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Randomized Double Blind Placebo Controlled Clinical Trial of *Solanum melongena* L. Fruit in Moderate to Severe Asthmatics

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The efficacy and tolerability of *Solanum melongena* and placebo in moderate to Severe asthmatics was evaluated in a randomized, single center, three-arm, triple blind placebo controlled trial in a tertiary hospital setting in Sokoto, Nigeria . The Main outcome measures were weekly disease severity score, daily Salbutamol (Ventolin) inhaler use. Weekly FEV 1 and PEF all expressed as % above baseline and PEF% predicted. Incidence of side effects was the secondary outcome measure. The study revealed significant improvement in all outcome measures over placebo in the two test arm but no significant difference between test arms. At the end of two weeks of daily intake, the dried fruit of *Solanum melongena* significantly improves asthma symptoms and signs and disease severity score and apparently have a salbutamol sparing effect. No adverse effect was noted.

Key words: *Solanum melongena* L., *Lycospericum esculatum* L., moderate to severe asthma, randomized placebo controlled trial

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INTRODUCTION

In spite of the recent improvement in the understanding of the pathogenesis of asthma, much uncertainty remains about its etio-pathogenic pathways[1]. What appears undisputed is the redundancy of the linked events that lead to the signs and symptoms of asthma[2]. The provocateur focused on for therapy has evolved from myogenic alteration to inflammatory mediators[3]. More recently, neo-angiogenesis is gaining attention[4,5]. With so many uncertainties surrounding the ideal target in asthma, it is little surprise that targeted drug designs have either failed or at best produced drugs whose efficacy is still below that of steroids[6].Based on our current understanding of asthma, our best prediction of innovative therapies also appears gloom[7]. In a continued search for a magic bullet for asthma and like most other chronic illnesses, attention is increasingly focused on ethno pharmaceuticals /herbal agents[8]. Herbal agents remain a viable library for drug discovery because they may be considered to have undergone crude phase 3 clinical trials and it may be assumed that they must have shown some effectiveness for their continued use in the ethno medical settings. Perhaps, closely linked to culture based herbal medicine is culture based dietary delicacies. Indeed, Nina Etkins had suggested a role for diet in ethno pharmacology based on similar observations[9]. Using anthropometrics techniques previously described, *Solanum melongena* L. Fruit (SMF), a dietary delicacy of almost worldwide appeal has been shown to demonstrate a quasi dose-related reduction of symptoms of asthma between SMF consuming and non SMF consuming but otherwise matched communities in northwestern Nigerian and between self reported asthmatic within these communities[10]. Also, SMF is used for medicinal purposes, including asthma and allergic rhinitis. In the ethno medicinal contest, the recommended 'dose' is one SMF daily till cessation of symptom. Each SMF is dipped in honey, chewed and swallowed. However, we have shown that aqueous crude extract of SMF is both anti-inflammatory and bronchospastic; suggesting both an anti- and proasthmatic properties and that the latter effects may be mediated via a muscarinic or histerminergic pathway[10]. It is unlikely that the real influence of SMF on asthma maybe resolved by *ex vivo* studies nor by animal models of asthma; which have been criticized as being unpredictive of clinical asthma[11]. Perhaps a clinical trial of SMF closely copying the medicinal method of use may provide superior evidence of its utility in asthma. Moreover, the dietary history of SMF and the result of toxicological studies in animal suggest that it is quite safe[10]. This study was therefore undertaken to evaluate the efficacy of SMF in moderate to severe asthma and thus obtain higher level evidence of its utility.

MATERIALS AND METHODS

Principal Investigator (Medically qualified): Blinded-Responsible for patient recruitment, follow up and data analysis. (Unblinded only after performing data analysis)

Co-investigators (Medically qualified and/or Pharmacologists): Blinded-Responsible for allocation of patients into groups, trial audit and data analysis using alternative software.

Assistant investigators: Two Nurse practitioner of over 5 years experience: Both were blinded. One had no direct contact with the patients throughout the trial period and was responsible for issuing and keeping unique patient and trial arm identification codes while the other was responsible for dispensing coded dried fruit whose identity was not declared and who was not aware that there was a placebo arm or were she to assume so, was not aware of the identity of the placebo arm amongst the 3 experimental arms.

