Original Article

HEALTH RELATED QUALITY OF LIFE ASSESSMENT USING ST. GEORGE'S RESPIRATORY QUESTIONNAIRE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS ON COMBINED INHALED CORTICOSTEROIDS AND BRONCHODILATORS

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ABSTRACT

Objective: Chronic diseases like COPD have significant effects on patient's health-related quality of life (HRQoL). HRQoL measures additional indices as compared to objective measurements like spirometry. Our aim is to assess and compare the disease-specific quality of life in Chronic Obstructive Pulmonary Disease patients using St. George's Respiratory Questionnaire (SGRQ-C) receiving Salmeterol/Fluticasone (SF), Formoterol/Budesonide (FB), Formoterol/Fluticasone (FF).

Methods: A prospective, open-label, randomized, parallel group study conducted at a tertiary care teaching hospital in South India. A 6-months follow-up of 90 patients with severe and very severe COPD randomized to receive Salmeterol/Fluticasone, Formoterol/Budesonide, and Formoterol/Fluticasone in appropriate doses according to their global initiative for chronic obstructive lung disease (GOLD) severity. After spirometry, St. George's Respiratory Questionnaire (SGRQ-C) was administered at baseline and after 180 d to assess improvement in lung function and HRQoL. Statistical analysis used: Data analyzed using SPSS version: 13.0. General linear repeated measures using the post-hoc Bonferroni method assessed significance between treatment groups.

Results: Significant decrease ($P<0.05$) in each SGRQ-C domains and total scores as well as improvement in FEV1 ($P<0.05$) was observed in all study subjects. The mean SGRQ-C total score for the group I subjects (SF) at the initial visit was 86.69 and the scores reduced to 58.78 at final visit (i.e. after using SF for 6 mo). This reduction was highly significant statistically (t=10.989, p=0.000) at 95% CI. The mean SGRQ-C total scores for group II subjects (FB) at initial visit were 85.85 and the scores reduced to 67.98 at the final visit. This reduction was highly significant statistically (t=9.669, p=0.000) at 95% CI. The mean SGRQ-C total scores for group III subjects (FF) at initial visit were 83.96 and the scores reduced to 70.37 at final visit (after 6 mo). This reduction was highly significant statistically (t=12.285, p=0.000) at 95% CI.

Conclusion: Maximum improvement in HRQoL ($P<0.05$) was noted in patients receiving Salmeterol/Fluticasone with respect to SGRQ-C (activity, impact and total) scores and FEV$_1$. This improvement with SF was due to its greater effect in patients with severe and very severe chronic obstructive pulmonary disease. There was a significant improvement in QoL with SF as compared to FB and FF in severe and very severe COPD patients. Subsequently, the three combined inhaled corticosteroids and bronchodilators showed similar improvements in lung functions and Health related quality of life throughout the study.

Keywords: Chronic obstructive pulmonary disease, Bronchodilators, Health-related quality of life, Inhaled corticosteroids, St. George's respiratory questionnaire.

INTRODUCTION

Health-related quality of life (HRQoL) assessment in COPD is a more responsive outcome measure than spirometry. HRQoL measurement facilitates the evaluation of the efficacy of medical interventions and also detection of groups at risk for psychological or behavioral problems [1]. QoL unique to each individual is influenced by the perception of disease. COPD is one among the common chronic diseases, which has significant effects on patient's health and QoL. The prevalence of COPD has been increasing since the early 1980s for all age, sex, and racial groups [2]. Despite better understanding of the disease process and improved treatment modalities, the increasing incidence and prevalence of COPD in many parts of the world continue to make it a global health concern [3].

The basic pathology behind COPD is characterized by poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs. Hence, the main goal of treatment is to improve the airflow and reduce the inflammation. Current clinical (GOLD) guidelines recommend the use of combined inhaled corticosteroids and bronchodilators as the mainstay of therapy in COPD [4, 5].

The goals in using combined inhaled corticosteroids and bronchodilators in COPD treatment can be viewed in two ways. First to gain control over the underlying disease process and secondly to maintain this control for as long as possible with least amount of side effects [6].

