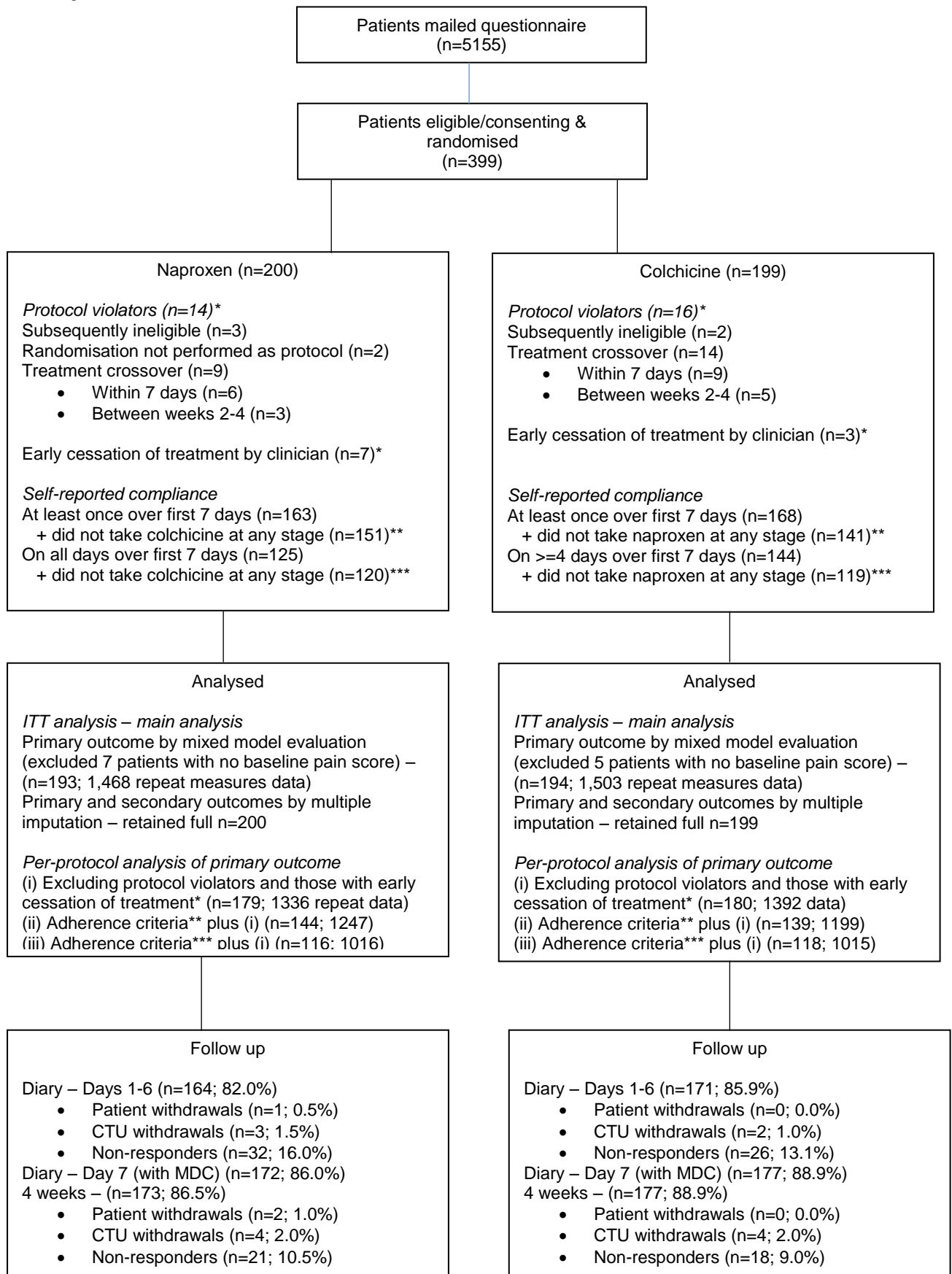


Participant flow



Baseline Characteristics:
Table 1: Comparability of baseline characteristics

| Key characteristics | Categories | Overall | Naproxen (n=200) | Colchicine (n=199) |
|----------------------------------|--------------------------------------|---------------|---------------------|-----------------------|
| Age: mean (SD) | - | 59.4 (13.9) | 58.7 (14.4) | 60.0 (13.4) |
| Gender, n (%) | Male | 347 (87.0%) | 173 (86.5%) | 174 (87.4%) |
| | Female | 52 (13.0%) | 27 (13.5%) | 25 (12.6%) |
| Site of recruitment, n (%) | Keele | 107 (26.8%) | 55 (27.5%) | 52 (26.1%) |
| | Southampton | 189 (47.4%) | 88 (44.0%) | 101 (50.8%) |
| | Nottingham | 31 (7.8%) | 16 (8.0%) | 15 (7.5%) |
| | Oxford | 72 (18.0%) | 41 (20.5%) | 31 (15.6%) |
| Preferred mode of contact, n (%) | Electronic | 122 (30.6%) | 59 (29.5%) | 63 (31.7%) |
| | Postal | 277 (69.4%) | 141 (70.5%) | 136 (68.3%) |
| Pain NRS (0-10), mean (SD) | - | 7.0 (2.1) | 7.1 (2.1) | 6.9 (2.2) |
| | <i>Missing data, n</i> | 12 | 7 | 5 |
| First instance of gout, n (%) | Yes | 86 (22.0%) | 35 (17.9%) | 51 (26.2%) |
| | No | 305 (78.0%) | 161 (82.1%) | 144 (73.8%) |
| | <i>Missing data</i> | 8 | 4 | 4 |