Recruitment of patients: Patients were recruited from both the Usmanu Danfodiyo University Teaching Hospital and the Sokoto Specialist hospital, Sokoto and those that gave consent were referred to Karaye Hospital Sokoto (the central coordinating unit).

Inclusion criteria: Known asthmatic for at least 2 years, use of Salbutamol Inhaler with only mild or no symptom relief, use of inhaled steroid (irrespective of type) with only mild or no symptom relief, Forced Expiratory Volume in 1 sec (FEV 1) and Peak Expiratory Flow (PEF) consistent with asthma, unsatisfactory response to current affordable and available drugs, written informed consent of patients and/or parent (for aged below 18 years). Regular intake of *Lycopersicon esculentum* Fruit (LEF). 'Regular intake' was described as intake of, or equivalent of, at least one LEF daily irrespective of weather it was consumed raw or cooked.

Exclusion criteria: Absence of any of the above, pregnancy or Last menstruation above 10 days, history suggestive of status asthmaticus or history of hospital admission in the last 6 month, history of intolerance of honey, LSF, or SMF. Obvious co-morbidities (except obesity provided quatelet index was under 40%). Use of steroid (including contraceptives) in the last 6 month. Routine intake of SMF as a delicacy. 'Routine intake' was

described as intake of, or equivalent of, more than 3 fruits in the 3-preceding months.

Standardization of SMF and LEF and 'dose' consideration: In the ethno medicinal setting, the 'dose' used in asthma is 1 fruit/day. However, the size of SMF varies widely. To standardize the 'dose', SMF was randomly purchased from Salka Market in Niger state (northwestern Nigeria) and 100 fully dried SMF were randomly selected from a box, weighed and the mean weight and standard error were determined. This mean weight was taken as the standard weight and SMF with weight difference not more than 10% of this mean were carefully selected for the study. The fruits selected were then weighed and the mean plus standard error was determined. The dose of fully dried SMF used was thus 89±0.6 g/fruit (95%CI=0.233 p=0.0001) per day irrespective of patient's age or weight. In choosing the 'placebo' our criteria was a fruit whose dried form would have some similarity with SMF in look and taste and because fruits may have some compounding biological activities, we wanted a fruit that is also consumed sufficiently regularly by all members of the three experimental arms in quantities quite above that of the experiment and in some form in which such biological effects may be expected to either exist or be absent in all experimental arms. After careful evaluation, including tasting experiments, out of 5 selected fruits, the local variant of LEM best fit these criteria and the total fitness was scored 7/10,8/10 and 8/10 by three independent auditors . Using the weight of the selected SMF as reference, LEF with dry weight within 88.4-89.6 g were carefully selected for the placebo arm.

Randomization of patient: The uncertainty principle was the moral underpin used for randomization of patients. All patients were not responding to local standards of treatment and we felt genuinely uncertain as to which treatment arm was the best. Included patients were randomized using the random numbered table.

Intervention: Two weeks run-in period during which Salbutamol inhaler (same brand) was supplied to the patients but was allowed to use as needed medication in emergencies but should report such to the principal investigator. Patients were allowed 24 h/day access to the principal investigator throughout the trial period. After the run in period baseline readings were taken and patients were given one of either SMF , SMF dipped in honey(SM plus), or LEF as directly observed therapy by an assistant investigator. Fruits were given once daily for 5 consecutive weeks. Test agents were administered in three independent groups without crossover. All non-responders to test SMF were offered one either of oral prednisolone, methylprednisolone or Triamcinolone acetonamide at the end of the trial period. All patients were informed that they had the option to demand an end of trial and a switch to steroid at any time (such events was considered trial failures).

Outcome measure: Weekly disease activity score, daily Salbutamol inhaler use chart recorded as product of number of times required per day and number of puffs required per use (bronchodilator usage or BDU). Entry (baseline) and weekly FEV1 and PEF expressed as percent above baseline and PEF expressed as percentage predicted. A week was defined as 7 consecutive 24 h.

