A Double-Blinded Randomised Placebo-controlled Clinical Trial of Individualised Homeopathic Treatment of Hyperthyroid Cats

Bodey, AL[1], Almond, CJ[2] and Holmes, MA[3].

1. The Hyperthyroid Cat Centre, 433 Birch Park, Thorp Arch Estate, Wetherby. LS23 7FG.
2. Forrest House Veterinary Ltd, 5 Little Market Place, Masham, Ripon, North Yorkshire. HG4 4DY
3. University of Cambridge, Department of Veterinary Medicine, Madingley Road, Cambridge CB3 0ES

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Abstract

Feline hyperthyroidism is a common endocrine disorder in older cats for which homeopathic treatment has been advocated. A double-blinded, placebo-controlled randomized trial was performed to look for evidence of efficacy for the use of individualized homeopathy in the treatment of this disease. Using a case definition of a concentration of the thyroid hormone T4 >66 nmol/l cats were randomized into two treatment arms. Either a placebo or a homeopathic treatment was given to each cat blindly. After 21 days the T4 levels, weight (Wt) and heart rate (HR) were compared to pre-treatment values. There were no statistically significant differences in the changes seen between the two treatment arms following placebo or homeopathic treatment (T4 P=0.96, Wt P=0.16, HR P=0.36) or between the means of each parameter for either treatment arm before and after placebo or homeopathic treatment (all P values > 0.13). In a second phase of the study patients in both treatment arms were given methimazole treatment for 21 days and T4, Wt and HR determined again. Again there were no statistically significant differences between the groups, but there were statistically significant reductions in T4 ($P < 0.0001$) and HR (P=0.02), and a statistically significant increase in Wt (P=0.004) in both groups compared to their pre-methimazole treatment levels. The results of this study failed to provide any evidence of the efficacy of homeopathic treatment of feline hyperthyroidism.

Introduction

Feline hyperthyroidism is the commonest endocrine disorder in older cats with a worldwide but non-uniform distribution (De Wet et al., 2009). A survey of first opinion practices in England reported a prevalence of 8.66% amongst cats older than 10 years of age (Stephens et al., 2014) whereas a 2013 survey identified up to 21% of cats in southern Ireland in the same age group as hyperthyroid during routine screening (Gallagher and Mooney, 2013). Clinical signs result from thyrotoxicosis and commonly include weight loss, polyphagia, tachycardia, palpable goitre, polydipsia and polyuria, diarrhoea and vomiting, secondary hepatopathy, secondary left ventricular hypertrophy and behavioural changes including restlessness and aggression (Peterson, 2006). Left untreated, hyperthyroidism can impact adversely on both life quality and expectancy. Currently, a proven method of prevention is not available (Peterson, 2012a). Current treatment options include lifelong management with oral or transdermal medication (using methimazole, carbimazole or thiamazole), exclusive feeding with iodine-restricted food, and the curative options of thyroidectomy or ablation using iodine 131. These conventional modalities have limitations. Methimazole and the related drugs require ongoing compliance of cat and owner alike; difficulty with long term medication has been reported in approximately 25% of cat owners (Caney, 2013). Sixty-nine per cent of UK first-opinion vets surveyed over a 12-month period observed vomiting as an adverse effect of methimazole or related drugs, with other side effects in decreasing frequency including anorexia, facial pruritus, anaemia, leukopenia, hepatic damage, neutropenia, thrombocytopenia, lymphadenomegaly and sudden death (Higgs et al., 2014; Niessen et al., 2007; Peterson et al., 1988). Azotaemia was reported but this is not unique to methimazole since all modalities have the potential to uncover pre-existing renal insufficiency. Iodine-restricted food was unpalatable in approximately 75% of 225 hyperthyroid cats (van der Kooij et al., 2014), whilst the suitability of such a diet for the lifelong feeding of older cats is questioned (Peterson, 2012b). A more recent retrospective study of 49 hyperthyroid cats maintained on an iodine-restricted diet failed to show statistically significant changes in either heart rate or weight for the 39/47 (83%) that became euthyroid over a 180-day period (Hui et al., 2015). Bilateral thyroidectomy can result in hypoparathyroidism with life-threatening hypocalcaemia a potential sequel (Naan et al., 2006). Cat owner-perceived barriers to the routine use of iodine 131 in decreasing order of importance include the duration of the hospitalisation period post treatment, cost, possible side effects for the cat, long travel times to treatment centres, possible side effects for the owner, and delay to treatment (resulting from waiting lists) (Boland et al., 2014). Efficacy in achieving euthyroidism is

generally good but varies according to the therapy, reported as 87.4% using oral methimazole (Peterson et al., 1988), 23% - 90% after 8 and 12 weeks of iodine-restricted diet respectively (Hui et al., 2015; Melendez, 2012; van der Kooij et al., 2014), 78 – 95% after thyroidectomy (Naan et al., 2006; Welches et al., 1989) and 94.2% after radio-iodine (Peterson and Becker, 1995). Following homeopathy, a moderate or major improvement in clinical signs has been reported in 66.7 – 75 % of 21 and 8 cats respectively (Mathie et al., 2010; Mathie et al., 2007), and a subsequent report described a successful clinical response in 3 out of 4 cases (Chapman, 2011).

Homeopathic treatment is relatively inexpensive, easy to administer, without adverse effects and preferred by those cat owners sceptical of conventional treatments. However, reports of efficacy are generally from small-scale studies relying on owner-assessed change (Mathie et al., 2010; Mathie et al., 2007), poorly defined case definitions or a diagnosis without elevation of total T4 above normal range (Chapman, 2011). The aim of this study was to investigate the effect of individualized homeopathic treatment on hyperthyroid cats using measurement of an elevated serum concentration of the thyroid hormone T4 as the case definition, and change in its concentration as the main outcome measure, in a double-blinded placebo-controlled trial. A secondary trial included in the study aimed to demonstrate the responsiveness of cases, in both treatment arms, to methimazole treatment.

Materials and Methods

The study design was a blinded randomized controlled trial (RCT) in which neither the clinicians, owners or statistician were aware of which individual received homeopathic treatment or placebo. Cats diagnosed with hyperthyroidism were randomly allocated to either homeopathic treatment or a placebo. Following the RCT all cats still having a diagnosis of hyperthyroidism were then treated with methimazole. Figure 1 illustrates the study design.

An estimation of the sample size required for the study indicated that a minimum of 17 subjects in each group would be required to have an 80% power to detect a 10 nmol/l difference in T4 between the homeopathy treatment group and the controls.

Forty cases of feline hyperthyroidism were prospectively enrolled between 2006 and 2012 at participating veterinary practices overseen by one of the investigators. The primary inclusion

criterion was based on the patient having a serum level of the thyroid hormone T4 of ≥ 66nmol/l used to describe moderate to severe hyperthyroidism in previous studies (Peterson et al, 2001). All T4 measurements were performed by a commercial laboratory (Immulite 2000, IDEXX Laboratories, Wetherby, UK). Additional inclusion criteria were the cat owner being able to attend the required appointments, being able to administer the homeopathic treatment or placebo during the first phase, and methimazole (Felimazole, Dechra) during the second phase, and willingness to provide informed consent. Exclusion criteria were total T4 > 160nmol/l (to avoid delaying effective treatment for cats with severe or advanced hyperthyroidism), or concurrent illness. indicated by laboratory parameters (including haematology, total protein, albumin, globulin, alanine transferase, alkaline phosphatase, bilirubin, amylase, urea, creatinine, glucose, sodium, potassium and chloride) outside reference ranges and/or presence of clinical signs suggesting concurrent disease that were inconsistent with a diagnosis of uncomplicated hyperthyroidism.

At the first clinical examination a blood sample was taken and base-line data (including T4, heart rate, body weight, haematology, total protein, albumin, globulin, alanine transferase, alkaline phosphatase, bilirubin, amylase, urea, creatinine, glucose, sodium, potassium and chloride) were recorded (Supplementary table 1). The age, sex and breed of each subject are shown in Supplementary table 2. Data required to provide an individualised homeopathic remedy were collected using a questionnaire to establish the "constitution" of the patient (the behavioural and physical characteristics of the healthy individual, in contrast to those behavioural or physical changes associated with disease; see Supplementary figure 1). As cases were recruited they were assigned to one of the two treatment arms ('red' or 'blue') using a computer generated random list created using Microsoft Excel (Office 2011, Microsoft Corp).