| Age when diagnosed, mean (SD) | - | 52.8 (14.9) | 52.1 (15.2) | 53.4 (14.6) |
| | <i>Missing data</i> | 13 | 6 | 7 |
| Body part affected, n (%) | Shoulder | 3 (0.8%) | 2 (1.0%) | 1 (0.5%) |
| | Elbow | 15 (3.8%) | 4 (2.0%) | 11 (5.6%) |
| | Wrist | 15 (3.8%) | 8 (4.1%) | 7 (3.6%) |
| | Thumb base | 14 (3.6%) | 5 (2.6%) | 9 (4.6%) |
| | Small finger joints | 19 (4.9%) | 11 (5.6%) | 8 (4.1%) |
| | Hip | 3 (0.8%) | 2 (1.0%) | 1 (0.5%) |
| | Knee | 36 (9.2%) | 17 (8.7%) | 19 (9.7%) |
| | Ankle | 64 (16.4%) | 31 (15.8%) | 33 (16.9%) |
| | Mid-foot | 73 (18.7%) | 41 (20.9%) | 32 (16.4%) |
| | Big toe bunion joint | 277 (70.8%) | 142 (72.4%) | 135 (69.2%) |
| | Other toes | 56 (14.3%) | 28 (14.3%) | 28 (14.4%) |
| | <i>Missing data</i> | 8 | 4 | 4 |
| | Number of body parts affected, n (%) | 1 | 284 (72.6%) | 139 (70.9%) |
| 2 | | 61 (15.6%) | 34 (17.3%) | 27 (13.8%) |
| 3 | | 22 (5.6%) | 13 (6.6%) | 9 (4.6%) |
| 4 | | 19 (4.9%) | 6 (3.1%) | 13 (6.7%) |
| >=5 | | 5 (1.4%) | 4 (2.0%) | 1 (0.5%) |
| <i>Missing data</i> | | 8 | 4 | 4 |
| EQ5D-5L, mean (SD) | - | 0.666 (0.217) | 0.665 (0.210) | 0.666 (0.225) |
| | <i>Missing data</i> | 14 | 8 | 6 |

Outcome measures

Primary outcome measure

Table 2: Comparison of pain scores (primary outcome measure) at follow up – ITT analyses