Relatively little is known about the impact of COPD on health-related quality of life, even with the existing epidemiological and economic literature on COPD. Health-related quality of life is increasingly being used in the evaluation of medical interventions on chronic diseases. The clinical measures provide valuable information only about the affected organ system but not the functional impairment (physical, emotional and social) which is also important to the patients in their everyday lives. Thus it is important that treatment goals should not only be directed towards improving physiologic end points but also patient's physical and mental health (i.e. quality of life) with the overall goal of reducing the debilitating impact of COPD on patient's lives [7, 8].

Salmeterol/Fluticasone (SF), Formoterol/Budesonide (FB), Formoterol/Fluticasone (FF) are the three different combinations of inhaled corticosteroids and bronchodilators used commonly in severe and very severe COPD patients.

Disease-specific health status measures are distinguished by its higher responsiveness than the generic measures and are widely used in clinical trials. St. George's Respiratory Questionnaire (SGRQ)

was designed to measure HRQoL both in asthma and COPD patients, but no studies measuring the improvement in HRQoL in COPD patients using the SGRQ-C comparing three different combined inhaled corticosteroids and bronchodilators is reported [9].

This study was conducted to assess and compare quality of life in patients with COPD receiving Salmeterol/Fluticasone (SF), Formoterol/Budesonide (FB), and Formoterol/Fluticasone (FF) at six months duration so as to assist in making an informed decision when choosing one of the three different combined inhaled corticosteroids and bronchodilators.

MATERIALS AND METHODS

Study design

The study was conducted at Princess Esra Hospital, a tertiary care teaching hospital in Hyderabad, South India, during the period September 2013 to February 2014. The patients enrolled into the study were COPD patients taken from the Departments of Pulmonology and Medicine. It was a prospective open-labeled randomized study of 6 mo duration in which 90 severe ($30 \leq FEV1 < 50\%$ predicted) and very severe ($FEV1 < 30\%$ predicted) COPD patients (OP/IP) who are prescribed with any one of the following combinations (SF/FB/FF) were selected. In our study, we have divided 90 COPD patients into 3 groups (Group I, Group II & Group III) each group consisting of 30 patients. Group I was prescribed with medication SF (Salmeterol/Fluticasone), Group II with medication FB (Formoterol/Budesonide) and Group III with medication FF (Formoterol/Fluticasone). We used two different parameters such as St. George's Respiratory Questionnaire (SGRQ-C) and Spirometry test (mean FEV1 initial & final visit) to assess and compare the health-related quality of life (HRQoL) in COPD patients.

The three therapeutic alternatives considered were:

✓ Salmeterol/Fluticasone (SF): use of combined salmeterol/fluticasone 25/250 µg bid in GOLD stages III and IV patients in addition to the standard therapy already in use.

✓ Formoterol/Budesonide (FB): use of combined formoterol/budesonide 6/200 µg bid in GOLD stages III and IV patients.

✓ Formoterol/Fluticasone (FF): use of combined formoterol/fluticasone 6/250 µg bid in GOLD stages III and IV patients.

Patients who were able to perform study-related tests after signing the consent form were included in the study. Those who were already using inhaled or oral steroids, having an acute exacerbation of COPD or with any other co-morbidities (Tuberculosis, Asthma, Cardiac complications), pregnant or lactating woman, pediatric patients and those less than 85% adherent to medication were excluded from the study. Medication adherence checking was done by the accepted methods like a patient interview, medication checking, and prescription refill and health outcome measures. Patients satisfying inclusion criteria after giving informed consent were randomized by simple randomization method. Institutional review board ethics approval for the study protocol was obtained from Deccan College of Medical Sciences, Princess Esra Hospital, Hyderabad.

Health-related quality of life (HRQoL) questionnaire

Enrolled patients received either Salmeterol/Fluticasone (SF), Formoterol/Budesonide (FB), Formoterol/Fluticasone (FF). A validated version of St. George's Respiratory Questionnaire (SGRQ-C) was administered. SGRQ-C is a disease specific questionnaire used to measure health-related quality of life in respiratory diseases like asthma and COPD. It contains 40 items, categorized in 3 domains like symptoms, impacts, and activity. The total score of all these domains gives the overall quality of life estimate of each patient. The threshold for a clinically significant difference between groups of patients and for changes within groups of patients is four units. Decrease in the total score reflects improved QoL [10,11].