Various scores have been developed for assessing disease severity in asthma but most do not allow for unaccounted use of medication. The standard asthma score criteria is apparently adversely affected by regular use of steroids[12]. Because our clinical situation and patient profile provided some degree of uncertainty as to drug history (poor record of previous drug use) we preferred the score pattern of Colm *et al.*[12], which to our mind was, applied in somewhat similar situation. However, we modified this score (Table 1) to include a maximum score of 4 (instead of 2) to increase sensitivity in detecting wheeze evolutions, revalidated this section (Clinical findings) on moderate asthmatics on bronchodilators plus inhalational steroids (irrespective of type) and confirmed significant correlation with changes in PEF (Spearman's r^2=0.98).

At the end of each week, the principal investigator and a co-investigator independently scored each patient. The focus for potential discrepancies was Clinical findings and where present, the highest score was taken (this occurred in only one patient). Each section of the structured score criteria was of interest.

For respiratory function studies, two assessors, each with 7 years experience in spirometry, performed all the lung function examinations. One supervised PEF and the other took spirometric readings independently. Both were blinded as to which patient was taking which arm. Spirometric measurements (Puritan-Bennett PB 100) were conducted in accordance with the reproducibility and acceptability criteria of the American Thoracic Society[13]. Direct morning (before 10 am) PEF assessment was done with a domiciliary Wright peak flow meter and patients personal best of 3 was recorded . Predicted PEF for each patient was calculated using the curvilinear formulae of Njoku and Anah[14] which was derived from patients with similar demographic profiles.

Table 1: Asthma Severity score criteria of Colm *et al.*[11] as modified to increase sensitivity of clinical findings

Score	Symptomatic disease score criteria
Symptom	
0	No wheezing episodes
1	Infrequent wheeze, < 2/mo
2	Wheeze 1-2/week
3	Wheeze 3-5 times/week
4	Daily wheeze or wheeze every night
Rescue bronchodilator usage	
0	No requirement for rescue inhaler
1	Rescue inhaler 1-2 times/mo
2	Rescue inhaler 1-2 times/week
3	Rescue inhaler 3-5 times/week
4	Daily rescue inhaler requirement
Clinical findings	
0	No audible wheeze
1	Audible wheeze on forced expiration detectable with stethoscope at the nasal orifice
2	Audible wheeze on forced expiration detectable without aid
3	Audible wheeze at rest detectable with stethoscope at the nasal orifice
4	Audible wheeze at rest without aid

Ethical approval: All patients gave written informed consent. At each recruitment point, ethical approval was obtained from the local standing committee. For the whole study, ethical consultation[15] was used.

Statistical analysis: The comparisons of interest were the difference between repeat measures within and between the three trial arms and between the two test arms. Statistical analyses were performed using Microsoft Excel add in resampling statistics, Analyze it and SYSTAT 10. Software. We ran normality checks on resampled data using the Kolmogorov-Smirnov test. Data were analyzed using both the Intent-to-treat (ITT) and per-protocol populations. Symptom scores, bronchodilator usage and clinical scores were analyzed with Friedman test within test arm (Matched), with Kruscal Wallis test between the three trial arms (unmatched) and by Mann-Whitney test between SM and SM plus arms (unmatched) . Baseline was defined as the end of the run-in period. Chi-square was used to analyze change in PEF% above baseline (FEFAB), PEF% predicted (FEFP), FEV 1% above baseline (FEV 1AB). Withdrawals were analyzed using Fisher's exact test. The comparisons of interest in this study were considered different hypotheses of equal interest and therefore required no adjustment for multiplicity. Data are presented as Mean±SD instead of standard error because we predicted biological variability rather than experimental imprecision as the most likely source of between patient differences.

RESULTS

Twenty nine patients, aged 30.8±7.2 year (range 17-47 year), were recruited to participate in the trial (Fig. 1) but 2 withdrew to complementary medical therapy and one changed residence before allocation and 26 patients, aged 30.1±6.1 year (range 17-45) were randomized. There were 4 drop outs: one (aged 17 year) was withdrawn by parents because weekly lung function studies was inconvenient for their schedules, one was placed on erythromycin for a non respiratory infection and 2 had major protocol violations.

In the placebo group (Table 2), there was no significant difference between baseline and values at end of week 5 as regards symptoms (p=0.32), CF (p=0.16) and PEF% P (p=0.26). However, there was significant difference baseline and week 5 BDU (p=0.01) , PEFAB (p=0.008) and FEV1B (p=0.008).