| | Naproxen | | Colchicine | | Unadjusted* | | Adjusted** | | Sensitivity*** | |
|--------------------|-------------------------|-----------------------|-------------------------|-----------------------|--------------------------|---------|--------------------------|---------|--------------------------|---------|
| | Absolute mean (SD) n | Change mean (SD) n | Absolute mean (SD) n | Change mean (SD) n | Mean difference (95% CI) | P value | Mean difference (95% CI) | P value | Mean difference (95% CI) | P value |
| Day 1 | 6.7 (2.1) 160 | 0.6 (2.0) 157 | 6.5 (2.4) 164 | 0.5 (2.1) 161 | -0.09 (-0.40, 0.22) | 0.565 | -0.06 (-0.36, 0.24) | 0.700 | -0.05 (-0.45, 0.35) | 0.802 |
| Day 2 | 4.9 (2.4) 161 | 2.3 (2.7) 158 | 5.2 (2.4) 164 | 1.8 (2.5) 161 | -0.52 (-0.93, -0.11) | 0.012 | -0.48 (-0.86, -0.09) | 0.015 | -0.47 (-0.95, -0.01) | 0.049 |
| Day 3 | 3.8 (2.5) 163 | 3.3 (2.9) 160 | 3.9 (2.4) 166 | 3.1 (2.7) 163 | -0.24 (-0.70, 0.23) | 0.321 | -0.18 (-0.57, 0.20) | 0.354 | -0.21 (-0.69, 0.28) | 0.404 |
| Day 4 | 2.8 (2.3) 158 | 4.4 (2.9) 155 | 2.8 (2.3) 168 | 4.1 (2.8) 165 | -0.20 (-0.67, 0.27) | 0.399 | -0.13 (-0.52, 0.26) | 0.512 | -0.16 (-0.62, 0.30) | 0.494 |
| Day 5 | 2.3 (2.4) 156 | 4.9 (2.8) 153 | 2.3 (2.2) 159 | 4.6 (2.9) 156 | -0.22 (-0.69, 0.25) | 0.360 | -0.15 (-0.54, 0.24) | 0.445 | -0.18 (-0.64, 0.28) | 0.442 |
| Day 6 | 1.8 (2.2) 157 | 5.3 (2.7) 154 | 2.0 (2.1) 160 | 5.0 (2.8) 158 | -0.23 (-0.70, 0.25) | 0.349 | -0.15 (-0.54, 0.24) | 0.459 | -0.17 (-0.61, 0.26) | 0.442 |
| Day 7# | 1.4 (2.0) 171 | 5.7 (2.6) 168 | 1.5 (2.0) 173 | 5.4 (2.7) 171 | -0.32 (-0.78, 0.15) | 0.184 | -0.21 (-0.59, 0.17) | 0.270 | -0.28 (-0.68, 0.13) | 0.180 |
| Overall (Days 1-7) | 3.4 (2.9) 1126 | 3.8 (3.2) 1105 | 3.5 (2.8) 1154 | 3.5 (3.1) 1135 | -0.26 (-0.66, 0.14) | 0.203 | -0.19† (-0.55, 0.16) | 0.283† | -0.22 (-0.57, 0.13) | 0.221 |
| Week 4 | 1.2 (2.0) 173 | 5.9 (2.9) 170 | 1.2 (2.1) 177 | 5.7 (2.8) 174 | -0.22 (-0.80, 0.36) | 0.461 | -0.08 (-0.54, 0.39) | 0.748 | -0.19 (-0.63, 0.25) | 0.403 |

*/** Between-group difference in mean change scores (colchicine – naproxen) by linear mixed model * unadjusted for baseline covariates ** adjusted for age, gender and baseline pain score (autoregressive (1st order) residual covariance structure was assumed for the model of daily differences).

*** By MI (multiple imputation via chained equations) adjusted for baseline pain, age and gender plus previous gout, age at first episode, single or multisite location, EQ5D (health dimensions), GP-Practice index of multiple deprivation [fixed effects] and GP-Practice site [random effect].

Summary is inclusive of minimum data collection (for scores at day 7).

† Primary endpoint.

Standardized mean difference (effect size) based on adjusted** evaluation i.e. absolute mean difference relative to overall baseline SD of 2.1: 0.03 (day 1); 0.23 (day 2); 0.09 (day 3) 0.06 (day 4); 0.07 (days 5 and 6); 0.10 (day 7); 0.09 (overall); 0.04 (week 4).

Secondary outcome measures

Table 2a: Daily medication use within the first week of follow up – complete case data

