Stepwise Improvement in prognosis in ALL
-Landmark UK Trials 1972 – 1999

Simple therapy
Frequent breaks

Simple therapy
Greater intensity

Intensified therapy for all patients

Risk directed therapy
Based on age and WCC and early response
## Stepwise Improvement in prognosis in ALL
### - Landmark UK Trials 1972 – 1999

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment Description</th>
</tr>
</thead>
</table>
| 1972- UKALL II | Simple therapy  
Frequent breaks                                   |
| 1984 UKALL VIII | Simple therapy  
Greater intensity                                   |
| 1990 UKALL X D   | Intensified therapy  
for all patients                                    |
| 1999 ALL 97/99   | Risk directed therapy  
Based on age and WCC and early response                |

### TREATMENT INTENSITY AND OVER-TREATMENT

- **5yr OS**
- **4yr EFS**
US CCG Risk Stratification as used in UKALL 99

**Standard Risk**
- Age < 10
- WCC < 50
- Day 15 RER

**Intermediate Risk**
- Age ≥10
- WCC ≥ 50
- Day 8 RER

**High Risk**
- Ph+ve
- Hypodiploid <44
- t(4;11)
- iAMP 21
- Day 8/15 SER

- Regimen A: 62%
- Regimen B: 22%
- Regimen C: 16%
### ALL 99 and 2003 treatment regimes

**Regimen A = 3 drug (Vincristine, Asparaginase, Steroid) induction, 2 x Delayed Intensification**

<table>
<thead>
<tr>
<th>Induction</th>
<th>CNS + IM I</th>
<th>DI I</th>
<th>IMII</th>
<th>DI II</th>
<th>CT</th>
</tr>
</thead>
</table>

- girls = 105 weeks
- boys = 156 weeks
ALL 99 and 2003 treatment regimes

Regimen A = 3 drug (Vincristine, Asparaginase, Steroid) induction, 2 x Delayed Intensification

Induction | CNS + IM I | DI I | IMII | DI II | CT
---|---|---|---|---|---

- 2 x DI

Regimen B = 4 drug (Vinc Asp, Steroid, Daun) induction, Prot IB, 2 x DI

Induction | BFM consol + CNS. | IMI | DI I | IMII | DI II | CT
---|---|---|---|---|---|---

- 2 x DI

Girls = 105 weeks
Boys = 156 weeks
ALL 99 and 2003 treatment regimes

Regimen A = 3 drug (Vincristine, Asparaginase, Steroid) induction, 2 x Delayed Intensification

Regimen B = 4 drug (Vinc Asp, Steroid, Daun) induction, Prot IB, 2 x DI

Regimen C = as per B with Augmented (Vincristine Asparaginase and Methotrexate) BFM
### Outcome of ALL 99 by treatment arm

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number</th>
<th>5 year EFS %</th>
<th>Events</th>
<th>% of failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>557</td>
<td>85 (82-88)</td>
<td>84</td>
<td>43</td>
</tr>
<tr>
<td>B</td>
<td>231</td>
<td>80 (75-85)</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>C</td>
<td>150</td>
<td>58 (50-66)</td>
<td>64</td>
<td>33</td>
</tr>
</tbody>
</table>
Outcome of ALL 99 by treatment arm

<table>
<thead>
<tr>
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<tr>
<td>C</td>
<td>150</td>
<td>58 (50-66)</td>
<td>64</td>
<td>33</td>
</tr>
</tbody>
</table>

Only 33% of events occur in highest risk group
>70% of those cured are “over - treated”
UKALL 2003

Allocate A or B based on NCI risk, post induction directed by MRD
Slow early responder by morphology and or high risk cytogenetics allocated arm C

MRD day 28 $> 1 \times 10^{-4}$ = MRD High Risk

Arm C, 2 x DI

A or B, 2 x DI
UKALL 2003

Allocate A or B based on NCI risk, post induction directed by MRD
Slow early responder by morphology and or high risk cytogenetics allocated arm C