In the SM group (Table 3) there was no significant difference between baseline and values at the end of week 1 as regards symptoms (p=0.71),BDU(p=0.41), CF(p=0.32),PEFP(p=0.1) but there was significant improvement in PEFAB and PEF1AB in the same period. At the end of the second week of treatment, there was significant improvement in symptom (p=0.005), BDU (p=0.005), CF (p=0.005), PEFAB (p=0.005), PEFP (p=0.005) and PEF1B (p=0.005). This improvement was maintained at the end of the 5th week of trial.

In the SM plus group (Table 4) there was also no significant difference between baseline and values at the end of week 1 as regards symptoms (p=0.66), BDU (p=0.44), CF (p=0.32), PEFP (p=0.77) but there was significant improvement in PEFAB and PEF1AB (p=0.005) in the same period. At the end of the second week of treatment, there was significant improvement in symptom (p=0.005), BDU (p=0.005), CF (p=0.005), PEFAB (p=0.005), PEFP (p=0.005) and PEF1B (0.005). This improvement was also maintained at the end of the 5th week of trial.

Table 2: Clinical outcome of the trial among the placebo group

Parameters evaluated	Score mean±SD (95%CI) Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Symptom score	3.6±0.53 (3.1-4.1)	3.6±0.53 (3.1-4.1)	3.0±0.58 (2.5-3.5)	2.7±0.49 (2.3-3.2)	2.7±0.49 (2.3-3.2)	3.3±0.49 (2.8-3.7)
BDU	3.6±0.53 (3.1-4.1)	3.3±0.49 (2.8-3.7)	2.9±0.38 (2.5-3.2)	2.6±0.53 (2.1-3.1)	2.7±0.49 (2.3-3.2)	2.7±0.49 (2.3-3.2)
Clinical findings	2.3±0.49 (1.8-2.7)	2.1±0.38 (1.8-2.5)	2.1±0.38 (1.8-2.5)	2	2	2
PEF% above baseline	Baseline	1.1±1.07 (0.2-2.1)	0.4±1.13 (-0.6-1.5)	0.9±1.46 (-0.5-2.2)	4.1±1.86 (2.4-5.9)	5.4±0.53 (4.9-5.9)
PEF% predicted	51.7±1.5 (50.3-53.1)	52.3±1.7 (50.7-53.9)	52.7±0.95 (51.9-53.6)	53.3±1.5 (51.9-54.7)	54.7±4.68 (50.4-59.0)	53.3±1.6 (51.8-51.4)
FEV 1% above baseline	Baseline	2.7±0.49 (2.3-3.2)	baseline baseline	0.1±0.38 (-0.2-0.5)	4.6±0.53 (4.1-5.1)	5.0±0.58 (4.5-5.5)

Table 3: Clinical outcome of the trial among test group 1

Parameters evaluated	Score mean±SD (95%CI) Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Symptom	3.5±0.53 (3.1-3.9)	3.6±0.52 (3.2-4.1)	0.3±0.46 (-0.1-0.6)	0	0.1±0.35 (-0.2-0.4)	0
BDU	3.8±0.46 (3.4-4.1)	3.5±0.53 (3.1-3.9)	0	0	0	0
Clinical findings	2.8±0.46 (2.4-3.1)	2.1±0.38 (2.6-3.2)	0	0	0	0
PEF% above	Baseline	2.9 ±0.64 (2.3-3.4)	36.6±2.33 (34.7-38.6)	54.1±4.73 (50.2-58.1)	64.4±5.76 (59.6-69.2)	69.0±5.26 (64.6-73.4)
Baseline PEF % predicted	52.6±1.06 (51.7-53.5)	53.5±0.53 (53.1-53.9)	66.0±2.14 (64.2-67.8)	80.0±3.46 (77.1-82.9)	86.1±3.48 (83.2-89.0)	88.9±2.59 (86.7-91.0)
FEV 1% above baseline	Baseline	3.8±0.46 (3.4-4.1)	33.1±3.68 (30.0-36.2)	46.6±2.20 (44.8-48.5)	64.8±4.3 (61.2-68.3)	66.0±5.88 (61.1-70.9)