| | Day1 | | Day2 | | Day3 | | Day4 | | Day5 | | Day6 | | Day7 | |
|------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------|----------------|---------------|----------------|---------------|
| | NP (n=160) | CC (n=164) | NP (n=161) | CC (n=164) | NP (n=163) | CC (n=166) | NP (n=160) | CC (n=168) | NP (n=160) | CC (n=162) | NP (n=158) | CC (n=162) | NP (n=160) | CC (n=160) |
| Naproxen | 155 (96.9%) | 0 (0.0%) | 157 (97.5%) | 0 (0.0%) | 157 (96.3%) | 0 (0.0%) | 147 (91.9%) | 1 (0.6%) | 145 (90.6%) | 3 (1.9%) | 137 (86.7%) | 7 (4.3%) | 136 (85.0%) | 7 (4.4%) |
| Colchicine | 0 (0.0%) | 159 (97.0%) | 1 (0.6%) | 160 (97.6%) | 2 (1.2%) | 157 (94.6%) | 4 (2.5%) | 143 (85.1%) | 4 (2.5%) | 67 (41.4%) | 3 (1.9%) | 47 (29.0%) | 4 (2.5%) | 44 (27.5%) |
| Paracetamol | 15 (9.4%) | 25 (15.2%) | 13 (8.1%) | 19 (11.6%) | 10 (6.1%) | 16 (9.6%) | 10 (6.3%) | 13 (7.7%) | 10 (6.3%) | 18 (11.1%) | 10 (6.3%) | 11 (6.8%) | 8 (5.0%) | 14 (8.8%) |
| Tramadol | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) |
| Codeine | 4 (2.5%) | 19 (11.6%) | 3 (1.9%) | 16 (9.8%) | 5 (3.1%) | 12 (7.2%) | 3 (1.9%) | 8 (4.8%) | 5 (3.1%) | 8 (4.9%) | 4 (2.5%) | 7 (4.3%) | 2 (1.3%) | 10 (6.3%) |
| Ibuprofen | 9 (5.6%) | 15 (9.1%) | 5 (3.1%) | 11 (6.7%) | 5 (3.1%) | 10 (6.0%) | 4 (2.5%) | 9 (5.4%) | 5 (3.1%) | 10 (6.2%) | 5 (3.2%) | 9 (5.6%) | 6 (3.8%) | 10 (6.3%) |
| Diclofenac | 1 (0.6%) | 1 (0.6%) | 0 (0.0%) | 2 (1.2%) | 0 (0.0%) | 3 (1.8%) | 0 (0.0%) | 3 (1.8%) | 0 (0.0%) | 4 (2.5%) | 0 (0.0%) | 3 (1.9%) | 1 (0.6%) | 3 (1.9%) |
| Indomethacin | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Prednisolone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 2 (1.3%) | 1 (0.6%) | 2 (1.3%) | 3 (1.3%) |
| Any 'other' analgesia* | 20 (12.5%) | 42 (25.6%) | 17 (10.6%) | 32 (19.5%) | 16 (9.8%) | 26 (15.7%) | 14 (8.8%) | 20 (11.9%) | 16 (10.0%) | 25 (15.4%) | 15 (9.5%) | 17 (10.5%) | 11 (6.9%) | 20 (12.5%) |
| Any 'other' NSAIDS** | 10 (6.3%) | 16 (9.8%) | 5 (3.1%) | 13 (7.9%) | 5 (3.1%) | 13 (7.8%) | 4 (2.5%) | 11 (6.5%) | 5 (3.1%) | 14 (8.6%) | 5 (3.2%) | 12 (7.4%) | 6 (3.8%) | 13 (8.1%) |
| Any 'other' medication*** | 28 (17.5%) | 52 (31.7%) | 21 (13.0%) | 40 (24.4%) | 20 (12.3%) | 35 (21.1%) | 18 (11.3%) | 30 (17.9%) | 20 (12.5%) | 37 (22.8%) | 20 (12.7%) | 28 (17.3%) | 16 (10.0%) | 29 (18.1%) |

NP = Naproxen; CC = Colchicine

* Paracetamol or codeine or tramadol

** Ibuprofen or diclofenac or indomethacin

*** Paracetamol or codeine or tramadol or ibuprofen or diclofenac or indomethacin

Table 2b: Medication use over the first week (diary days 1-7) and between weeks 2-4 (week 4 follow up).

| | Days 1-7 | | | | Weeks 2-4 | | | |
|--------------------------|--------------------|----------------------|---|------------------------------|--------------------|----------------------|---|------------------------------|
| | Naproxen n (%)# | Colchicine n (%)# | OR (95% CI) [P-value] Complete-case# | [P-value] Imputed## | Naproxen n (%)# | Colchicine n (%)# | OR (95% CI) [P-value] Complete-case# | [P-value] Imputed## |
| Naproxen | 148 (99.3%) | 6 (4.2%) | n/a | n/a | 69 (51.5%) | 26 (16.9%) | n/a | n/a |
| Colchicine | 6 (4.0%) | 142 (98.6%) | n/a | n/a | 7 (5.2%) | 52 (33.8%) | n/a | n/a |
| Paracetamol | 20 (13.4%) | 34 (23.6%) | 2.09 (1.11, 3.93) [0.022] | 1.91 (1.05, 3.51) [0.035] | 10 (7.5%) | 11 (7.1%) | 1.12 (0.45, 2.82) [0.808] | 1.03 (0.42, 2.51) [0.957] |
| Ibuprofen | 16 (10.7%) | 20 (13.9%) | 1.54 (0.72, 3.29) [0.267] | 1.58 (0.80, 3.12) [0.191] | 12 (9.0%) | 27 (17.5%) | 2.34 (1.11, 4.94) [0.026] | 1.92 (0.96, 3.83) [0.065] |
| Diclofenac | 2 (1.3%) | 4 (2.8%) | - | - | 4 (3.0%) | 6 (3.9%) | - | - |
| Indomethacin | 1 (0.7%) | 0 (0.0%) | - | - | 2 (1.5%) | 5 (3.2%) | - | - |
| Tramadol | 1 (0.7%) | 0 (0.0%) | - | - | 1 (0.7%) | 2 (1.3%) | - | - |
| Codeine | 7 (4.7%) | 21 (14.6%) | 3.62 (1.47, 8.93) [0.005] | 3.20 (1.35, 7.57) [0.008] | 12 (9.0%) | 8 (5.2%) | 0.60 (0.22, 1.65) [0.322] | 0.66 (0.26, 1.66) [0.379] |
| Prednisolone | 3 (2.0%) | 2 (1.4%) | - | - | 2 (1.5%) | 1 (0.6%) | - | - |
| 'Other' analgesia* | 26 (17.4%) | 49 (34.0%) | 2.58 (1.46, 4.56) [0.001] | 2.54 (1.48, 4.36) [0.001] | 22 (16.4%) | 19 (12.3%) | 0.83 (0.41, 1.68) [0.606] | 0.77 (0.40, 1.48) [0.426] |
| 'Other' NSAIDS** | 17 (11.4%) | 23 (16.0%) | 1.68 (0.81, 3.47) [0.163] | 1.64 (0.84, 3.22) [0.147] | 18 (13.4%) | 37 (24.0%) | 2.21 (1.17, 4.18) [0.014] | 1.87 (1.03, 3.38) [0.039] |
| 'Other' medication*** | 39 (26.2%) | 61 (42.4%) | 2.39 (1.40, 4.06) [0.001] | 2.25 (1.37, 3.70) [0.001] | 37 (27.6%) | 52 (33.8%) | 1.55 (0.91, 2.64) [0.105] | 1.32 (0.77, 2.27) [0.309] |