Prior to commencing the study two sets of identical 10ml dropper bottles were pre-filled with 8mls of purified water and 2mls of 40% ethanol (as preservative) and labelled with a sequential case number by a homeopath. One set of bottles was retained by the homeopath, the other given to the 'key holder' (see below). The homeopath prepared individual remedies for all patients recruited into the trial by adding the sarcode thyrodinum (a homeopathic medicine derived from healthy animal tissue addressing the main clinical signs associated with hyperthyroidism) and an appropriate individualized simillimum (a homeopathic medicine most similar to the constitution and totality of clinical signs shown by the patient) using information from the constitutional questionnaire, aided by the homeopathic software Radar (version 8). The potency of the remedy

was achieved by a process of sequential dilution and vigorous shaking (termed succussion) with increasing potency resulting from increased dilution and succussion. Potency 30c indicates a dilution of 1:100, repeated 30 times. The individual homeopathic remedies prepared for each case are shown in Supplementary table 3. A third party, the 'key holder' whose only role was the allocation of animals to treatment groups, provided the clinical investigator blindly with either placebo or homeopathic remedy for each case, to be dispensed. This individual held the allocation key and did not unblind the trial until the analysis was complete. For subjects allocated to the 'red' treatment group they dispensed the placebo, for subjects allocated to the 'blue' treatment group they dispensed the personalised treatment provided by the homeopath.

Each client was instructed to administer 1-3 drops of the treatment (not knowing if it was placebo or the homeopathic remedy) once daily for 21 days, to the cat's oral mucous membrane, while avoiding direct contact with the dropper. A record of successful administration was kept.

The study was divided into two phases (illustrated in Figure 1). Trial subjects were evaluated on recruitment (Visit 1 sampling; as described above), after 21 days treatment with either a homeopathic remedy or placebo (Visit 2 sampling), and after 21 days treatment with methimazole (Felimazole, Dechra, 2.5mg bid; Visit 3 sampling). In addition to recording T4 levels at Visits 2 and 3 results of a clinical examination were recorded, together with the heart rate and weight of each subject.

Statistical analyses were performed using SPSS v20 (IBM corp. New York, USA) and Prism v6 (Graphpad Software, La Jolla, USA). Comparison of changes in T4 levels, heart rate and weight between treatment groups was performed using the Student's T test. Comparison of T4 levels, heart rate, and weight between treatment groups and over time was performed using two-way analysis of variance with post hoc pairwise comparisons adjusted for multiple testing. No additional adjustment for multiple testing was applied and a threshold of $P<0.05$ was chosen to indicate statistical significance.

Ethical approval for the study was given by the Cambridge Veterinary School Ethics Committee (CR-2006-1). An important condition of the approval was that no patient was to be recruited to the study that was deemed likely to be of risk of harm resulting from a delay in commencement of treatment with proven efficacy for a period of 21 days, as judged by an experienced veterinary

surgeon. The documentation and process of obtaining informed consent, and the instructions to owners, were also carefully scrutinised to ensure that owners were alerted to the risks and signs of possible deterioration in health that might be due to a delay in effective treatment. The instructions to owners were to report any signs of deterioration in their cats, and if at any stage during the trial the cat's clinical condition deteriorated prompt investigation and treatment would be initiated, and the case would leave the trial immediately (although during the study no patients had to be removed due to deterioration in their condition). The 21 day treatment period used for each phase of the trial was chosen because conventional medication is effective in that time period (Peterson et al., 1988) and no published papers indicate a minimum duration for homeopathy to become effective. A short duration was chosen to minimise the potential delay in commencing conventional treatment for the placebo group.

Results

A total of 40 cats were recruited, 19 allocated to placebo and 21 to individualized homeopathic remedy. The changes in total plasma T4, heart rate and weight for the 2 treatment groups between Visit 1 sampling (pre-treatment) and Visit 2 sampling (after 21 days of homeopathic or placebo treatment) are shown in Table 1 and Figure 2. Unpaired T tests comparing the changes in total plasma T4 levels, heart rate, and weight gave P values of 0.96, 0.36 and 0.16 respectively, indicating that there was no statistically significant difference between the changes between time points in the two treatment groups.

Following the primary trial two cases (11 and 35) from the homeopathy group had reduced plasma T4 levels which meant that they no longer met the inclusion criteria and so were removed from the study. Case 11 entered the study with a T4 of 71.6 nmol/l which fell to 60.0 nmol/l. This patient was subsequently euthanased due to diabetes mellitus and renal insufficiency. Case 35 entered the study with a T4 of 66.3 nmol/l which fell to 40.7 nmol/l and was also euthanased following a diagnosis of multicentric lymphosarcoma involving the liver, kidneys and thyroid (this individual also had adenomatous multinodular thyroid hyperplasia diagnosed at post mortem).

The secondary trial was performed to determine the remaining study participants' response to methimazole treatment. The results of this trial are shown in Table 1 and Figure 3. Unpaired T tests comparing the changes (between the groups previously treated with homeopathy or a placebo) in

total plasma T4 levels, heart rate and weight gave P values of 0.80, 0.40 and 0.93 respectively, indicating that there was no statistically significant difference between the changes between time points in the two treatment groups.

Two-way analysis of variance of the total plasma T4 levels, heart rates and weights in both groups over all three time points also showed that there was no statistically significance between the two treatment groups for T4 ($P = 0.19$), heart rate ($P = 0.14$) or body weight ($P = 0.09$) for the full dataset. There were statistically significant changes for both treatment groups over time when looking at total plasma T4 ($P < 0.0001$), heart rate ($P < 0.0001$), and weight ($P < 0.0001$). A pairwise comparison of time points confirmed that neither T4 nor heart rate nor weight at Visit 2 (after homeopathy or placebo treatment) were statistically significantly different from Visit 1 (prior to any treatment) with all P values > 0.13. A comparison of the values at Visit 3 (after methimazole treatment) with Visit 1 and Visit 2 were significant for plasma T4 (Visit 1-Visit 3: $P < 0.0001$, Visit 2-Visit 3: $P < 0.0001$), heart rate (Visit 1-Visit 3: $P = 0.001$, Visit 2-Visit 3: $P = 0.02$) and body weight (Visit 1-Visit 3: $P = 0.031$, Visit 2-Visit 3: $P = 0.004$).

Discussion

The primary objective of this study was to test the hypothesis that individualised homeopathic treatments produced changes in objective clinical measures of disease in cases of feline hyperthyroidism compared to a placebo. A secondary clinical trial, using the same patients, tested the hypothesis that the patients in both treatment arms were responsive to conventional methimazole treatment as indicated by the same measures of disease. The study was sufficiently powered to detect a 10 nmol/l difference in plasma T4 levels. The results found no statistically significant difference between the homeopathic treatment group and the placebo for any of the measures recorded. In contrast the fall in plasma T4, fall in heart rate, and increase in body weight was statistically significant between all cats (whether first treated with homeopathy or placebo) before and after 21 days of methimazole. The results from the primary trial indicate that the homeopathic remedies listed, administered for a duration of 21 days, were not an effective therapy for the treatment of feline hyperthyroidism. The results from the secondary trial confirm that the cases recruited were responsive to methimazole treatment which adds to its evidence of efficacy in feline hyperthyroidism.

While the study attempted to ensure that each patient receiving homeopathic treatment was given an individualised treatment the study might be criticised for the universal use of the sarcode thyrodinum. Individuals did receive a variety of simillimums (Supplementary Table 2). While not necessarily perfect from a homeopathic perspective nonetheless we believe this reflects how homeopathy is often used in general veterinary practice.

Two cases receiving homeopathy did experience a fall in total T4 sufficient to leave the trial. These 2 cases had the lowest total T4 levels of all subjects at recruitment (case 11, 71.6 nmol/l, case 35, 66.3 nmol/l). Case 11 was euthanased 13 days after leaving the trial because of diabetes mellitus and renal failure. Case 35 was euthanased 5 months after leaving the trial because of multicentric lymphosarcoma in the liver, kidneys and thyroid (adenomatous multinodular thyroid hyperplasia was also confirmed at post-mortem). Although not diagnosed at the time of recruitment it is likely that these conditions were present during the trial period. It is known that total T4 can return to reference range as a result of non-thyroidal illness (Peterson et al., 2001) and therefore does not in itself confirm successful control of hyperthyroidism. The change in mean total T4 for the homeopathic group was not statistically different from placebo and the clinical progress alone of the only 2 cases showing a reduction in total T4 should not be over interpreted.