Table 4: Clinical outcome of the Trial among test group 2

Parameters evaluated	Score mean±SD (95%CI) Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Symptom	3.8±0.46 (3.4-4.1)	3.4±0.52 (2.9-3.8)	0+.1±0.35 (-0.2-0.4)	0	0.1±0.35 (-0.2-0.4)	0
BDU	3.9±0.35 (3.6-4.2)	3.8±0.46 (3.4-4.1)	0	0	0	0
Clinical findings	2.9±0.35 (2.6-3.2)	0	0	0	0	0
PEF% above baseline	Baseline	3.4 ±0.92 (2.6-4.1)	55.6±1.51 (54.4-56.9)	63.8±7.38 (57.6-69.9)	67.6±3.81 (64.4-70.8)	70.1±4.36 (66.5-73.8)
PEF % predicted	53.1±1.13 (52.2-54.1)	54.1±1.25 (53.1-55.2)	76.0±2.51 (73.9-78.1)	81.9±7.06 (76.0-87.8)	88.0±0.76 (87.4-88.6)	90.9±1.55 (89.6-92.2)
FEV 1% above baseline	Baseline (3.4-4.1)	3.8±0.46 (43.5-46.5)	45.0±1.85 (64.2-70.8)	67.5±3.93 (65.4-68.4)	66.9±1.81 (66.9-68.1)	67.0±1.31

There was no significant difference between the test arms and placebo at baseline symptoms (p=0.59), BDU (p=0.42), CF (p=0.51), PEFAB (p=0.1), PEFP (p=0.06) and PEF1AB (p=0.72). At the end of week 1, the test arms did not perform significantly better than placebo as regards symptoms and BDU but improved significantly better than placebo as regards CF(p=0.004), PEFAB(p=0.003), PEFP(p<0.0001) and PEF1AB(p=0.003). However, from the end of the second week and up to the end of the study period, the test arms significantly performed better than placebo (p<0.0002) in all the parameters evaluated.

There was no significant difference between the SM (Table 3) and SM plus group (Table 4) (p>0.05) as regards baseline, weekly and week 5 parameters. No adverse effect was noted in all the trial arms.

DISCUSSION

This study revealed that SMF taken daily with or without honey has significant and clinically important antiasthmatic effect that is well established by the end of the second week. This delay in onset of therapeutic effect suggests that it may modulate pathways other than the

