European Pharmacogenetics of Anticoagulation Therapy (EU-PACT) Trial

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What is Warfarin ?

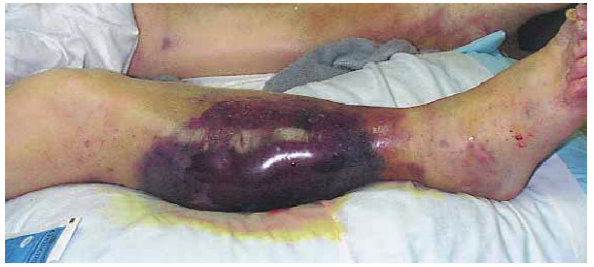
- Anticoagulant of choice in the UK
- Coumarin anticoagulant prescribed for:
    - Venuous thrombosis
    - Pulmonary embolism
    - Chronic atrial fibrillation
    - Prosthetic heart valves
- 1% (600,000) of entire UK population[1]
- 6% (154,000) of those >80 years old[1]

Notes

1. Source: IMS Health

Efficacy of Warfarin

- Efficacy well demonstrated BUT depends on maintaining anticoagulation within clinically acceptable 'therapeutic range' – not always easy
- Therapeutic range measured in terms of INR (International Normalised Ratio). Usually 2-3.
- Very narrow 'therapeutic index': dose needed for therapeutic anticoagulation very close to dose leading to over-anticoagulation
- Large inter-individual variability in maintenance dose required to achieve therapeutic range: 0.5mg/day to over 10mg/day
- Most feared adverse event related to warfarin: major



Current treatment practice for warfarin

I. Days 1-3: Loading dose e.g. 10mg/5mg/5mg, or 5mg/5mg/5mg for elderly

II. Day 4 : INR taken. Dose adjustment with reference to INR, calculated using software e.g. RAID/DAWN

III. Stage II repeated regularly until stable anticoagulation achieved

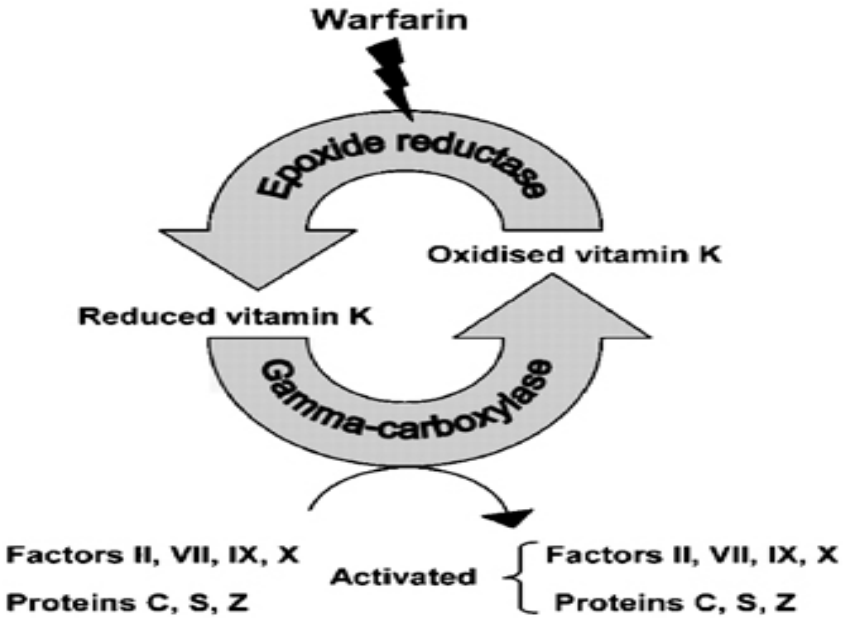
IV. Once stability achieved, INR measured occasionally

CYP2C9

- Genotype at SNPs in CYP2C9 gene found to have a dramatic effect on Warfain response in several studies
- Gene involved in metabolism of Warfarin
- Carriers of mutant-type allele at CYP2C9*2 and CYP2C9*3 SNPs found to have decreased clearance of Warfarin[1,2]
- CYP2C9*2 mutant-type allele = 17% reduction in required mean daily maintenance dose[3]
- CYP2C9*3 mutant-type allele = 37% reduction in required mean daily maintenance dose[3]
- Controlling INR within therapeutic range at commencement more difficult
- Increased risk of bleeding

1. Rettie AE et al. Pharmacogenetics 1994; 439-42
2. Haining RL et al. Biophys 1996; 333: 447-458
3. Sanderson s et al. Genet Med 2005; 7: 97-104

VKORC1



- Understandable that genes involved in Vit K cycle crucial in determination of warfarin response
- Several studies found association between SNPs in VKORC1 gene and dose requirements[1-4]

1. D'Andrea G et al. Blood 2005; 105: 645-649
2. Wadelius M et al. Pharmacogenomics J 2005; 5: 262-270
3. Rieder MJ et al. N Engl J Med 2005; 352: 2285-2293
4. Sconce EA et al. Blood 2005; 106: 2329-2333

Why do we need a RCT ?