The evidence-base upon which homeopathy depends is largely devoid of RCTs of useful quality with only 2 of 18 placebo-controlled trials free from bias (Mathie and Clausen, 2014). There are only 3 studies that describe feline hyperthyroidism, none of which are RCTs. Two of these aim to describe the impact of homeopathy across all veterinary species and conditions and lack the detail of the diagnostic method or the severity of the condition. Response to treatment is documented based on the cat owners' observations alone (Mathie et al., 2010; Mathie et al., 2007). The later study had the larger population of cats (21) and recorded a moderate or major improvement in 66.7% of cases, and no change or minor deterioration in 33.3%. Details of the treatment used and its duration are not recorded in either study, although the earlier study had no recorded durations of treatment less than one month (Mathie, personal communication). The third paper reported a response to treatment in a case series of 4 cases within 2-4 weeks of starting homeopathic treatment (Chapman, 2011). Of these cases only 1 had a total T4 in the hyperthyroid range (81.1 nmol/l, reference interval up to 51 nmol/l), the diagnosis in the 3 remaining cases reliant on clinical signs and free T4 above reference range (58, 72 and 59 pmol/l, reference interval up to 50 pml/l) because total T4 remained within normal range (38.4, 42.5 and 38.4 nmol/l respectively). Laboratory results were

deemed consistent with hyperthyroidism if total T4 exceeded 32 nmol/l and free T4 exceeded 50 pmol/l, or if total T4 alone exceeded 51 nmol/l. The only case remaining unresponsive to homeopathy was that diagnosed with total T4 alone. It is known that free T4 has poor specificity meaning that up to 20% of sick or normal euthyroid cats may have false-positive results (Peterson, 2013) and it is possible that the 3 "responding" cases were not hyperthyroid (Peterson et al., 2001). The homeopathic remedy used initially in all cases was thyroidinum of potency 6c. Potency describes the degree of potentisation, a process of sequential dilution and shaking (termed succussion) whereby greater efficacy is claimed with increasing potentisation (Vickers & Zollman, 1999). The potency 6c indicates that the individualised remedy was diluted to 1:100 and underwent succussion and this process repeated 6 times. Chapman records that it is generally thought by homeopaths that potencies less than 7c exert a stimulatory effect on hormone production whereas potencies above are thought inhibitory (Chapman, 2011). In their case series report all 4 cases were given the stimulatory potency following the apparent successful response in the first case (total T4 38.4 nmol/l, free T4 58 pmol/l). Our study followed the convention of high potency (30c) to exert an inhibitory effect. Our study made use of multiple homeopathic remedies being presented in the same carrier and opinions differ as to whether this impacts on efficacy.

In the absence of a multi-centre design, use of a constitutional questionnaire avoided the welfare impact of transporting uncontrolled hyperthyroid cats over significant distances to attend consultations with the homeopath, and also allowed consistent homeopathic assessments. A sample of such assessments were quality-controlled by an external homeopath (JG Saxton, veterinary Fellow of the Faculty of Homeopathy). The homeopathic assessment could have been improved by replacing questionnaires with homeopathic consultations. Reliance on questionnaires may have adversely impacted on the individualisation of the remedies.

All conventional modes of treatment result in a return to euthyroidism. It is recognised by homeopathic practitioners that the homeopathic thyroidinum sarcode of potency 7c or higher appears to suppress the production of thyroid hormone, hence the reliance on total T4 to provide an objective outcome measure. The use of placebo enhanced the sensitivity of the trial to detecting homeopathic efficacy, minimising the caseload required. However, some homeopathic veterinarians and doctors share the opinion that homeopathic treatment of hyperthyroidism does not result in a reduction in T4 levels, but that the clinical signs of the condition improve with treatment. Given that the mechanism of homeopathy in potentially treating hyperthyroidism has not been described

clinical signs were recorded intending to describe any clinical change not mirrored by change in total T4. None of the owners of the cats in the trial who received homeopathic treatment wanted to withdraw their cats from the second phase of the trial (methimazole treatment); presumably they did not detect a sufficient improvement in their cats' health. It seems reasonable to consider reversal of the weight loss and improvement in tachycardia associated with hyperthyroidism to be a general indication of return to health that might be expected regardless of the mechanism by which any treatment might work.

Our study confirmed a correlation between falling heart rate, rising body weight and falling total T4 for cats receiving methimazole for 21 days. Body weight has been shown to increase once euthyroidism is restored following treatment with radio-iodine or methimazole or its pro-drug (Boag et al., 2007; Boretti et al., 2014; van Hoek et al., 2008), and heart rate shown to decrease following methimazole (Trepanier et al., 2003). This correlation was not observed when euthyroidism was achieved by using iodine-restricted diet (Hill's y/d) in a retrospective study (Hui et al., 2015). Suggested explanations for the lack of clinical response to Hill's y/d were given as vulnerability of heart rate to many variables, the possibility that euthyroid cats were still physiologically hyperthyroid or that undiagnosed concurrent illness prevented weight gain. Hill's y/d has a restricted protein content and carbohydrate increased to provide metaboliseable energy. It is possible that underweight obligate carnivores find this dietary composition insufficient to regain lost weight (Peterson, 2012b). When using methimazole or its pro-drug, in the absence of laboratory data changes in body weight and heart rate can be useful in guiding patient management.

Although two of the investigators conducting this study are sceptical about the efficacy of homeopathy this study was performed with an open mind taking all possible steps to avoid investigator bias. All clinicians would like to be able to employ an effective therapeutic approach with minimal side effects. Given the well-documented adverse effects associated with conventional treatments an efficacious homeopathic approach would provide an effective alternative. In the disease addressed by this study we found no evidence that homeopathy is an effective treatment in comparison to a placebo. This study aimed to overcome the difficulties of the RCT design when investigating individualised homeopathic remedies by not restricting the homeopath to a pre-defined remedy. This approach may have potential in investigating other clinical conditions with a clearly defined diagnosis. The limitations of information gathering through use of a questionnaire in

this study may have diminished the effectiveness of the homeopathic assessment and the individualisation of each remedy. Future similar studies would benefit from appropriate funding to facilitate greater involvement by homeopaths.

The design phase of this study included a rigorous ethical review process during which there was considerable discussion about the potential for pain, suffering or lasting harm to patients assigned to the placebo treatment group. In contrast, patients could be assigned to the homeopathic treatment group without justification as this is recognised as an 'act of veterinary surgery' by the Royal College of Veterinary Surgeons (RCVS) in the UK. It is possible that a longer study period would have resulted in different outcomes being detected although successful response to homeopathic treatment in a similar period to this study has been claimed (Chapman, 2011). However, there are welfare implications for a prolonged placebo group, and also potentially in prolonged use of homeopathy when evidence of efficacy cannot distinguish it from placebo.

Conclusion and Clinical Significance

This study does not support the use of homeopathy in the treatment of feline hyperthyroidism, demonstrating no benefit [in terms of reduced T4, increased body weight or reduced heart rate] when compared with placebo. This study design provides an example of how clinical trials of individualised homeopathy can be performed that may be of use in other well-defined conditions. Rising body weight and falling heart rate were shown to correlate with falling total T4 when using methimazole and may guide management of patients receiving this treatment when laboratory measurement of T4 is not available.

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Conflict of Interest

ALB is clinical director of The Hyperthyroid Cat Centre, UK, providing iodine 131 for hyperthyroid cats. CJA is a practicing veterinary homeopath.

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Figure 1: A flow diagram illustrating the design of the study. *The placebo treatments were prepared prior to commencing the trial as one of two sets of sequentially numbered identical bottles containing the carrier for the homeopathic treatment (8mls of purified water and 2mls of 40% ethanol) and given to the 'key holder'. The homeopath added the homeopathic remedy to the bottle matching the case number in the second set as each case was recruited. This homeopathic treatment was delivered to the 'key holder'. The 'key holder' provided the clinical investigator with either the homeopathic treatment or the placebo according to the group to which the patient had been randomised.