Complete response to medication questions: diary days 1-7 - 149 in naproxen group and 144 in colchicine group; week 4 - 134 in naproxen group and 154 in colchicine group.

Imputed dataset: 200 in naproxen group; 199 in colchicine group (full ITT analysis).

OR = Odds Ratio for colchicine relative to naproxen (adjusted for age, gender and baseline pain score): # analysis of complete-case data (days 1-7: n=288; 5 cases excluded due to missing baseline pain scores; week 4: n=283; 5 cases excluded due to missing baseline pain scores) ## analysis of imputed data (n=399). n/a: analysis not applicable (as it is an evaluation of compliance with allocated treatment). – Odds ratios not estimated due to small frequency counts.

* Paracetamol or codeine or tramadol.

** Ibuprofen or diclofenac or indomethacin.

*** Paracetamol or codeine or tramadol or ibuprofen or diclofenac or indomethacin.

Table 3a: Daily side effects within the first week of follow up – complete case data

| | Day1 | | Day2 | | Day3 | | Day4 | | Day5 | | Day6 | | Day7 | |
|---------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|----------------|
| | NP (n=160) | CC (n=164) | NP (n=161) | CC (n=164) | NP (n=163) | CC (n=166) | NP (n=160) | CC (n=168) | NP (n=160) | CC (n=162) | NP (n=158) | CC (n=162) | NP (n=172)* | CC (n=176)* |
| | NP | CC | NP | CC | NP | CC | NP | CC | NP | CC | NP | CC | NP | CC |
| Feeling sick | 17 (10.6%) | 15 (9.1%) | 11 (6.8%) | 16 (9.8%) | 7 (4.3%) | 17 (10.2%) | 6 (3.8%) | 11 (6.5%) | 6 (3.8%) | 6 (3.7%) | 2 (1.3%) | 6 (3.7%) | 3 (1.7%) | 5 (2.8%) |
| Being sick | 3 (1.9%) | 1 (0.6%) | 2 (1.2%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) |
| Felling/being sick | 19 (11.9%) | 16 (9.8%) | 12 (7.5%) | 17 (10.4%) | 7 (4.3%) | 18 (10.8%) | 6 (3.8%) | 11 (6.5%) | 6 (3.8%) | 6 (3.7%) | 2 (1.3%) | 7 (4.3%) | 3 (1.7%) | 5 (2.8%) |
| Indigestion | 10 (6.3%) | 13 (7.9%) | 11 (6.8%) | 11 (6.7%) | 11 (6.7%) | 14 (8.4%) | 9 (5.6%) | 11 (6.5%) | 5 (3.1%) | 7 (4.3%) | 6 (3.8%) | 6 (3.7%) | 4 (2.3%) | 6 (3.4%) |
| Stomach pain | 5 (3.1%) | 7 (4.3%) | 6 (3.7%) | 8 (4.9%) | 7 (4.3%) | 8 (4.8%) | 7 (4.4%) | 8 (4.8%) | 3 (1.9%) | 9 (5.6%) | 2 (1.3%) | 6 (3.7%) | 4 (2.3%) | 6 (3.4%) |
| Headache | 9 (5.6%) | 16 (9.8%) | 10 (6.2%) | 12 (7.3%) | 3 (1.8%) | 13 (7.8%) | 3 (1.9%) | 13 (7.7%) | 5 (3.1%) | 10 (6.2%) | 4 (2.5%) | 5 (3.1%) | 3 (1.7%) | 4 (2.3%) |
| Constipation | 8 (5.0%) | 1 (0.6%) | 15 (9.3%) | 2 (1.2%) | 16 (9.8%) | 5 (3.0%) | 8 (5.0%) | 4 (2.4%) | 6 (3.8%) | 3 (1.9%) | 6 (3.8%) | 2 (1.2%) | 5 (2.9%) | 3 (1.7%) |
| Diarrhoea | 7 (4.4%) | 20 (12.2%) | 7 (4.3%) | 28 (17.1%) | 12 (7.4%) | 40 (24.1%) | 10 (6.3%) | 52 (31.0%) | 3 (1.9%) | 34 (21.0%) | 7 (4.4%) | 18 (11.1%) | 5 (2.9%) | 13 (7.4%) |
| Skin | 2 (1.3%) | 3 (1.8%) | 2 (1.2%) | 2 (1.2%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 2 (1.1%) |
| Any side effect(s)# | 54 (33.8%) | 54 (32.9%) | 50 (31.1%) | 64 (39.0%) | 52 (31.9%) | 76 (45.8%) | 45 (28.1%) | 78 (46.4%) | 38 (23.8%) | 52 (32.1%) | 35 (22.2%) | 36 (22.2%) | 26 (15.1%) | 32 (18.2%) |