Spirometry was performed before and after bronchodilation to assess the baseline status and to confirm the diagnosis of COPD. Patients were educated on the use of inhaled medicines. Clinical evaluation, SGRQ and spirometry was done during initial (day 1) and follow-up visits (after 180 d).

Table 1: Patient demographic characteristics at baseline

Demography	SF	FB	FF	Total (%), (±SD)
No. of patients enrolled	30	30	30	90
Study completers	30	30	30	90
Gender				
Male	22	21	19	62
Female	8	9	11	28
Duration in y*(mean±SD)	3.76±2.77	3.12±2.06	2.95±1.89	3.27±2.24
Age**(mean±SD)	60.5±9.41	62.5±9.69	63.1±10.6	62.0±9.90
Educational status*				
Illiterate	12	8	10	30
≤5th Std	10	15	12	37
6th to 10th	5	6	6	17
Intermediate	3	1	2	6
Family history*				
Positive	8	9	6	23
Negative	26	18	23	67
Smoking history*				
Current Smoker	10	10	15	35
Non Smoker	8	9	11	28
Past Smoker	7	11	9	27
Lung function**				
FEV_1	33.47±7.12	33.73±7.37	33.20±7.72	33.46±7.40
Quality of life SGRQ-C domains (mean±SD)**				
Symptom	81.32±7.74	81.95±6.21	81.63±5.61	81.63±6.52
Activity	85.04±10.4	84.71±10.1	81.26±9.43	83.67±9.99
Impact	89.53±6.67	87.87±6.81	86.37±7.70	87.91±7.06
Total	86.69±5.39	85.85±5.01	83.96±5.51	85.50±5.30

SF: Salmeterol/Fluticasone, FB: Formoterol/Budesonide, FF: Formoterol/Fluticasone, FEV_1: Forced expiratory volume in 1s, SD: Standard deviation, SGRQ-C: St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease patients, *p value>0.05 not significant by ('t' test), **p value>0.05 not significant by analysis of variance

Statistical analysis

Data were analyzed by using Statistical Program for Social Science (SPSS) version: 13.0. ANOVA was used to test significance within the groups at different time intervals. For testing significance between groups, students't' test was used.

Descriptive statistics for improvement in QoL scores and lung functions are presented as mean and 95% confidence interval (CI). To assess the similarities between the groups at baseline, ANOVA (Analysis of Variance) was used. General linear repeated measures using post-hoc Bonferroni method assessed significance between treatment groups during the study. The significant improvements in treatment groups were assessed by one-way ANOVA using post hoc-Bonferroni that compared means of SGRQ-C scores and lung functions during individual follow-ups.

RESULTS

Study population

A total of 90 patients randomized for an equal distribution of 30 patients in each group i.e. Group-I (Salmeterol/Fluticasone), Group-II (Formoterol/Budesonide) and Group-III (Formoterol/ Fluticasone). The mean age of Group-I, II, III patients who participated in the study was 60.5 y (±9.41), 62.5 y (±9.69) and 63.13 y (±10.61). Out of 90 patients enrolled to the study, 69% were males and 31% were females and most of them were illiterate (33.33%) and current smokers (33.33%). Demographic data, spirometry and QoL scores of the three groups were well matched at baseline ($P > 0.05$) as shown in table 1.

Spirometry (FEV$_1$)

At baseline there is no significant difference in FEV$_1$ ($P > 0.05$), but at the final visit there is significant improvement in FEV$_1$ ($P<0.05$) for patients who were taking Salmeterol/Fluticasone (SF), Formoterol/Budesonide (FB), but not for patients who were taking Formoterol/Fluticasone (FF). The average FEV$_1$ for group I, group II and group III subjects at the initial visit was 33.47%, 33.73% & 33.20% and was increased to 36.60%, 35.8% and 33.4 as shown in table 2 and fig. 1. A 3% increment in FEV$_1$ was reported for the group I subjects (SF) and was highly significant statistically (t=-8.833, p=0.000) at 95% CI. For group II subjects (FB), a 2% increment in FEV$_1$ was reported and was highly significant statistically (t=-9.001, p=0.000) at 95% CI. For group III subjects 0.2% increment in FEV$_1$ was reported which was not significant statistically.
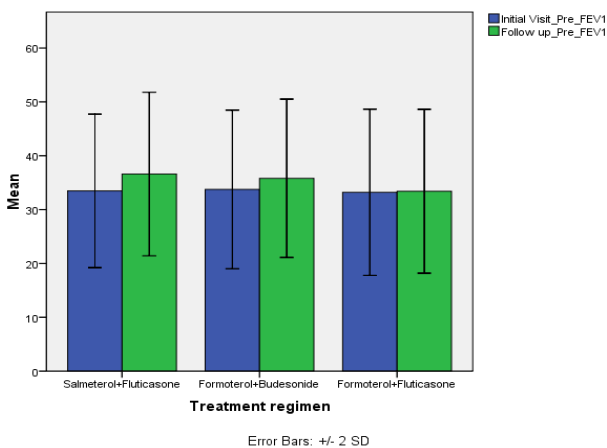