MRD day 28 > 1x 10^{-4} = MRD High Risk

MRD day 28 < 1x 10^{-4}, week 11 negative = MRD Low Risk
UKALL 2003

Allocate A or B based on NCI risk, post induction directed by MRD
Slow early responder by morphology and or high risk cytogenetics allocated arm C

MRD day 28 > 1x 10^{-4} = MRD High Risk

MRD day 28 < 1x 10^{-4}, week 11 < 1x 10^{-4} OR no MRD Result = Indeterminate Risk

MRD day 28 < 1x 10^{-4}, week 11 negative = MRD Low Risk

Arm A or B, 1x DI

Arm A or B, 2x DI

Arm C 2 x DI
Outcome (EFS) of ALL 2003 v ALL 99 OCT 2011

Improved EFS in ALL 2003 likely due to wider use of DEX and PEG Aspase
UKALL2003 MRD LOW RISK
EVENT FREE SURVIVAL BY RANDOMISED TREATMENT

1DI = 96%
2DI = 94%

<table>
<thead>
<tr>
<th></th>
<th>1DI</th>
<th>2DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs/N</td>
<td>10/260</td>
<td>9/261</td>
</tr>
<tr>
<td>Any event</td>
<td>10/260</td>
<td>6/261</td>
</tr>
<tr>
<td>Relapse</td>
<td>10/260</td>
<td>3/261</td>
</tr>
<tr>
<td>Remission death</td>
<td>0/260</td>
<td>3/261</td>
</tr>
<tr>
<td>Grade 3/4 toxicity</td>
<td>177 (68%)</td>
<td>191 (71%)</td>
</tr>
<tr>
<td>SAEs</td>
<td>64 (25%)</td>
<td>77 (29.5%)</td>
</tr>
</tbody>
</table>

At risk:
Reduced (1DI) 260 233 175 113 70 34
Standard (2DI) 261 231 167 114 65 35

OCT 2011
UKALL2003 MRD HIGH RISK (FEB 2012)
EVENT FREE SURVIVAL BY RANDOMISED TREATMENT

At risk:

<table>
<thead>
<tr>
<th></th>
<th>A/B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>266</td>
<td>267</td>
</tr>
<tr>
<td>No. Events</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Obs./Exp.</td>
<td>1.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

2P = 0.03

17-FEB-12 13:15:25
### Treatment related mortality in ALL 2003

<table>
<thead>
<tr>
<th>Event</th>
<th>Induction</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial sepsis</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>Fungal Infection</td>
<td>10*</td>
<td>6</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Sino-venous thrombus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Viral infection</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Resistant disease</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HLH</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Second malignancy</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>48</strong></td>
<td><strong>52</strong></td>
</tr>
</tbody>
</table>

77% of TRM due to bacterial or fungal infection – mostly in induction or DI
Four issues from ALL 2003 to be addressed in ALL 2011

1. Treatment related mortality and morbidity too high in context of DFS of 87%
   - TRM = 3.2%, 100 deaths in CR, 25% of patients have at least one SAE,
   - TRM commonest during induction and delayed intensification
   - marked decrease in HRQoL as measured by Peds QL

2. Very poor prognosis of early marrow relapse
   - 2.7% of patients relapse in BM with in 18 months of diagnosis
   - Less than 20% survival even after SCT in CR2
   - BFM 2000 shows that some of these can be identified through persistent MRD in CR1
Four issues from ALL 2003 to be addressed in ALL 2011

1. Treatment related mortality and morbidity too high in context of DFS of 87%
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Reduction in TRM and unsalvageable relapse are key to raise OS to 95%
Four issues from ALL 2003 to address in ALL 2011

3. Concerns over efficacy and burden of therapy of CNS prophylaxis
   - Cranial RT only in high risk CNS 3, all others receive continuing IT and pulses
   - CNS relapse risk is low at 4% but up to 50% of relapse now has a CNS component
   - Isolated CNS relapse is ”not predicted“ by MRD and is only curable by SCT

4. Superior outcome for young adults treated on “paediatric protocol”
   - Comparative studies suggest 20% EFS benefit with less recourse to SCT
   - As of October 2011, 199 pats aged 16-24 in ALL 2003, EFS 74%
   - Need unified approach for this group of patients
ALL 2011: main features