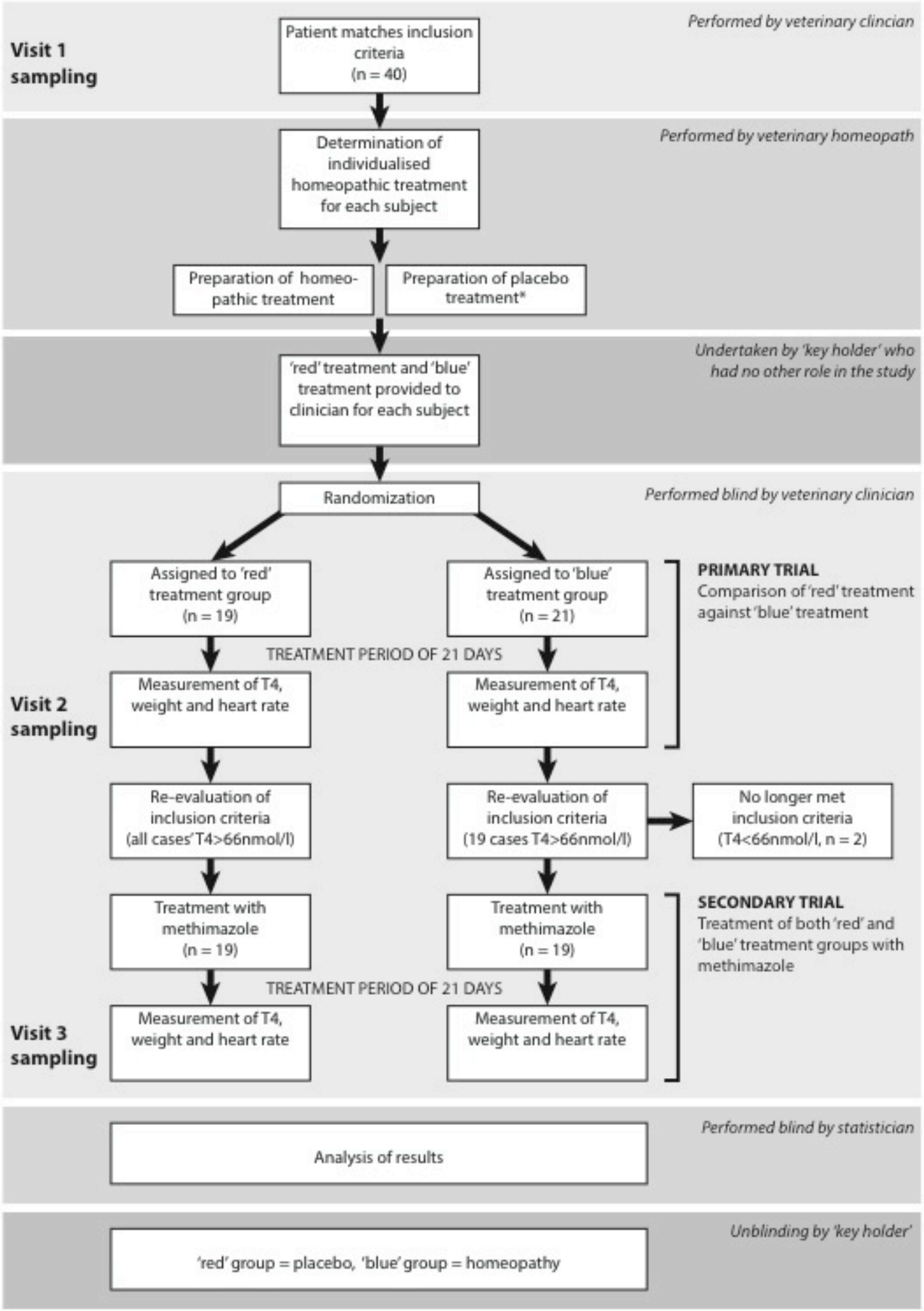
Visit 1 sampling
Patient matches inclusion criteria (n = 40)
Performed by veterinary clincian
Determination of individualised homeopathic treatment for each subject
Preparation of homeo-pathic treatment
Preparation of placebo treatment*
Performed by veterinary homeopath
'red' treatment and 'blue' treatment provided to clinician for each subject
Undertaken by 'key holder' who had no other role in the study
Randomization
Performed blind by veterinary clinician
Assigned to 'red' treatment group (n = 19)
Assigned to 'blue' treatment group (n = 21)
PRIMARY TRIAL
Comparison of 'red' treatment against 'blue' treatment
TREATMENT PERIOD OF 21 DAYS
Visit 2 sampling
Measurement of T4, weight and heart rate
Measurement of T4, weight and heart rate
Re-evaluation of inclusion criteria (all cases' T4>66nmol/l)
Re-evaluation of inclusion criteria (19 cases T4>66nmol/l)
No longer met inclusion criteria (T4<66nmol/l, n = 2)
Treatment with methimazole (n = 19)
Treatment with methimazole (n = 19)
SECONDARY TRIAL
Treatment of both 'red' and 'blue' treatment groups with methimazole
TREATMENT PERIOD OF 21 DAYS
Visit 3 sampling
Measurement of T4, weight and heart rate
Measurement of T4, weight and heart rate
Analysis of results
Performed blind by statistician
'red' group = placebo, 'blue' group = homeopathy
Unblinding by 'key holder'

Figure 2: Graphs showing the change in total plasma T4 levels (graph A), heart rate (graph B) and bodyweight (graph C) in the homeopathy and placebo treatment groups between Visit 1 sampling (prior to treatment) and Visit 2 sampling (after 21 days of homeopathic treatment or placebo). Range bars indicate 95% confidence intervals about the means.

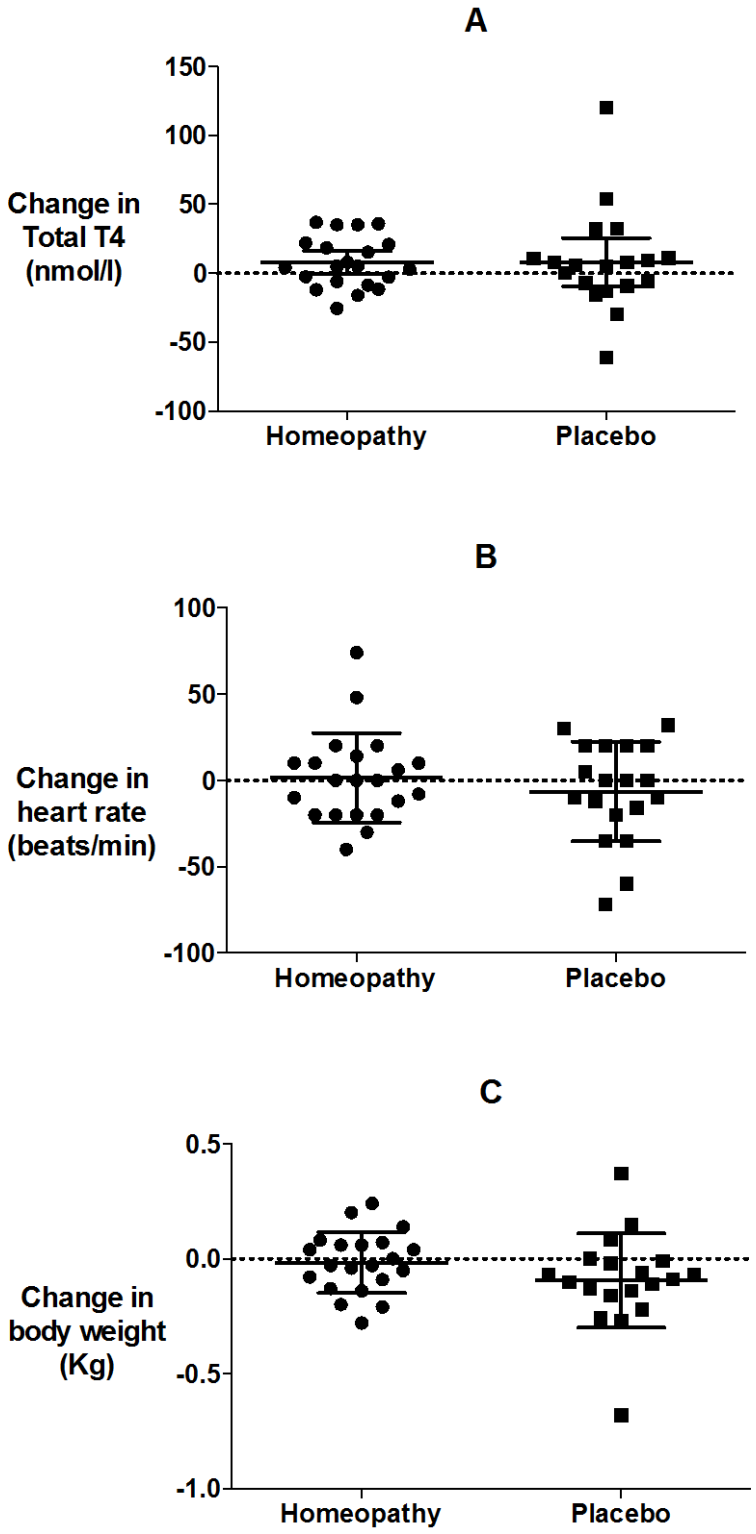

Figure 3: Graphs showing the change in total plasma T4 levels (graph A), heart rate (graph B) and bodyweight (graph C) in the homeopathy and placebo treatment groups between Visit 2 sampling (prior to methimazole treatment) and Visit 3 sampling (after 21 days of methimazole treatment). Range bars indicate 95% confidence intervals about the means.