- FDA recommendations (August 2007):

  "...dosage adjustments based on results of pharmacogenetic test'/INR determinations...lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1..."

- Science makes sense – how to implement in practice ?
- Need user-friendly solution: triggered significant research efforts in developing dosing algorithms
- Potential benefit of algorithms in terms of clinical utility/safety not yet adequately proven
- Need evidence from well-designed and adequately powered RCT

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Previous Trials

- Three previous RCTs[1-3] of warfarin pharmacogenetics, with conflicting results
- Only one[1] demonstrated statistically significant difference (time in INR range, time to stable dose, minor bleeds) but concerns over methodological rigour
- Studies generally small and potentially underpowered
- Need for larger, methodologically robust trials
- Significant research activity ongoing currently: EU-PACT, COAG, GIFT (and others...). Have had discussions/shared protocols

1.Caraco Y, Blotnick S, Muszkat M. CYP2C9 Genotype-guided Warfarin Prescribing Enhances the Efficacy and Safety of Anticoagulation: A Prospective Randomized Controlled Study. Clin Pharmacol Ther. Sep 12 2007
2.Anderson JL, Horne BD, Stevens SM, et al. Randomized Trial of Genotype-Guided Versus Standard Warfarin Dosing in Patients Initiating Oral Anticoagulation. Circulation. Nov 7 2007
3.Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clin

EU-PACT

- Funded by EU Seventh Framework Programme
- One project: three trials
- Trial for each of three different
- coumarin-derived anticoagulants:
  - Warfarin
  - Acenocoumarol
  - Phenprocoumon
- Underlying aim same: comparing genotype-to non-genotype-gui narin therapy