NP = Naproxen; CC = Colchicine

* These are higher denominator numbers since questions on side-effects on day 7 were included in minimal data collection retrieval.

Table 3b: Side effects over the first week and between weeks 2-4 (week 4 follow up).

| | Days 1-7 | | | | Weeks 2-4 | | | |
|-----------------------------------|--------------------|---------------------|---|-------------------------------|--------------------|----------------------|---|------------------------------|
| | Naproxen n (%)# | Colchicine n (%) | OR (95% CI) [P-value] Complete-case# | [P-value] Imputed## | Naproxen n (%)# | Colchicine n (%)# | OR (95% CI) [P-value] Complete-case# | [P-value] Imputed## |
| Nausea (feeling/being sick) | 21 (14.0%) | 30 (20.5%) | 1.82 (0.96, 3.46) [0.066] | 1.28 (0.71, 2.30) [0.415] | 7 (5.2%) | 5 (3.2%) | 0.51 (0.14, 1.83) [0.304] | 0.59 (0.19, 1.90) [0.377] |
| Indigestion | 20 (13.3%) | 20 (13.7%) | 0.89 (0.48, 1.90) [0.952] | 1.09 (0.58, 2.04) [0.786] | 13 (9.7%) | 8 (5.2%) | 0.44 (0.17, 1.15) [0.094] | 0.59 (0.24, 1.45) [0.251] |
| Stomach pain | 16 (10.7%) | 16 (11.0%) | 1.07 (0.51, 2.25) [0.864] | 0.83 (0.40, 1.71) [0.610] | 4 (3.0%) | 8 (5.2%) | 1.57 (0.44, 5.53) [0.487] | 1.32 (0.43, 4.09) [0.626] |
| Headache | 16 (10.7%) | 30 (20.5%) | 2.38 (1.21, 4.68) [0.012] | 1.92 (1.03, 3.55) [0.039] | 4 (3.0%) | 4 (2.6%) | 0.92 (0.22, 3.86) [0.907] | 0.80 (0.21, 3.10) [0.750] |
| Constipation | 29 (19.3%) | 7 (4.8%) | 0.20 (0.08, 0.48) [<0.001] | 0.24 (0.11, 0.54) [<0.001] | 9 (6.7%) | 6 (3.9%) | 0.49 (0.16, 1.54) [0.222] | 0.57 (0.21, 1.55) [0.267] |
| Diarrhoea | 30 (20.0%) | 67 (45.9%) | 3.54 (2.10, 5.99) [<0.001] | 3.31 (2.01, 5.44) [<0.001] | 5 (3.7%) | 10 (6.5%) | 1.75 (0.58, 5.26) [0.323] | 1.59 (0.54, 4.66) [0.397] |
| Skin problems | 3 (2.0%) | 3 (2.1%) | 1.13 (0.22, 5.83) [0.881] | 1.06 (0.21, 5.39) [0.947] | 3 (2.2%) | 3 (1.9%) | 0.98 (0.19, 5.09) [0.981] | 0.97 (0.19, 5.03) [0.971] |
| 'Any side effect(s)* | 91 (60.7%) | 101 (69.2%) | 1.49 (0.92, 2.43) [0.106] | 1.60 (1.03, 2.49) [0.038] | 37 (27.6%) | 28 (18.2%) | 0.58 (0.33, 1.03) [0.064] | 0.71 (0.41, 1.23) [0.227] |

Complete response to side-effect questions: diary days 1-7 - 150 in naproxen group and 146 in colchicine group; week 4 - 134 in naproxen group and 154 in colchicine group.

Imputed dataset: 200 in naproxen group; 199 in colchicine group (full ITT analysis).

OR = Odds Ratio for colchicine relative to naproxen (adjusted for age, gender and baseline pain score): # analysis of complete data (days 1-7: n=291; 5 cases excluded due to missing baseline pain scores; week 4: n=283; 5 cases excluded due to missing baseline pain scores) ## analysis of imputed data (n=399). n/a: analysis not applicable (as it is an evaluation of compliance with allocated treatment). – Odds ratios not estimated due to small frequency counts.