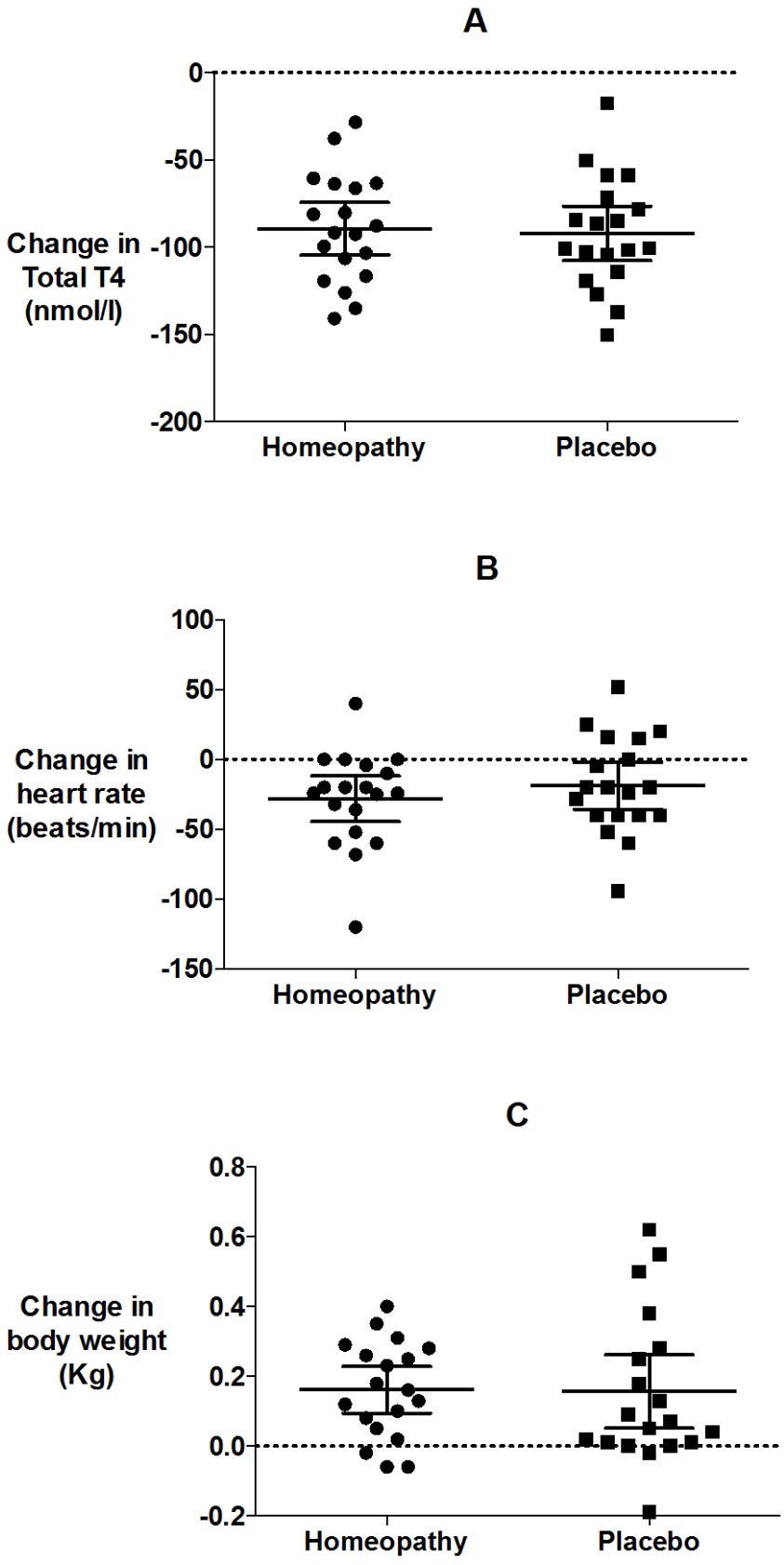

Table 1: Results of the measurement of the serum levels of T4 (nmol/l), weight (Wt in Kg), and heart rate (HR in beats per minute) taken at the start of the study (Visit 1 sampling), after treatment with either placebo or homeopathy (Visit 2 sampling), and following methimazole treatment (Visit 3 sampling) for the homeopathy group (a), and the placebo group (b). The differences in T4 levels, weight and heart rate between Visit 1 and Visit 2, and Visit 2 and Visit 3 are indicated in the columns headed dT4, dWt and dHR respectively (d=difference). The mean values and 95% confidence intervals (CI) are shown in the last two rows of each table.

(a) Homeopathy treatment group (n=21)

	Pre-treatment (Visit 1 sampling)			Post-homeopathy/placebo (Visit 2 sampling)						Post methimazole treatment (Visit 3 sampling)					
ID	T4	Wt1	HR1	T4	dT4	Wt2	dWt	HR2	dHR	T4	dT4	Wt3	dWt	HR3	dHR
2	86.0	3.55	240	83.1	-2.9	3.61	0.06	240	0	19.6	-63.5	3.73	0.12	240	0
3	83.7	2.60	210	99.1	15.4	2.60	0.00	216	6	6.5	-92.6	2.70	0.10	164	-52
6	121.0	4.06	248	156.0	35.0	4.20	0.14	240	-8	39.4	-116.6	4.45	0.25	216	-24
8	122.0	3.70	212	158.0	36.0	3.94	0.24	200	-12	17.1	-140.9	4.25	0.31	180	-20
10	75.2	5.40	200	72.7	-2.5	5.60	0.20	210	10	9.0	-63.7	5.65	0.05	200	-10
11	71.6	3.86	240	60.0	-11.6	3.82	-0.04	200	-40						
14	123.0	3.75	220	111.0	-12.0	3.81	0.06	200	-20	44.7	-66.3	3.75	-0.06	240	40
23	108.0	5.40	152	145.0	37.0	5.37	-0.03	200	48	57.3	-87.7	5.72	0.35	168	-32
25	118.0	2.38	208	139.0	21.0	2.45	0.07	228	20	12.9	-126.1	2.85	0.40	160	-68
27	156.0	3.76	190	140.0	-16.0	3.62	-0.14	204	14	40.4	-99.6	3.75	0.13	180	-24
33	101.0	2.90	200	136.0	35.0	2.82	-0.08	180	-20	16.5	-119.5	3.05	0.23	176	-4
35	66.3	2.75	190	40.7	-25.6	2.79	0.04	200	10						
37	104.0	3.05	220	107.0	3.0	3.77	0.72	240	20	78.5	-28.5	2.93	-0.84	220	-20
44	74.4	3.10	200	92.8	18.4	2.89	-0.21	200	0	55.0	-37.8	2.97	0.08	200	0
45	92.8	3.40	176	84.2	-8.6	3.27	-0.13	250	74	4.0	-80.2	3.53	0.26	130	-120
49	77.2	2.60	240	85.3	8.1	2.68	0.08	230	-10	4.0	-81.3	2.66	-0.02	205	-25
50	107.0	3.47	200	112.0	5.0	3.44	-0.03	180	-20	8.6	-103.4	3.73	0.29	180	0
56	139.0	2.39	190	144.0	5.0	2.30	-0.09	160	-30	52.3	-91.7	2.24	-0.06	140	-20
58	124.0	3.50	240	128.0	4.0	3.45	-0.05	240	0	21.6	-106.4	3.47	0.02	180	-60
62	124.0	3.09	200	118.0	-6.0	2.89	-0.20	180	-20	57.4	-60.6	3.17	0.28	144	-36
64	118.0	3.25	230	140.0	22.0	3.29	0.04	240	10	4.9	-135.1	3.47	0.18	180	-60
Mean	104.4	3.43	210	112.0	7.6	3.46	0.03	211	2	28.9	-89.6	3.58	0.11	184	-28
CI	10.2	0.3	10.2	13.7	7.7	0.4	0.1	10.5	10.8	9.9	13.3	0.4	0.1	13.3	14.5