Fig. 1: Mean FEV$_1$ (Initial & final visit) with different treatment groups

Quality of Life Improvement (SGRQ-C)

A rapid improvement in all the domains of QoL was noted in study subjects. All the domains of SGRQ-C were well matched at

baseline between the three groups. Inter-group comparisons revealed a more significant (*P<0.05*) response to SF compared to FB and FF in all the domains of SGRQ-C after 6 mo. The mean SGRQ-C symptom score for Group-I, Group-II and Group-III subjects at the initial visit was 81.32, 81.95 and 81.63 and the scores reduced to 54.76, 61.96 and 56.54 (fig. 2) at final visit i.e. after 180 d. The mean SGRQ-C activity score for Group-I, Group-II and Group-III subjects at the initial visit was 85.04, 84.71 and 81.26 and the scores reduced to 60.29, 68.41 and 74.21 (fig. 3). The mean SGRQ-C impact score for Group-I, Group-II and Group-III subjects at the initial visit was 89.53, 87.87 and 86.37 and the scores reduced to 59.26, 69.80 and 72.88 (fig. 4) at final visit i.e. after 180 d. The mean SGRQ-C total score for group I subjects (SF) at the initial visit was 86.69 and the scores reduced to 58.78 at final visit (i.e. after using SF for 6 mo). This reduction was highly significant statistically (t=10.989, p=0.000) at 95% CI. The mean SGRQ-C total scores for group II subjects (FB) at initial visit were 85.85 and the scores reduced to 67.98 at the final visit. This reduction was also highly significant statistically (t=9.669, p=0.000) at 95% CI. The mean SGRQ-C total scores for group III subjects (FF) at initial visit were 83.96 and the scores reduced to 70.37 at final visit (after 6 mo). This reduction was highly significant statistically (t=12.285, p=0.000) at 95% CI as shown in table 2 and fig. 5.
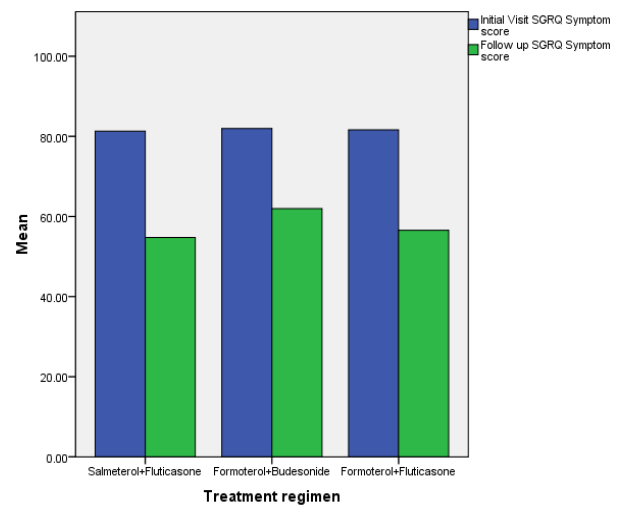