- Independent UK trial, open to age 1-24 years from late 2011
ALL 2011: main features

• Independent UK trial, open to age 1-24 years from late 2011

• 3 or 4 drug induction with Dexamethasone acc to immuno / age / WCC
  – Day 1 randomise to 14 day 10mg/m² v 28 day 6mg/m² Dexamethasone
  – “Split” dexamethasone in patients aged > 10 at diagnosis
ALL 2011: main features

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• Further therapy stratified by day 29 MRD in all except high risk cytogenetics
  – MRD > 0.005% day 29 = “MRD Risk” :- allocate augmented consolidation (Arm C)
  – MRD < 0.005% day 29 = “MRD Low Risk” standard consolidation (A or B) & single DI
ALL 2011: main features

• Independent UK trial, open to age 1-24 years from late 2011

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  – MRD > 0.005% day 29 = “MRD Risk” :- allocate augmented consolidation (Arm C)
  – MRD < 0.005% day 29 = “MRD Low Risk” standard consolidation\(^n\) (A or B) & single DI

• Further MRD assessment of MRD Risk group at week 14
  – MRD > 0.5% = High risk:- off protocol, enter R3
  – MRD < 0.5% = Intermediate risk- allocate augmented IM and a single DI (Arm C)
ALL 2011: main features

- Independent UK trial, open to age 1-24 years from late 2011
- 3 or 4 drug induction with Dexamethasone acc to immuno / age / WCC
  - Day 1 randomise to 14 day 10mg/m² v 28 day 6mg/m² Dexamethasone
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  - MRD > 0.5% = High risk:- off protocol, enter R3
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- Factorial randomised examination of benefit of IV HD MTX and 4 weekly pulses of Vincristine and Dexamethasone on relapse, toxicity, QoL and HE
**Figure 2 Trial Schema ALL 2011.** Induction is directed by immuno and NCI risk. R1 Dexamethasone randomisation at day 1. R2 Methotrexate and pulses randomisation at week 14 (MRD risk group) and week 16 (MRD low risk group)

* = NCI High Risk Only
UKALL 2011: Allocation of Therapy Post Induction

- Immuno and NCI directed induction A or B
- Randomised Dexamethasone
- MRD measured at day 29
ALL 2011 Dexamethasone Randomisation

- Primary outcome measures and power calculation
  - Treatment related mortality and steroid induced morbidity
  - All 2,520 entrants eligible, expect 2,268 randomised
  - Assume 85% EFS & 8% steroid related or contributory SAE
  - 88% power to detect reduction in TRM or grade IV toxicity to 4.8%

- Secondary outcome measure
  - Rate of remission, EFS, OS, Flow MRD day 8, 15 and 29

- Additional studies
  - Dexamethasone pharmacology,
  - physiotherapy based assessment of neuromuscular morbidity (with COG)
  - AVN prospective imaging and biology
UKALL 2011: Allocation of Therapy Post Induction

Immuno and NCI directed induction A or B
Randomised Dexamethasone
MRD measured at day 29

Day 29 MRD < 0.005% = MRD Low Risk
  Continue A or B, Single DI
  Methotrexate / pulses randomisation

Day 29 MRD > 0.005% = MRD Risk
  Allocate Arm C consolidation
  Repeat MRD at week 14
UKALL 2011: Allocation of Therapy Post Induction

NCI directed induction A or B MRD measured at day 29

Day 29 MRD < 0.005% = MRD Low Risk
   - Continue A or B, Single DI

Day 29 MRD > 0.005% = MRD Risk
   - Allocate Arm C consolidation
   - Repeat MRD at week 14

Week 14 MRD < 0.5% = MRD Intermediate
   - Continue Arm C, Single DI

Week 14 MRD > 0.5% = MRD High Risk
   - Off Protocol
Proposed ALL 2011: power calculations

Second (Methotrexate and Pulses randomisation)