(a) Placebo treatment group (n=19)

	Pre-treatment (Visit 1 sampling)			Post-homeopathy/placebo (Visit 2 sampling)						Post methimazole treatment (Visit 3 sampling)					
ID	T4	Wt1	HR1	T4	dT4	Wt2	dWt	HR2	dHR	T4	dT4	Wt3	dWt	HR3	dHR
4	156.0	4.05	240	161.0	5.0	4.03	-0.02	260	20	46.7	-114.3	4.10	0.07	232	-28
7	115.0	5.56	220	126.0	11.0	5.30	-0.26	148	-72	41.4	-84.6	5.58	0.28	200	52
9	160.0	3.47	200	192.0	32.0	3.62	0.15	184	-16	87.8	-104.2	3.75	0.13	200	16
17	143.0	3.74	240	149.0	6.0	3.67	-0.07	220	-20	29.6	-119.4	3.92	0.25	240	20
19	105.0	5.01	230	225.0	120.0	4.80	-0.21	260	30	87.6	-137.4	5.00	0.20	220	-40
29	133.0	4.53	240	103.0	-30.0	4.40	-0.13	260	20	17.9	-85.1	4.40	0.00	220	-40
32	138.0	3.60	195	125.0	-13.0	3.68	0.08	160	-35	23.3	-101.7	3.86	0.18	160	0
34	99.1	2.90	190	107.0	7.9	2.81	-0.09	180	-10	4.0	-103.0	2.86	0.05	156	-24
36	101.0	2.68	180	101.0	0.0	2.68	0.00	200	20	83.4	-17.6	2.49	-0.19	180	-20
39	95.5	3.72	240	106.0	10.5	3.50	-0.22	240	0	34.2	-71.8	3.51	0.01	220	-20
43	149.0	3.92	252	203.0	54.0	3.65	-0.27	240	-12	52.5	-150.5	3.63	-0.02	220	-20
55	74.0	3.79	280	68.2	-5.8	3.72	-0.07	270	-10	9.4	-58.8	3.74	0.02	176	-94
60	149.0	4.74	232	157.0	8.0	4.64	-0.10	264	32	56.2	-100.8	4.73	0.09	212	-52
63	121.0	4.11	240	105.0	-16.0	4.48	0.37	240	0	4.0	-101.0	5.03	0.55	200	-40
65	73.0	4.08	160	82.5	9.5	3.97	-0.11	165	5	4.0	-78.5	4.47	0.50	160	-5
68	113.0	4.25	180	104.0	-9.0	4.19	-0.06	200	20	17.5	-86.5	4.20	0.01	160	-40
69	156.0	3.60	240	149.0	-7.0	3.46	-0.14	205	-35	98.5	-50.5	3.50	0.04	220	15
71	98.7	3.44	240	131.0	32.3	3.28	-0.16	240	0	4.0	-127.0	3.66	0.38	180	-60
73	124.0	3.71	280	62.7	-61.3	3.03	-0.68	220	-60	4.0	-58.7	3.65	0.62	245	25
Mean	121.2	3.94	225	129.3	8.1	3.84	-0.10	219	-6	37.2	-92.2	4.00	0.17	200	-19
CI	11.9	0.3	14.4	19.4	15.9	0.3	0.1	16.8	12.6	14.2	14.1	0.3	0.1	12.6	15.2

Supplementary figure 1: Questionnaire used to establish the "constitution" of the patient (relevant characteristics of the whole patient leading to the current clinical signs).

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Study into Hyperthyroid Cats and Homoeopathic Treatment

Study Case Number ☐

CONSTITUTIONAL QUESTIONAIRE

Please answer the following questions about your cat as fully as you can. Your answers are used by the homeopathic vet, along with the laboratory results, in deciding the most appropriate homeopathic treatment for your cat.
Do not worry if you do not know the answers to every question – just write 'don't know'. We appreciate that some of the questions call for a subjective judgement, but please do not guess at an answer if you are not sure. No information is better than wrong information!

Age		**Breed**	**Colour**			
Sex	Male	Female	**Neutered**	Yes	No	
If neutered, was this done:	Routinely as a kitten					
	As an adult due to illness/behavioural problem (if so, please state what)					
Vaccinated against:	'Flu	Enteritis	Feline Leukaemia	Others (please state which)	Not at all	
Vaccination Frequency:	As a kitten, and annually since					
	As a kitten, but not since					
	Only recently for the first time					
	As a kitten and then intermittently					
Have homeopathic nosodes been used as a form of protection?	No					
	Used instead of vaccination all life					
	Was vaccinated when young but now use nosodes					
Please outline previous medical history:						

Department of Veterinary Medicine Madingley Road Cambridge CB3 OES
T: +44 (1223) 764666 F: +44 (1223) 764667
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PLEASE ANSWER THE FOLLOWING QUESTIONS IN RELATION TO YOUR CAT BEFORE THE PRESENT HYPERTHYROIDISM STARTED
How would you describe your cat? Please give a score of 1(weak) to 5(strong) to each of the following characteristics that apply by ticking the appropriate box. More than one may apply.

Temperament	WEAK———STRONG 1	2	3	4	5
Affectionate					
Independent					
Aggressive – all show and bluster or will really fight?					
Timid					
Antisocial					
Sociable with people and animals					
Dislikes other cats/dogs					
Dislikes people that are not known					
Especially attached to certain members of the family					
Fear/dislike of members of one sex generally					
Likes to play with people/animals					
Plays on it's own					
Are there any great fears? Please state of what					

Appetite	1	2	3	4	5
Large					
Greedy					
Small					
Average					
Changeable – wants different foods					
Variable - sometimes will eat normally, sometimes not					

What is your cat fed on?
Are there any foods/titbits your cat particularly likes?
Please state the desires even if you do not give them to your cat.
Are there any foods/titbits your cat strongly dislikes?
Does your cat have any strong preference for wet or dry food? If applicable, please state which.
Does your cat eat quickly or slowly? For example eat part of meal at one time and return later?
Does your cat suffer from flatulence?
If yes to flatulence, is it at any particular time?

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T: +44 (1223) 764666 F: +44 (1223) 764667
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Thirst	WEAK———STRONG 1	2	3	4	5
Large					
Small					
Never thought about it					

Does your cat drink:	Little and often	
	Large quantities frequently	
	Large quantities at long intervals	
Where does your cat drink from? (please delete those that do not apply)	Water bowl only	
	Any or all of puddles	
	Bowls	
	Sinks/toilets/baths	
	Taps	
Does you cat prefer water fresh and cold, or will it take any?		
Does your cat like/love milk?		

Creature Comforts		WEAK———STRONG 1	2	3	4	5
Does your cat prefer to be:	indoors					
	outside in all weathers					
	outside in fine weather only					
When inside, where does your cat prefer to be?	lying in the sun					
	Near a source of heat					
	Anywhere in a generally warm room					
	In a cool area of the house					
	On a soft surface such as a chair/basket with cushion					
	Near a person					
	Being cuddled by a person					
	Always on the move					
	On a high surface					
Is your cat active or lazy?						

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T: +44 (1223) 764666 F: +44 (1223) 764667
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Faeces and urine	
Does your cat use a litter tray?	Yes / no
Have you seen the tray being used?	Yes / no

		WEAK———STRONG 1	2	3	4	5
Does your cat tend to be:	Constipated/have difficulty passing motions? have loose motions all the time?					
	have normal motions?					
	Have dry motions?					

PLEASE STATE ANY PECULIAR OR INDIVIDUAL CHARACTERISTICS WHICH ARE NOT COVERED BY ANY OF THE ABOVE:

PLEASE LIST ANY CHANGES TO THE ABOVE WHICH HAVE OCCURRED SINCE THE HYPERTHYROIDISM STARTED:

Department of Veterinary Medicine Madingley Road Cambridge CB3 OES
T: +44 (1223) 764666 F: +44 (1223) 764667
www.vet.cam.ac.uk/cidc

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Supplementary table 1: Baseline values for haeamatological and biochemical parameters determined for the patients in (a) the homeopathy group, and (b) the placebo group measured from samples taken on visit 1 prior to recruitment into the study. The means and standard deviations (SD) for each parameter are shown in the final two columns of the table.