* Includes the side effects listed and 'other' (nominated free text) side effects.

Table 4: Comparison of secondary outcome measures at day 7 and week 4 follow up.

| | Naproxen | Colchicine | OR (95% CI) [P-value]* | OR (95% CI) [P-value]** |
|---|-------------|-------------|---------------------------|----------------------------|
| Global change, n (%) | | | | |
| 7 days | | | | |
| Completely better now | 52 (32.5%) | 43 (28.3%) | 1.10# | 1.14# |
| Much better now | 62 (38.8%) | 67 (44.1%) | (0.73, 1.67) | (0.75, 1.69) |
| Somewhat better now | 35 (21.9%) | 27 (17.8%) | [P=0.638] | [P=0.528] |
| About the same | 9 (5.6%) | 13 (8.6%) | | |
| Somewhat worse now | 2 (1.3%) | 0 (0.0%) | | |
| Much worse now | 0 (0.0%) | 2 (1.3%) | | |
| 4 weeks, n (%) | | | | |
| Completely better now | 70 (40.5%) | 81 (45.8%) | 0.90# | 0.85# |
| Much better now | 70 (40.5%) | 62 (35.0%) | (0.60, 1.33) | (0.57, 1.27) |
| Somewhat better now | 19 (11.0%) | 20 (11.3%) | [P=0.591] | [P=0.422] |
| About the same | 11 (6.4%) | 12 (6.8%) | | |
| Somewhat worse now | 2 (1.2%) | 2 (1.1%) | | |
| Much worse now | 1 (0.6%) | 0 (0.0%) | | |
| Global change - dichotomised, n (%) | | | | |
| 7 days | | | | |
| Completely/much better now | 114 (71.3%) | 110 (72.4%) | 1.11 | 1.03 |
| Not completely/much better | 46 (28.8%) | 42 (27.6%) | (0.67, 1.84) | (0.62, 1.70) |
| | | | [P=0.688] | [P=0.909] |
| 4 weeks, n (%) | | | | |
| Completely/much better now | 140 (80.9%) | 143 (80.8%) | 0.88 | 0.96 |
| Not completely/much better | 33 (19.1%) | 34 (19.2%) | (0.51, 1.52) | (0.56, 1.64) |
| | | | [P=0.641] | [P=0.872] |
| Another attack of gout within 4 weeks follow up, n (%) | 40 (30.1%) | 54 (35.1%) | 1.28 | 1.24 |
| | | | (0.78, 2.13) | (0.77, 1.99) |
| | | | [P=0.333] | [P=0.370] |
| Further contact with health professional [§] during 4 weeks follow up, n (%) | 30 (22.6%) | 41 (26.6%) | 1.43 | 1.39 |
| | | | (0.82, 2.51) | (0.82, 2.34) |
| | | | [P=0.213] | [P=0.217] |
| Re-consulted GP for gout problem within 4 weeks follow up, n (%) | 26 (19.4%) | 39 (25.3%) | 1.69 | 1.56 |
| | | | (0.93, 3.05) | (0.89, 2.72) |
| | | | [P=0.083] | [P=0.118] |
| <i>Number of times</i> | | | | |
| 1 | 14 (58.3%) | 27 (69.2%) | - | - |
| 2 | 8 (33.3%) | 10 (25.6%) | | |
| 3 | 2 (8.3%) | 2 (5.1%) | | |
| Consulted Practice Nurse for gout problem within 4 weeks follow up, n (%) | 7 (5.3%) | 10 (6.6%) | 1.31 | 1.23 |
| | | | (0.47, 3.64) | (0.45, 3.32) |
| | | | [P=0.609] | [P=0.691] |
| <i>Number of times</i> | | | | |

| | | | | |
|--|-----------|-----------|-----------------------------------|-----------------------------------|
| 1 | 5 (71.4%) | 9 (90.0%) | - | - |
| 2 | 1 (14.3%) | 1 (10.0%) | | |
| 3 | 1 (14.3%) | 0 (0.0%) | | |
| Consulted emergency GP for gout problem within 4 weeks follow up, n (%) | 6 (4.5%) | 6 (3.9%) | 0.84 (0.26, 2.68) [P=0.765] | 0.87 (0.30, 2.57) [P=0.805] |
| Attended Accident & Emergency for gout problem within 4 weeks follow up, n (%) | 1 (0.8%) | 1 (0.7%) | - | 1.23 (0.07, 21.5) [P=0.885] |
| Taken time off work because of gout within 4 weeks follow up, n (%) | 11 (8.6%) | 8 (5.3%) | 0.61 (0.22, 1.64) [P=0.325] | 0.76 (0.31, 1.91) [P=0.565] |
| <i>No. of days, median (IQR)</i> | 4 (2, 12) | 3 (3, 17) | - | - |

Odds ratios for colchicine relative to naproxen.