Fig. 2: Mean SGRQ-C symptom score (Initial & final visit) with different treatment groups
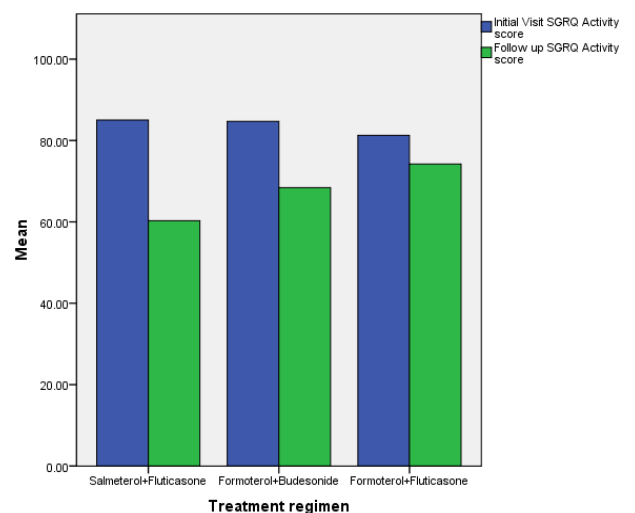

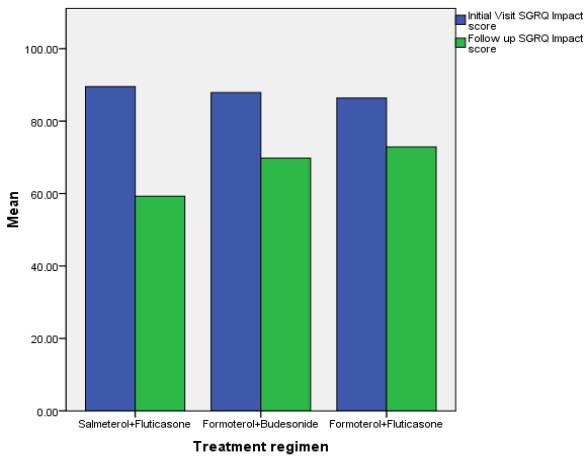**Fig. 3: Mean SGRQ-C activity score (Initial & final visit) with different treatment groups**

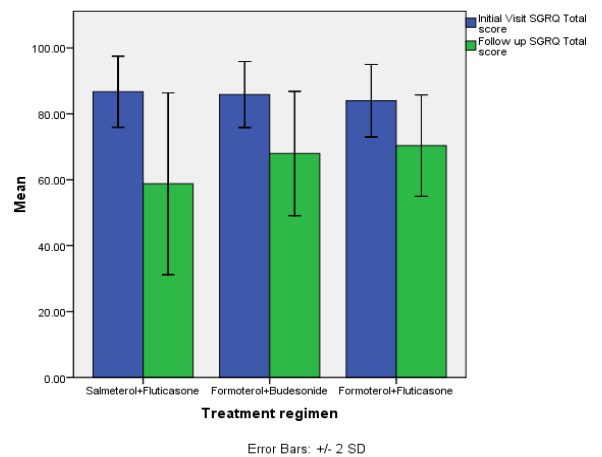**Fig. 4: Mean SGRQ-C impact score (Initial & final visit) with different treatment groups**

Fig. 5: Mean SGRQ-C total score (Initial & final visit) with different treatment groups

Table 2: Mean FEV$_1$, SGRQ-C total score (initial & final visit) with different treatment groups

Strategy	FEV$_1$		SGRQ-C total score	
	Initial visit	Final visit	Initial visit	Final visit
SF	33.47	36.60	86.69	58.78
FB	33.73	35.80	85.85	67.98
FF	33.20	33.40	83.96	70.37

FEV$_1$: Forced expiratory volume in 1s, SGRQ-C: St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease patients, SF: Salmeterol/Fluticasone, FB: Formoterol/Budesonide, FF: Formoterol/Fluticasone

DISCUSSION

Combined Inhaled corticosteroids and bronchodilators have been the mainstay of therapy in patients with COPD. Hence new formulations and dosage forms are being continuously developed. Clinical studies have shown that treatment with inhaled steroids plus bronchodilators improves not only the symptoms of COPD but also the quality of life. The present study was designed as an open-label, randomized trial to compare the quality of life for patients using Salmeterol/Fluticasone, Formoterol/Budesonide, Formoterol/ Fluticasone.