(a) Homeopathy Group

Subject ID	**2**	**3**	**6**	**8**	**10**	**11**	**14**	**23**	**25**	**27**	**33**	**35**	**37**	**44**	**45**	**49**	**50**	**56**	**58**	**62**	**64**	**Mean**	**SD**
RBC 10^{12}/l	8.97	7.73	8.52	8.74	8.23	9.02	8.63	7.06	9.95	9.04	8.37	10.9	6.94	8.65	11.6	8.49	8.93	8.75	9.66	9.35	9.48	8.91	1.10
Hb g/dl	13.6	11.4	13.9	13.6	12.1	11.3	12.4	10.2	11.3	10.8	10.7	14.5	8.8	12.5	14.8	13.6	11	12	11.5	12.3	12.1	12.11	1.50
HCT l/l	0.42	0.386	0.39	0.41	0.38	0.38	0.41	0.35	0.34	0.35	0.35	0.41	0.268	0.41	0.43	0.469	0.341	0.40	0.37	0.38	0.40	0.39	0.04
MCV fl	47.2	49.9	46.4	47.8	46.2	43.1	48.3	49.7	34.4	39.2	41.9	38.2	38.6	48.1	36.9	55.2	38.2	46.4	38.7	41.2	42.4	43.71	5.35
MCH pg	15.2	14.7	16.3	15.6	14.7	12.5	14.4	14.4	11.4	11.2	12.8	13.3	12.7	14.5	12.7	16	12.3	13.7	11.9	13.2	12.8	13.63	1.48
MCHC g/dl	32.2	29.5	35.2	32.5	31.8	29	29.7	29.1	33	30.5	30.5	34.7	32.8	30	34.3	29	32.3	29.6	30.7	31.9	30.1	31.35	1.92
WBC 10^9/l	6.6	6.4	10.3	11.5	9.3	11.5	5.5	7	14.9	5.83	10.8	9.1	9.8	8.4	8.8	10.3	7.1	9	13.9	9.4	10.9	9.35	2.48
Neutrophils 10^9/l	4.49	3.01	6.08	7.25	5.02	6.67	2.7	3.29	12.6	4.37	7.88	5.73	8.23	4.54	5.02	6.8	4.12	5.67	7.09	7.05	6.21	5.90	2.21
% Neutrophils	68	47	59	63	54	58	49	47	85	75	73	63	84	54	57	66	58	63	51	75	57	62.19	11.15
Lymphocyte.10^9/l	1.58	3.07	3.61	1.61	3.07	3.57	2.2	2.38	1.04	1.11	1.94	1.91	0.49	2.52	3.17	2.58	2.2	1.62	5.84	1.97	3.49	2.43	1.17
% Lymphocytes	24	48	35	14	33	31	40	34	7	19	18	21	5	30	36	25	31	18	42	21	32	26.86	11.17
Monocytes 10^9/l	0.26	0.19	0.31	0.35	0.37	0.12	0	0.77	0.6	0.12	0.43	0.36	0.49	0.08	0.26	0.21	6	0.45	0.28	0.19	0.65	0.59	1.25
% Mono	4	3	3	3	4	1	0	11	4	2	4	4	5	1	3	2	6	5	2	2	6	3.57	2.34
Eosinophils 10^9/l	0.26	0.13	0.31	2.3	0.84	1.15	0.61	0.56	0.6	0.23	0.54	1.09	0.59	1.26	0.35	0.72	0.36	1.26	0.7	0.19	0.55	0.70	0.50
% Eosinophils	4	2	3	20	9	10	11	8	4	4	5	12	6	15	4	7	5	14	5	2	5	7.38	4.76
Platelets	348	320	370	395	360	531	336	515	782	259	307	230	242	221	404	284	323	283	325	355	399	361.4	125.7
Tot.Protein g/l	74	60.1	66.3	72.2	69.6	76.6	66.6	72.9	75.2	67.8	70	80.6	69.3	66.2	62.3	77.1	67.3	69.6	62.3	67.9	70.8	69.75	5.17
Albumin g/l	31.8	28.8	34	30.9	31.2	33.7	30.7	27.5	30.5	33	30.3	31.1	30	31.4	29.2	32.4	28.2	33.7	29.2	32.7	33.3	31.12	1.89
Globulin g/l	42.2	31.3	32.3	41.3	38.4	42.9	35.9	45.4	44.7	34.8	39.7	49.5	39.3	34.8	33.1	44.7	39.1	35.9	33.1	35.2	37.5	38.62	4.95
A:G Ratio	0.75	0.92	1.05	0.75	0.81	0.79	0.86	0.61	0.68	0.95	0.76	0.63	0.76	0.9	0.88	0.72	0.72	0.94	0.88	0.93	0.89	0.82	0.11
Urea mmol/l	6	17.6	9.3	10.3	9.9	15.3	6.9	18.9	11.4	13.4	13.1	8.7	10.3	11.7	9.5	10.2	10	14.2	8.9	9.9	7.9	11.11	3.29
Creatinine µmol/l	64.2	182.6	74.3	127	132	87.7	85.5	155	107	131	121	90.8	86.9	93.9	88.9	108.2	94.9	96.1	94.5	65.8	85.2	103.5	29.19
ALT (SGPT) iu/l	89.7	1599.4	94.5	48.9	65.1	302.1	73.7	102.3	122	187	56.8	98.4	96.4	298.7	155.2	440.8	207.4	426.1	130.7	712.6	248.3	264.58	347.10
ALKP iu/l	80.3	118.8	63.8	69.7	36.4	142.2	55.4	88	126.9	119.4	40.6	40.7	49.5	69.3	68.9	108.3	97.7	124	60.6	83.9	79.6	82.10	31.37
Bilirubin µmol/l	2.1	4.4	0.1	0.2	0.1	1.6	2.6	0.5	0.2	0.6	0.9	0.1	0.3	1.8	0.5	2.6	2.5	1.5	0.5	2.8	0.3	1.25	1.20
Amylase iu/l	645.1	927.9	436.4	676.8	1039	737.2	643.3	773.1	911.2	933.8	826	881.6	1235.5	868	847.7	1685.6	1156.2	685	762.7	598.8	767.7	858.98	264.81
Sodium mmol/l	152.3	156.4	153.5	155.7	155.5	154.7	154.8	156.1	156.7	151.8	155.9	150.1	151.5	156	154.2	154.7	156	153.7	154.6	153.9	154.9	154.43	1.77
Potassium mmol/l	4.3	4.4	4.5	4.2	4.3	4.1	4	4.3	5.5	4.4	5	4.4	4.5	4.1	4.7	4.3	4.1	4.5	4.4	4.3	4.6	4.42	0.33
Na:K	35.42	35.55	34.11	37.07	36.16	37.73	38.7	36.3	28.49	34.5	31.18	34.11	33.67	38.05	32.81	35.98	38.05	34.16	35.14	35.79	33.67	35.08	2.42
Chloride mmol/l	117.1	121.5	119.2	119.7	118.9	122.2	120.7	117.7	115.3	116.5	114.5	115.6	117.9	119.5	121.3	119.2	120.2	117.6	120.6	117.1	119.1	118.64	2.13
Glucose mmol/l	6.7	7.5	6	4.8	4.5	7.6	4.8	4.2	4	6.8	4	4.5	7.3	4.8	5.8	5.8	4.3	4.6	4.5	6.1	4.9	5.40	1.20

