ten subjects demonstrated BDR during the twelve months of serial spirometry measurements. Five subjects were taking beta-blockers, two of whom had been beta-blocker naïve. Initially, of seven subjects demonstrating BDR, three were taking beta-blockers. At the discharge assessment, of five subjects with BDR, three were taking beta-blockers. The trend was for the proportion with BDR to reduce in both groups over the remainder of the study. The author presented these results to stimulate interest in further research. Firm conclusions cannot be drawn. The results may be in keeping with a differential beta-blocker effect between acute and chronic dosing, but ideally research into this requires much larger subject numbers, a subject population which is beta-blocker naive and comparison of sequential spirometry and BDR for individuals, rather than sequential comparison of the population proportions manifesting BDR.

The examiner requests additional information about the longitudinal analysis of adverse cardiac and respiratory events (6.4.3.2 Respiratory Exacerbations, page 116 and 6.4.3.3 Acute Cardiac Events, page 117).

The statistical software used to analyse these data has not provided unadjusted event rates for the Poisson regressions of adverse respiratory and cardiac events. As the examiner points out, determining the event rates from raw data is possible but cumbersome, and it is made more challenging by the incorporation into the analyses of the changes to beta-blocker status of some subjects during the course of the study. However, it is unlikely that the unadjusted event rates will add insight into the true effect. The more important question is whether the statistical strategies utilised, including the adjustments, have been sufficient to account for any bias present – a question which has been debated in an earlier section of this response.

The examiner also enquired as to the proportion of subjects who experienced at least one adverse event. The data are as follows: for acute cardiac events 37.5%, for cardiac hospital admissions 90.6%, for symptoms-based respiratory exacerbations 73.4%, for treated respiratory exacerbations 54.7% and for respiratory-related hospital admissions 23.4%. To compare these figures, it is necessary to know that the duration of data collection for adverse cardiac events was approximately half that of the other events for which results have been reported.

Chapter 7: Clinical applications and implications

Discriminating the source of deterioration of respiratory symptoms in cardiac patients (7.3 Screening and Monitoring, page 145)

The point here is not to say that spirometry is a better discriminatory tool than the other investigations mentioned in this section. As the examiner points out, none of the tests are particularly good discriminators, and given this situation the astute clinician should gather information from multiple sources before making a decision. In the author's experience, spirometry is rarely utilised in this situation, except only very occasionally in the patient who has known comorbid respiratory disease. Hence, for the patient with undiagnosed airflow limitation, this differential diagnosis may not be considered, and for those with known respiratory disease the extent of deterioration is usually not quantified.

Chapter 8: Directions for future research

The evidence for a beneficial effect of beta-blockers is discussed, despite the finding of increased respiratory exacerbations

The research presented in Chapter 6 shows increased respiratory exacerbations, but no adverse effect on lung function, symptoms or survival with use of beta-blockade. Hence, the results do not imply an overall adverse effect of beta-blockers in the subject population. However, carefully planned, adequate duration, prospective studies are needed to confirm the potential for beta-blockers to cause increased respiratory exacerbations.

As an observational study, this current one has inherent limitations, some of which have been raised by the examiner. Although the statistical strategies utilised in the analyses of the data have attempted to minimise the effects of bias, some may still be present. Hence, the exacerbation results do not preclude the potential for finding of beneficial beta-blocker effects in future prospective studies of patients with obstructive airways disease.

Examiner 2

Minor emendations

The presence of beta-3 adrenoreceptors in the myocardium; the thesis has been amended to describe the distribution of beta-3 receptors in adipose tissue, gastrointestinal tract and myocardium and a reference has been inserted (1.1 The Beta-adrenergic Receptor, page 16, reference 6).

The reasoning behind enhanced selectivity of extended-release beta-blocker preparations (1.2 Beta-blocker Medications, page 19) is clarified within the main body of the thesis and a reference pertaining to this has been inserted (reference 15). The explanation relates to the pharmacokinetics of extended release formulations; peak serum levels are much lower in comparison with short-acting agents at equivalent dose. Beta receptor selectivity is reduced at high doses due to variations in receptor density between tissue types and the tissue distribution of the various receptor subtypes.

Table 1.1 "Characteristics of beta-blocker agents in common use" (page 20) has been altered to aid interpretation. The blank spaces have been labelled "No" to indicate that the characteristic is absent.

The meta-analysis of beta-blockers in congestive cardiac failure (reference 20) reports a combined odds ratio for total mortality of 0.65 (95% confidence interval 0.53 – 0.80), using a Bayesian random effects model. The confidence intervals have been included in the text (1.2.1.1 Heart Failure, page 22).

The definition of COPD provided by the author (2.5 Definitions, page 70) is that accepted internationally and the reference has been provided (reference 3). The examiner's requirement that FEV1 be less than 80% would define COPD of at least moderate severity and excludes those with mild COPD.

The examiner requests an explanation of reciprocal conversion (3.2.1 Demographics, page 74). This technique was used to transform the BMI data to achieve a normal distribution, so that parametric statistical tests could be applied. To apply statistical tests to non-parametric data, either the data must be transformed using a mathematical application, such as the reciprocal function used here to transform severely right-skewed data, or non-parametric tests must be used. There is some debate as to the best approach, but the non-parametric tests are less powerful detectors of statistically significant differences. Hence, given the small dataset, conversion was used when possible, and non-parametric tests when it was not, as described in Chapter 2, 2.6 Statistical Analysis. The population BMI data were transformed in preparation for statistical comparison in subsequent chapters. However, within Chapter 3 they could have been more simply summarised as median and range.

Discrepancies between text and tabulated results for beta-blocker use have been reconciled (3.2.4 Use of Beta-receptor Active Medication, page 79), and a typing error has been corrected in Table 3.2.1 Study Population Characteristics (page 76).

The subject numbers for the groups FEV<70% and FEV>70% have been clarified in Table 4.3.1 Study Population Characteristics According to FEV1/FVC Ratio (page 88) and Table 4.3.2 Symptoms According to FEV1/FVC Ratio (page 90)

The text accompanying Figure 6.4.1 Population Results - Subjects with Airways Obstruction and BDR (page 110) has been amended to include the subject numbers included in the analysis. Because the author is aware that the substantial amounts of missing spirometry data, due to subject attrition and technically inadequate spirometry

measurements, do limit the interpretation of these results, a caveat to this effect has also been added.

References

1. Eichhorn E, Bristow M. Practical guidelines for initiation of beta-adrenergic blockade in patients with chronic heart failure. American Journal of Cardiology 1997;79:794-8.

2. Global strategy for asthma management and prevention. In: Global initiative for asthma; 2007.