The study results, representing responses to a disease-specific quality of life instrument SGRQ, demonstrate that COPD treatment with Salmeterol/Fluticasone has an additional benefit in health-related quality of life over that of Formoterol/Budesonide, Formoterol/Fluticasone. At baseline, the demographics, SGRQ-C scores, and FEV1 values showed no significant difference between the three treatment groups. The initial greater SGRQ-C scores indicated the decreased quality of life in all the patients. The improvement in QoL was evaluated within the group as well as between the groups. There was a significant decrease in SGRQ scores (P<0.05) during the follow-ups in all the treatment groups showing improvement in the quality of life. Although the improvement was seen in all the treatment groups at 180 d of treatment, it was observed that the improvement seen with Salmeterol/Fluticasone group was significantly (P<0.05) greater than that of Formoterol/Budesonide, Formoterol/Fluticasone treatment group. This may be due to the reason that severe to very severe COPD patients (GOLD III & GOLD IV) have responded better to Salmeterol/Fluticasone when compared to Formoterol/ Budesonide, Formoterol/Fluticasone in the 6 mo course of treatment.

There is some evidence that Salmeterol/Fluticasone may be superior to other combined inhaled corticosteroids and bronchodilators in patients with severe and very severe COPD. A recent meta-analysis of clinical trials with Salmeterol/Fluticasone, Formoterol/Budesonide, and Formoterol/Fluticasone suggests that Salmeterol/Fluticasone may provide equal or greater COPD control

in patients with severe to very severe COPD. In the present study, the patients included varied from severe to very severe COPD (GOLD III to GOLD IV) which was more representative of the spectrum of COPD severity seen in routine clinical practice[12,13]. The improvements seen in QoL were clinically and statistically favorable to Salmeterol/Fluticasone after 180 d of follow-up as compared to Formoterol/Budesonide and Formoterol/Fluticasone, whereas transient difference was noted in the lung functions. On the continuation of treatment for six months, there was a maximum improvement in the quality of life of patients between the treatment groups. This may suggest that there is an advantage of Salmeterol/Fluticasone compared to Formoterol/Budesonide and Formoterol/Fluticasone on prolonged therapy. This is further supported by the studies reviewed by Neil Barnes [14] where the author has concluded that the difference between Salmeterol/Fluticasone, Formoterol/Budesonide, and Formoterol/ Fluticasone in terms of safety and efficacy may be of importance only in patients with COPD that is more difficult to control and require higher doses of inhaled steroids.

Pulmonary function test (FEV1) also improved with Salmeterol/Fluticasone and Formoterol/Budesonide during the 6 mo period of treatment. There was a significant improvement in lung function (p<0.05) after 180 d of treatment. There was no correlation (r = 0.2) between the changes in QoL scores and change in FEV1 values. This may be due to the reason that even with the small change in FEV1 values, patients felt much better, because of which their quality of life improved to a greater extent.

There are few studies on the improvement in the quality of life in COPD patients using combined inhaled corticosteroids and bronchodilators and all of them demonstrated significant improvement in the quality of life. They have used generic quality of life measures like SF-36. To our knowledge, this may be the first study in COPD patients using Saint George's Respiratory Questionnaire (SGRQ-C) to compare between three different combined corticosteroids and bronchodilators [15].

There is a good general consensus that combining medications of different pharmacological classes represent a much more

convenient strategy in COPD, particularly for severe or very severe disease. Additional effects have in fact been proven both in functional and in clinical terms under these conditions [16]. In particular, health status, quality of life, and exacerbations represent the most affected outcomes in more severe COPD (basal FEV1<50% predicted) when treated with combined long-acting β2-agonists and inhaled corticosteroids over time. These data highlighted the favorable therapeutic performance of three different combined inhaled corticosteroids and bronchodilators [17].

CONCLUSION

In conclusion, our study demonstrated that SGRQ-C is useful outcome measures in Chronic Obstructive Pulmonary Disease studies and is able to measure dimensions not measured by pulmonary function tests that help to identify subtle differences between drugs. All the three combined ICS and bronchodilators showed improvement in lung functions and QoL scores. The maximum improvement in the quality of life was obtained with Salmeterol/Fluticasone in severe and very severe COPD patients. More studies comparing different disease-specific instruments such as HADS and SGRQ are necessary to identify the ideal HRQoL measure in Chronic Obstructive Pulmonary Disease.

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CONFLICT OF INTERESTS

Declared none

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