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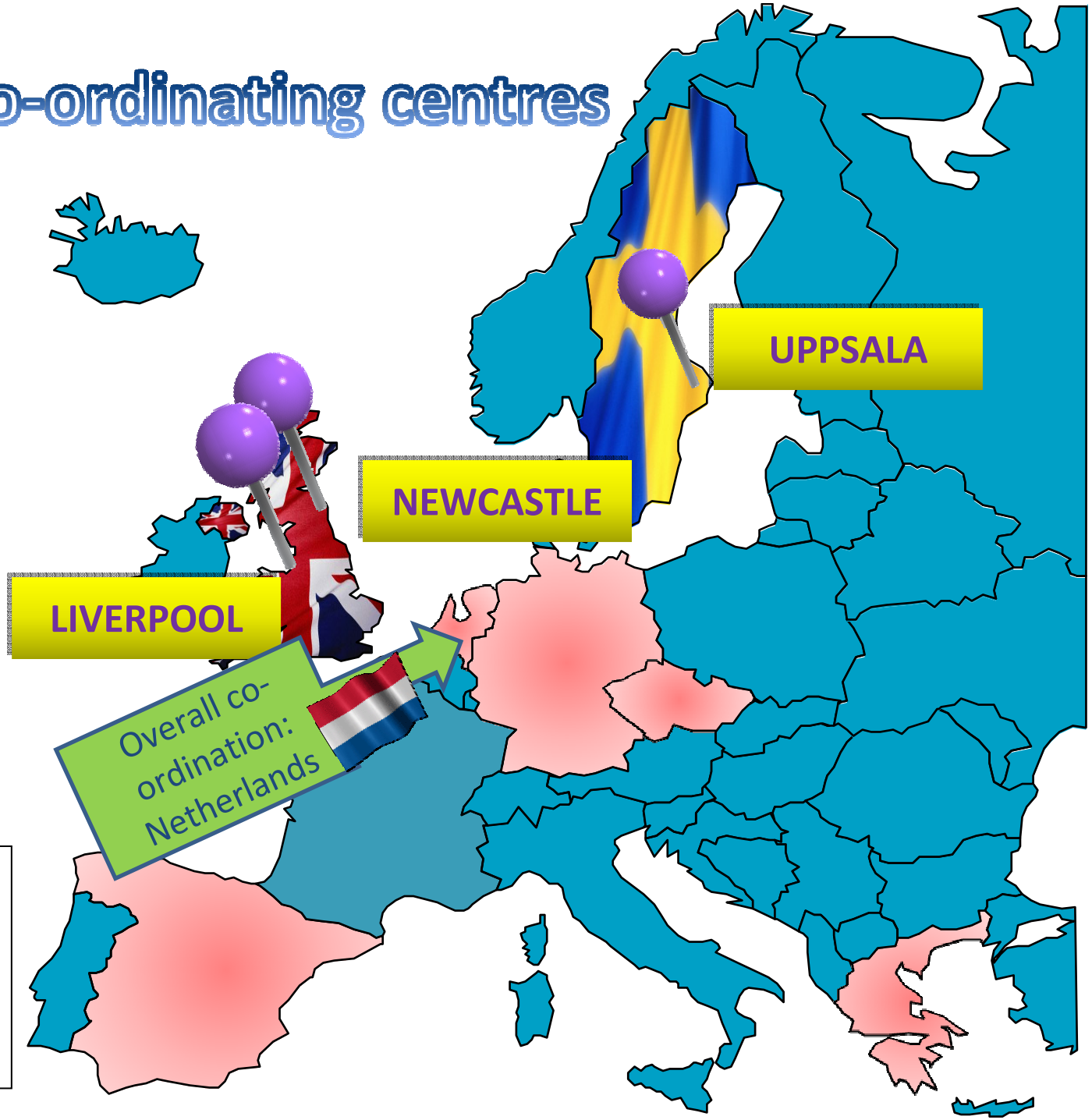
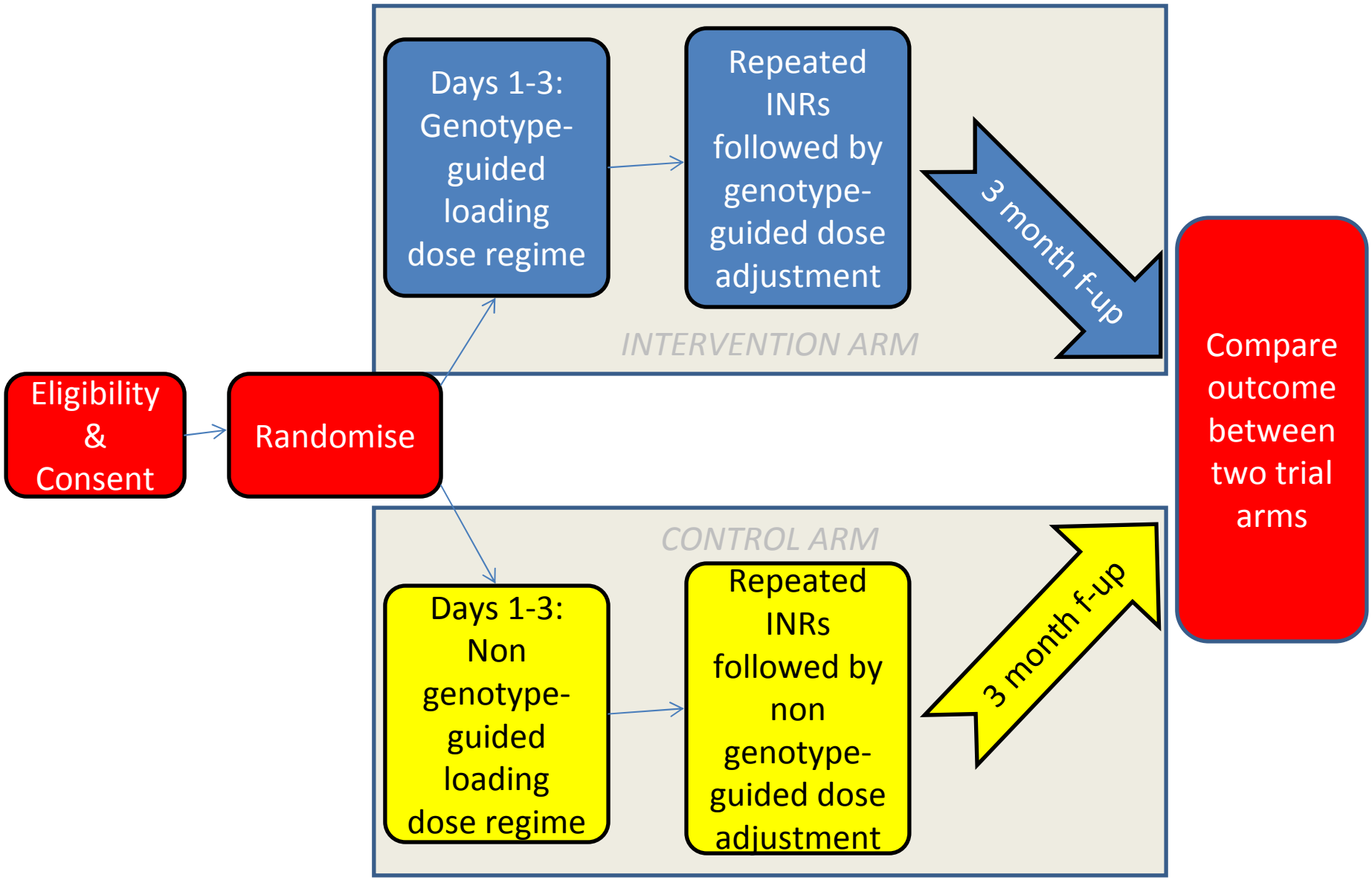
Warfarin Co-ordinating centres