* Analysis of complete-case data (adjusted for baseline pain, age and gender).

** Analysis through multiple imputation via chained equations with logistic (binary/ordinal) regression model (adjusted for age, sex and baseline pain) based on full-ITT on 50 imputations.

Based on ordinal logistic regression with four categories after pooling 'about the same', 'somewhat worse now' and 'much worse now' because of low frequencies.

\$ Health professional: GP, Practice nurse, emergency GP and/or A&E.

Table 5: Mean (SD) resource use, costs and outcomes per participant over 4 weeks follow up

| | Naproxen (n=200) | Colchicine (n=199) | Difference (CI) |
|------------------------------|------------------|--------------------|------------------------|
| RESOURCE USE | | | |
| GP visits | 0.19 (0.34) | 0.27 (0.40) | -0.08 (-0.15, 0.0002) |
| Nurse visits | 0.05 (0.19) | 0.07 (0.22) | -0.02 (-0.06, 0.03) |
| Emergency GP visits | 0.05 (0.17) | 0.04 (0.18) | 0.01 (-0.03, 0.04) |
| A and E visits | 0.006 (0.07) | 0.007 (0.07) | -0.001 (-0.02, 0.01) |
| COSTS (£) | | | |
| Drug costs | 0.83 (2.00) | 1.20 (2.22) | -0.37 (-0.78, 0.02) |
| GP costs | 6.44 (11.16) | 8.80 (13.16) | -2.36 (-4.74, 0.12) |
| Nurse costs | 0.66 (2.26) | 0.86 (2.71) | -0.20 (-0.68, 0.31) |
| Emergency GP costs | 2.45 (8.54) | 2.14 (8.68) | 0.31 (-1.28, 2.04) |
| A and E costs | 0.41 (5.10) | 0.48 (5.15) | -0.07 (-1.21, 0.95) |
| Intervention cost | 6.77 (4.56) | 9.83 (6.32) | -3.06 (-4.17, -2.08) |
| Total cost | 17.57 (20.38) | 23.31 (23.46) | -5.74 (-10.03, -1.64) |
| HEALTH OUTCOMES | | | |
| Baseline EQ-5D | 0.665 (0.21) | 0.663 (0.22) | 0.002 (-0.04, 0.04) |
| Day 7 EQ-5D | 0.882 (0.13) | 0.873 (0.14) | 0.009 (-0.02, 0.03) |
| Week 4 EQ-5D | 0.900 (0.11) | 0.894 (0.15) | 0.006 (-0.02, 0.03) |
| QALYs | 0.0663 (0.008) | 0.0657 (0.01) | 0.0006 (-0.001, 0.002) |
| Adjusted QALYs ⁺ | 0.0662 | 0.0658 | 0.0004 |
| WORK RELATED OUTCOMES | | | |
| Time off work (days) | 0.40 (2.47) | 0.35 (2.51) | 0.05 (-0.42, 0.53) |
| Productivity cost (£) | 32.16 (190.40) | 28.44(207.42) | 3.72 (-34.27, 40.73) |

⁺Adjusted for baseline EQ-5D

Table 6: Incremental cost-effectiveness over 4 weeks

| | | Interpretation |
|----------------------|---------|--|
| *Difference in cost | -£ 5.74 | <i>Naproxen less costly and more effective than colchicine. Naproxen is therefore a dominant and cost-effective intervention</i> |
| *Difference in QALYs | 0.0004 | |
| ICER | N/A | |

*Naproxen

–

Colchicine

Adverse events

Table 7: Serious Adverse Event report table

| | Outcome | Date of onset Time of onset | Suspect drug | Daily dose, route & formulation of IMP | Dates of treatment &/or treatment duration | Causality to IMP | Expectedness of event | Comments |
|--|-----------|--------------------------------|--------------|---|--|------------------|-----------------------|----------|
| Osteomyelitis | Recovered | 26/02/2015 | Colchicine | 500mcg (one tablet) every eight hours for four days. | 26/02/2015 - 28/02/2015 2 days | No | Not related | SAE |
| Non Cardiac chest pain | Recovered | 05/07/2015 | Naproxen | Single initial dose of 750mg (three tablets) followed by 250mg (one tablet) every eight hours up to seven days. | 23/06/2015 - 30/06/2015 7 days | No | Not related | SAE |
| Complication of TAVI procedure – readmitted with hospital acquired Pneumonia | Recovered | 03/03/2015 | Naproxen | Single initial dose of 750mg (three tablets) followed by 250mg (one tablet) every eight hours up to seven days. | 03/03/2015 - 07/03/2015 5 days | No | Not related | SAE |