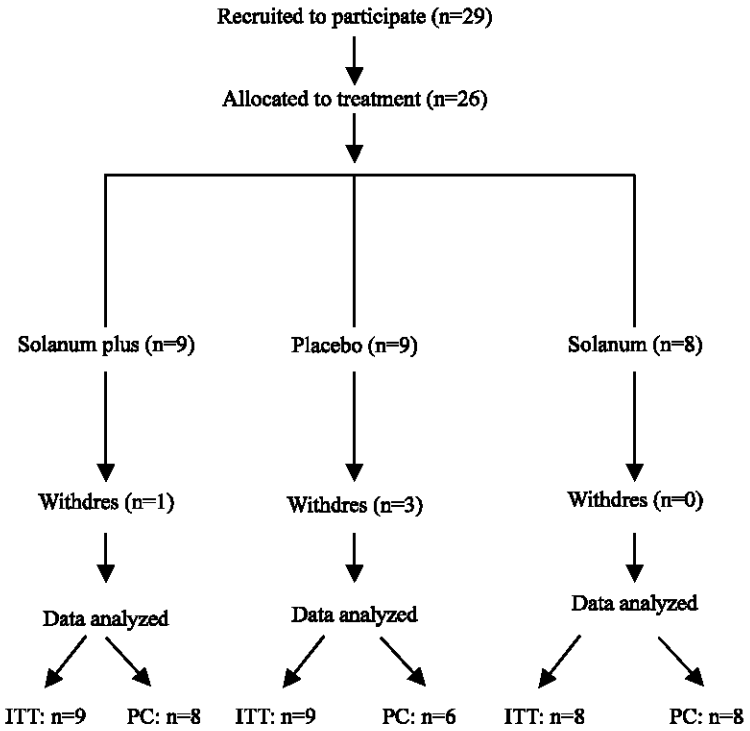

Fig. 1: Trail structure
ITT= Intention to treat, PC= Protocol complete

acute allergic responses. However, a pharmacokinetic delay that requires two weeks for the efficacious factor(s) in the SMF to reach plasma and/or site concentration at minimal effective level and/or modulation of pathways with intrinsic long decays and/or genomic effects may present such delays in clinically observed effects. From this study, there is no apparent difference between the rate and extent of clinical improvement between the SMF and the SMF PLUS arms. This suggests that in the trado-medicinal setting the honey is used as a 'coating' for the rather bitter SMF. It is conjectural if such coating is necessary considering that there were no drop outs in the SMF group, though the sample size is rather small for this particular conclusion. Its may be interesting to note the low placebo effect in this study (maximum =8.2%). The rather low 'dose' of SMF required to produce the observed effect suggest a highly potent antiasthmatic factor in the SMF or an antiasthmatic factor that is a high yield product of intra-luminal intestinal extraction of SMF. Major drawbacks of this study include possible undeclared use of complementary or orthodox medication, undeclared use of test/placebo agent above recommended dose especially by undetected inadvertently unblended patients and especially with signs of improvement and undetected co-morbidities. Within these limits, SMF may be useful for long term control of asthma. From the result of this trial it is tempting to suggest that SMF should be used for therapy in the form used in this trial(dried fruit), however bioassay guided fractionation of its aqueous extract may give useful candidates for optimization. One problem with such a process is the inherent limitations of animal models and the limitation of bioassays to known pathways of disease evolution. Elucidating how SMF improves clinical asthma may expose more about this disease.

REFERENCES

1. Elias, J.A., C.G. Lee, T. Zheng, B. Ma, R.J. Homer and Z. Zhu, 2003. New insights into the pathogenesis of asthma. J. Clin. Invest., 111: 291-297.
2. Grootendorst, D.C. and F.R. Klaus, 2004. Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc., 1: 77-87.
3. Djukanovic, R., W.R. Roche and J.W. Wilson, 1990. State of the art: Mucosal inflammation in asthma. Am. Rev. Respir. Dis., 142: 434-457.
4. Li, X. and J.W. Wilson, 1997. Increased vascularity of the bronchial mucosa in mild asthma. Am. J. Respir. Crit. Care. Med., 156: 229-233.

5. Wilson, J.W., 2001.Vessels: New targets for asthma treatment? Thorax., 56:899-900.
6. O'Byrne, P.M., 2004. Pharmacologic interventions to reduce the risk of asthma exacerbations. Proc. Am. Thorac. Soc., 1: 105-108.
7. Buhl, R. and F.G. Stephen, 2004. Current and future pharmacologic therapy of exacerbations in chronic obstructive pulmonary disease and asthma. Proc. Am. Thorac. Soc., 1: 136-142.
8. Huntley, A. and E. Ernst, 2000. Herbal Medicines for asthma: A systematic review. Thorax., 55: 925-929.
9. Etkin, N.L. and P.J. Ross, 1991b. Should we set a place for diet in ethnopharmacology? J. Ethnopharmacol., 32: 25-36.
10. Bello, S.O., 2003. Higher throughput epidemiological pharmacoprospecting for a potential antiasthmatic. A Ph.D Thesis presented to the Usmanu Danfodiyo University, Sokoto, Nigeria.
11. Coleman, R.A. and R. Sheldrick, 1999. Current animal models are not predictive of clinical asthma. Br. J. Pharmacol., 96: 688-692.
12. Colm, L., V. Tormey, C. Burke and L.W. Poulter, 1997. Allergen-induced cytokine production in atopic disease and its relationship to disease severity . Am. J. Respir. Cell Mol. Biol., 17: 368-375,
13. American Thoracic Society, 1995 . Standardization of spirometry: 1994 update. Am. J. Respir. Crit. Care. Med., 152: 1107-1136.
14. Njoku, C.H. and C.O. Anah, 2001. Curvilinear formulae for predicting Peak expiratory flow rate in Adult Nigerians. West African J. Medicine, 20: 37-41.
15. Reither-Theil, S., 2001. The freiburg approach to ethics consultation: Process, outcome and competencies. J. Med. Ethics., 27: i21-i23.