Note

*Countries shaded **red** co-ordinate the acenocumarol and phenprocoumon trials*

Study Design



Genotype Guided Dosing

- Trial's **intervention**
- Needs to be feasible in **clinical practice:** computer- based algorithm
- Need **'best'** dosing algorithms developed to date: look to large international consortia:
  - **IWPC maintenance dose algorithm[1]** (Loading dose days 1-3)
  - **Lenzini et al. dose revision algorithm[2]** (Dose adjustments once INR available)

1.Estimation of the warfarin dose with clinical and pharmacogenetic data. International warfarin pharmacogenetics consortium. *N Engl J Med. (*2009) Feb 19; **360**(8):753-64.

2. **Integration of genetic, clinical and INR data to refine warfarin dosing.** P Lenzini, M Wadelius, S Kimmel, J L Anderson, A L Jorgensen et al. *Clinical Pharmacology & Therapeutics* (2010) **87** 5, 572–578.

The genotype-guided algorithms

LOADING DOSES (DAYS 1-3)

- IWPC maintenance dose algorithm:
  - Age
  - Height
  - Weight
  - CYP2C9 genotype
  - VKORC1 genotype
  - Amiodarone usage
- Adjusted with reference to pharmacokinetic parameters to provide loading doses days 1-3 on sliding scale

INR BASED DOSE ADJUSTMENTS

- Lenzini et al. dose revision algorithm
  - Age
  - Target INR
  - INR
  - Previous doses taken
  - CYP2C9 genotype
  - VKORC1 genotype
- Applied on days 4 and 5 of treatment to calculate required dose adjustment

- Revert to standard clinical practice for dose revisions day 6 onwards (i.e. Dose revision software in routine use e.g DAWN/RAID)

Genotyping Instrument

- Rapid **point of care** testing ('GENIE')
- Instrument developed specifically for EU-PACT project by UK company LGC
- Results available within **2 hours**
- Allows dose to be tailored according to genotype from day 1 (i.e. genotype guided loading doses)
- All three trials will use instrument
- Rigorous validation prior to implementation
- QC procedures throughout trial

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The control arm

- Possible choices:
  - **Clinical dosing algorithm** (e.g. as per IWPC paper[1])
  - **Standard clinical care**
- **Standard clinical care** chosen: in line with hypothesis of whether genotype guided dosing is sufficiently *superior to current clinical practice*
- Loading doses days 1-3:
  - **10mg/5mg/5mg if ≤ 75 years of age**
  - **5mg/5mg/5mg if >75 years of age**
- Dose adjustments days 4 onwards:
  - According to **dose revision software in *routine* use** (e.g. 'RAID[2]', 'DAWN[3]')

1.Estimation of the warfarin dose with clinical and pharmacogenetic data. International warfarin pharmacogenetics consortium. *N Engl J Med. (*2009) Feb 19; **360**(8):753-64.

2. www.hirumed.co.uk

3. www.4s-dawn.com

Sample size

- With reference to primary outcome
- Parameter estimates obtained from large observational cohorts of warfarin patients in Liverpool, UK
- **5% improvement in time in therapeutic range**, with **80% power** requires **442** patients in **each arm**(total=884)
- Assuming **10% dropout rate**, target sample size = **985**

Challenges

- Data monitoring
  - Vital component of trial
  - Responsibility - locally or centrally ?
  - Local CTUs or external ?
  - Monitoring plan developed collaboratively
- ADR reporting
  - All AEs or only ADRs
  - As risk/benefit profile well established, decided to report ADRs only
  - SOPs produced regarding identifying and recording ADRs

Further Challenges

- CTIMP classification
  - Differed between countries
  - UK determined that trial was ***not*** CTIMP
  - Resulted in persuading other centres was not CTIMP
- Costings/Recruitment staff
  - Some centres allow PhD students to recruit patients
  - Minimise cost implications
  - Not possible in some centres due to governance/clinical structure
- Weekend visits
  - Some centres not customary to expect staff to work on weekend
  - Tailored follow-up visit schedule according to day warfarin commenced

Acknowledgements

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- The entire EU-PACT team (please visit www.eupact.org for further information)

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