(b) Placebo group

Subject ID	4	7	9	17	19	29	32	34	36	39	43	55	60	63	65	68	69	71	73	Mean	SD
RBC 10^{12}/l	7.05	7.91	8.95	9.31	9.57	8.24	8.52	8.34	6.38	8.81	9.26	9.2	11.36	11.3	10.51	9.57	7.51	9.43	8.93	8.96	1.28
Hb g/dl	9.9	11.9	14.5	13.7	14	11.6	12.8	12.1	11	11.9	13.1	13.4	13.9	14.7	12.7	12.7	10.4	14.9	12.4	12.72	1.41
HCT l/l	0.321	0.376	0.48	0.407	0.438	0.351	0.386	0.389	0.367	0.34	0.501	0.422	0.509	0.466	0.384	0.406	0.389	0.525	0.47	0.42	0.06
MCV fl	45.5	47.5	53.6	43.7	45.8	42.6	45.3	46.6	57.5	38.6	54.1	45.9	44.8	41.2	36.5	42.4	51.8	55.7	45	46.53	5.68
MCH pg	14	15	16.2	14.7	14.6	14.1	15	14.5	17.2	13.5	14.1	14.5	12.2	13	12.1	13.3	13.8	15.8	13.9	14.29	1.26
MCHC g/dl	30.8	31.6	30.2	33.7	32	33	33.2	31.1	30	35	26.1	31.7	27.3	31.5	33.1	31.3	26.7	28.4	31.1	30.94	2.40
WBC 10^9/l	9.3	9.3	10.4	14.1	13.4	17.8	7	10.7	7.7	7.25	15.9	6.78	11.8	5.7	17	14.4	11.5	7.8	10.1	10.94	3.64
Neutrophils 10^9/l	6.7	5.58	8.01	8.32	8.98	10.86	4.2	7.06	4	5.37	13.2	3.08	8.02	1.88	7.82	8.21	8.86	5.23	6.39	6.94	2.72
% Neutrophils	72	60	77	59	67	61	60	66	52	74	83	45	68	33	46	57	77	67	62	62.42	12.39
Lymphocyte.10^9/l	2.23	2.33	1.87	4.23	2.68	5.87	1.75	2.78	2.54	1.16	0.32	2.6	1.42	3.42	6.8	2.59	2.07	1.87	2.55	2.69	1.54
% Lymphocytes	24	25	18	30	20	33	25	26	33	16	2	40	12	60	40	18	18	24	26	25.79	12.41
Monocytes 10^9/l	0.37	0.37	0.1	0.42	0.27	0.36	0.42	0.21	0.08	0.51	0.8	0.42	1.06	0.17	0.85	0.29	0.23	0.16	0.5	0.40	0.26
% Mono	4	4	1	3	2	2	6	2	1	7	5	6	9	3	5	2	2	2	4	3.68	2.19
Eosinophils 10^9/l	0	1.02	0.42	1.13	1.47	0.71	0.63	0.64	1.08	0.22	1.59	0.58	1.3	0.23	1.53	3.31	0.35	0.55	0.8	0.92	0.74
% Eosinophils	0	11	4	8	11	4	9	6	14	3	10	9	11	4	9	23	3	7	8	8.11	5.07
Platelets	406	413	455	359	387	659	324	333	431	201	217	296	445	355	280	128	327	190	353	345.21	118.87
Tot.Protein g/l	70.8	71.9	70.5	69.8	74.5	68.4	73.4	66.4	73.2	75.3	64.9	70.9	79.8	65.8	68.1	77.1	64.3	77.3	70.4	71.20	4.37
Albumin g/l	29	31.8	34.5	30.7	33.7	28.7	33.9	31.3	34.1	29	23.5	30.3	32.3	31.8	30.4	33.9	28.8	33.4	31.1	31.17	2.68
Globulin g/l	41.8	40.1	36	39.1	40.8	39.7	39.5	35.1	39.1	46.3	41.4	40.6	47.5	34	37.7	43.2	35.5	43.9	39.2	40.03	3.59
A:G Ratio	0.69	0.79	0.96	0.79	0.83	0.72	0.86	0.89	0.87	0.63	0.57	0.75	0.68	0.94	0.81	0.78	0.81	0.76	0.8	0.79	0.10
Urea mmol/l	10.4	9.2	8.9	17.9	12.3	15.3	7.7	8.1	14.7	9.8	8.2	14	8.2	10	11.3	8.5	13.3	6.7	10.9	10.81	3.03
Creatinine µmol/l	113.9	79.1	85.5	134.7	106.2	92.2	66.3	60.1	114.1	109	67.7	144.7	78.3	76.6	92.6	102	109.3	104.7	100.2	96.69	22.57
ALT (SGPT) iu/l	375.8	154	143.6	270.7	170	228.5	362.8	56.4	98.6	236.1	120.8	100.4	138.6	63.9	124.1	143.7	341	473	234	201.89	116.56
ALKP iu/l	130.7	70.6	115.6	75.1	108.2	90.3	118.1	46.7	67.3	92.5	93.6	39.4	76.6	69.3	36.7	45.1	149.1	83.8	82.8	83.76	31.01
Bilirubin µmol/l	0.3	1.3	0.3	0.9	0.7	1	1.8	0.1	2.3	1.5	0.8	0.9	1	0.4	1.1	0.7	1.7	0.3	1.1	0.96	0.58
Amylase iu/l	765.1	709	601.4	709.6	815.2	860.2	595.7	981.9	1057.9	989.3	843.6	1294.8	1279.6	951.7	1340.5	1338.2	993.3	934.3	899.9	945.33	233.79
Sodium mmol/l	153.2	150.2	155.8	154.5	154.1	153.3	153.5	156.2	157.3	157.3	151.6	150.6	153.9	155.2	154.5	153.1	150.2	154.2	154.1	153.83	2.10
Potassium mmol/l	4.1	4.1	4.1	4.7	4	4.1	4.6	4.3	4.9	3.8	4.6	4.1	5.1	4.7	4.8	4.3	4.3	4.3	4.4	4.38	0.35
Na:K	37.37	36.63	38	32.87	38.53	37.39	33.37	36.33	32.1	41.39	32.96	36.73	30.18	33.02	32.19	35.6	34.93	35.86	35.18	35.30	2.74
Chloride mmol/l	116.8	118.3	117.1	115.4	115.9	119.5	117.6	4.7	112.2	118.7	116.9	119.8	116.3	116.5	119.3	117.2	118.6	122.3	115.2	111.49	25.95
Glucose mmol/l	5.2	7.1	5.8	5.4	5.3	4.8	4.7	4.7	4.1	4.3	3.8	n/d	4.6	4.3	4.2	4.9	4.9	5.4	5.18	4.93	0.76

Supplementary table 2: Details of the age, sex and breed of each cat in the trial.

(a) Homeopathy Group

Patient ID	Age	Sex	Breed
2	16	FN	DSH
3	14	FN	DSH
6	12	FN	DSH
8	11	FN	DSH
10	14yr 6m	MN	DSH
11	17	MN	DSH
14	12yr 11m	FN	DSH
23	12yr 6m	MN	DSH
25	17	FN	DSH
27	16yr 6m	MN	DSH
33	17	FN	DSH
35	11	FN	DSH
37	17	MN	DSH
44	16yr 10m	FN	DSH
45	11	MN	DSH
49	13	FN	Siamese
50	14	MN	DSH
56	17	FN	DSH
58	15	FN	DSH
62	10	FN	DSH
64	12	FN	DSH

(b) Placebo Group

Patient ID	Age	Sex	Breed
4	15yr 6m	MN	Norwegian Forest
7	12	MN	DSH
9	11	FN	DSH
17	13yr 6m	MN	DSH
19	23	MN	DSH
29	16yr 6m	MN	DSH
32	13	FN	DSH
34	12yr 6m	FN	Bengal cross
36	17	FN	DSH
39	19	FN	British shorthair
43	15	FN	DSH
55	6yr 7m	MN	DSH
60	9yr 8m	MN	DSH
63	13	FN	DSH
65	11	MN	American Tiger short hair
68	13	MN	DSH
69	13	MN	DSH
71	12	FN	DSH
73	12	FN	DSH

Supplementary Table 2: List of the individualized homeopathic treatments (simillimum) administered to the patients in the homeopathic ('blue') arm of the clinical trial.

Patient ID	Simillimum
2	Thyrodinum 30C and Calcium carbonate 30c
3	Thyrodinum 30C and Causticum 30c
6	Thyrodinum 30C and Pulsatilla 30c
8	Thyrodinum 30C and Calcium carbonate 30c
10	Thyrodinum 30C and Lycopodium 30c
11	Thyrodinum 30C and Lycopodium 30c
14	Thyrodinum 30C and Calcium carbonate 30c
23	Thyrodinum 30C and Calcium carbonate 30c
25	Thyrodinum 30C and Natrum muriaticum 30c
27	Thyrodinum 30C and Lycopodium 30c
33	Thyrodinum 30C and Phosphorous 30c
35	Thyrodinum 30C and phosphorous 30c
37	Thyrodinum 30C and Arsenicum album 30c
44	Thyrodinum 30C and Lycopodium 30c
45	Thyrodinum 30C and Calcium carbonate 30c
49	Thyrodinum 30C and Phosphorous 30c
50	Thyrodinum 30C and Phosphorous 30c
56	Thyrodinum 30C and Phosphorous 30c
58	Thyrodinum 30C and Natrum muriaticum 30c
62	Thyrodinum 30C and Lycopodium 30c
64	Thyrodinum 30C and Natrum muriaticum 30c