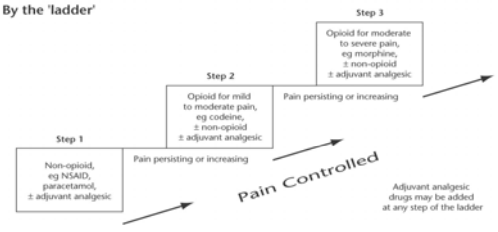
PRC

TVT Study: methodological approach

Acknowledgements

- Barry Laird,Stein Kaasa, Augusto Caraceni, Geoff Hanks & Colette Reid
- Prof Gordon Murray, Mr Robert Lee –U of E
- Dr John Forbes

1. **By the clock**
   Cancer pain is continuous - use regular dose intervals (**not** prn)
2. **By the 'ladder'**



The ladder has no "top rung" as there is no maximum dose for strong opioids. If pain is still a problem with high doses of morphine (eg >300mg/24 hours), or severe side effects, reconsider the cause of pain, eg bone pain may be better helped by NSAIDs, and/or seek specialist advice.

3. **By the mouth**
   The oral route is preferred for all steps of the analgesic 'ladder'.

TVT Study: An international, multicentre, open randomised parallel group trial comparing a two step approach for cancer pain relief with the standard three step approach of the WHO analgesic ladder in patients with cancer pain requiring step 2 analgesia

Supporting Evidence

Pilot Study (Reid&Hanks)
- 2 step vs 3 step WHO (Oxycodone)
- "worst pain" and "average pain" lower in 2 step approach ($p<0.05$)
- Pain control achieved faster in 2 step approach (Mean 7.1 days vs 10.8 days)

Other work
- 50% of patients needed to move from step 2 to step 3 after 2weeks due to lack of analgesic efficacy
  (De Conno et al. JPSM 1991)
- Use of strong opioids supported in opioid-naïve patients
  (Vielvoye-Kerkmeer et al JPSM 2000
  Mercadante S et al JPSM 2006)

Trial Objectives

- **Primary**:Can a two step approach achieve stable pain control more quickly but without increased side-effects compared to the standard 3 step approach?
- **Secondary**:Does a 2 step approach have improved health economics compared to the standard 3 step approach?

Trial Timeline

2007 – Pilot study
2010 - presented at EPCRC RN, Glasgow
2010 – international peer review
2011 – protocol finalised
2011-Start recruiting November

Key points

- Trial Design
- Entry criteria
- Choice of opioids
- Measure of Efficacy
- Measure of Side-effects
- Health Economics

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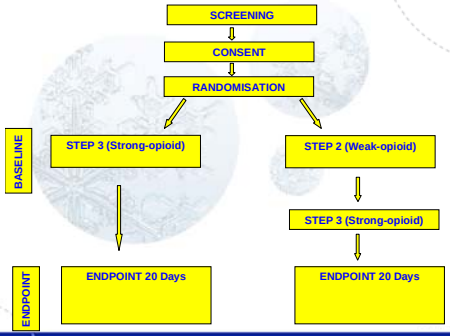
Trial Design



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Inclusion Criteria

- ≥18 years of age.
- Patient has a cancer diagnosis (based on radiological, histological, cytological, or operative evidence). Those with haematological malignancies are eligible.
- Cancer related pain – which in the opinion of the clinician is caused by the presence of tumour or metastases.
- Average pain score ≥ 4, on a numerical rating scale from 0-10, requiring step 2 analgesia (weak opioid).
- Patient is able to comply with trial procedures.

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Exclusion Criteria

- Received chemotherapy or radiotherapy in the preceding six weeks that is likely to affect pain during the trial.
- Expected to have a change in anti-cancer therapy during the period of the trial that is likely to alter pain during the trial.
- Pain due to surgery in the preceding 4 weeks.
- Life expectancy less than two months (based on clinical impression)
- Patients with psychotic disorders or cognitive impairment.
- Patients who have received regular doses (scheduled doses – NOT as required dosing) of weak or strong opioids in the preceding two weeks.
- Patients using immediate release opioids > 2 doses/24 hours, in the previous 24 hours.

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Trial Arms

- **Two step arm**: Participants will commence an approved strong opioid and this will be titrated as per local practice.
- **Three step arm**: Participants will commence an approved weak opioid. If pain control is not achieved on this (average pain≥ 4) participants will commence a strong opioid.

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Choice of opioids (oral only)

Weak Opioids
Codeine 240mg
Tramadol 400mg

Strong Opioids
Morphine
Oxycodone

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Baseline/Endpoint Assessments

- Worst/Average pain in last 24 hours
- Brief Pain Inventory
- NCCN Distress Thermometer
- Analgesic Use (previous, current)
- Non-analgesic Medication (previous, current)
- Opioid Toxicity and Side-effects Questionnaire
- SF12

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During the trial....

Every day
Average pain, worst pain, analgesic use
Every 2nd Day
Non-analgesic medication, side-effects
Day 10, 20
NCCN, SF-12, BPI

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Measures of Efficacy

Primary:

Time to achieving stable pain control: defined as the first day of three consecutive days with average pain score ≤ 3

Secondary:

Mean of daily average and worst pain scores

% of days with AP and WP≥ 6

BPI and NCCN baseline, day 10 and day 20.

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Measuring Side-effects

Primary

A score of 1 or more for each symptom (occurrence)

Secondary

Frequency of reporting a symptom score of 1 or more

Worst of alternate daily symptom scores

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Economic Analysis

- KEY COMPONENT!!
- Endpoints will include resource use and cost (NHS perspective)
- Assessed using SF-12 health survey(SF-6D)
- ITT cost-effectiveness within trial
- Net benefit cost effective analysis

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What now..

- Various regulatory steps
- MHRA approved
- Multicentre ethical approval submitted
- Start recruiting Scotland November 2011
- Other centres to follow as soon as any teething problems with database are resolved

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Summary

Key study in PRC portfolio

Unique challenges re design

……challenges to come in recruitment

Barry.Laird@ed.ac.ukl

Marie.Fallon@ed.ac.ukl

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Centres


•Edinburgh, M Fallon; Glasgow, B Laird; Bristol, C Reid, K Forbes; Leeds, M Bennett


•Trondheim, S Kaasa P Klepstad


•Seville, J Boceta (M Nabal)


•Cologne, S Simon (R Voltz, J Gartner)


•Milan, G Apolone, O Corli


•Flinders, D Currow; 3 other centres


•Makerere, M Leng