• Methotrexate randomisation expect 1,760 randomised
  – Assume 4% risk of relapse involving CNS in control arm
  – 89% power to detect reduction to 1.5% (relative hazard 0.37)

• Pulses randomisation expect 1,760 randomised
  – Assume 10% risk of relapse involving BM in control arm
  – 85% power to rule out a 5% increase in BM relapse
Proposed ALL 2011: power calculations
Second (Methotrexate and Pulses randomisation) HRQoL

- HRQoL study expect 1,760 randomised
  - end point: return to 80% HRQoL at 18 months
  - 340 per arm gives 90% power to detect difference of 0.25-0.4sd at 18mths
  - 250 per arm gives 90% power to detect difference of 0.25-0.4sd at 18mths
Shared care arrangements
Clare Brittain
Clinical Trial Coordinator
21st October 2011
TRIAL RESPONSIBILITY

Trial Sponsor
CRCTU

PTC

Shared care centre
27 PRINCIPAL TREATMENT CENTRES

- Royal Aberdeen Children’s Hospital
- Addenbrookes
- Alder Hey
- Birmingham Children’s Hospital
- Bristol Royal Hospital for Children
- Children’s Hospital for Wales
- GOSH
- Leeds General Infirmary
- Leicester Royal Infirmary
- Royal Victoria Infirmary, Newcastle
- Queen’s Medical Centre, Nottingham
- Oxford Radcliffe
- Royal Belfast Hospital for sick children
- Royal Hospital for sick children (Edinburgh)
- Royal Hospital for sick children (Glasgow)
- Royal Manchester Children’s Hospital
- Royal Marsden
- Sheffield Children’s Hospital
- Southampton General Hospital
- University College London Hospital
- Barts and The London
- Birmingham Heartland’s Hospital
- Queen Elizabeth Hospital, Birmingham
- Royal Hallamshire Hospital
- Royal Liverpool & Broadgreen
- The Christie
- University Hospital of North Staffordshire
# DEFINING CENTRE TYPE

<table>
<thead>
<tr>
<th>Principal Treatment Centre (PTC)</th>
<th>Shared Care centre</th>
<th>Other locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall local trial coordination</td>
<td>Patient selection</td>
<td>Radiotherapy where it is not part of trial question but given in accordance with protocol schedule: SLA should be in place</td>
</tr>
<tr>
<td>Patient selection</td>
<td>Administer treatment</td>
<td>Supportive care: ie emergency treatment, febrile neutropaenia (does not require access to trial protocol to manage)</td>
</tr>
<tr>
<td>Consent</td>
<td>• IMPs</td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>• Supportive care</td>
<td></td>
</tr>
<tr>
<td>Administer treatment</td>
<td>Assessments: provided</td>
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</tr>
<tr>
<td>Assessment decisions</td>
<td>interpretation decisions by PTC</td>
<td></td>
</tr>
<tr>
<td>Subsequent treatment decisions</td>
<td>AE reporting to PTC</td>
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</tr>
<tr>
<td>Randomisation</td>
<td>Scheduled dose adjustments</td>
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<tr>
<td>Stratifying treatment</td>
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<td></td>
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<tr>
<td>Dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE reporting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL TRIAL ACTIVITY IN SHARED CARE CENTRES

- Shared care centres will be set up according to level of trial associated activity undertaken

- Spreadsheet requesting details of trial-related activities has already been sent to PTCs
UKALL 2011 TRIAL ACTIVITIES

- Shared Care centre
  - Prescribe, dispense and administer IMPs
  - Report AEs to PTC
  - Long-term follow-up

- Trial-specific bone marrow and re-assessment scans (LBL patients) must be undertaken in the PTC.
PTC OVERSIGHT (1)

- PTC responsible for maintaining oversight of shared care centres
- PTC to ensure procedures are in place for PTC oversight trial related activities in shared care centre, for example:
  - For defining responsibilities
  - For SAE reporting process
  - For appropriate handling of IMPs
  - Archiving procedure
- Written agreement between PTC and shared care centre where relevant

Has this patient been recruited to a clinical trial?
PTC OVERSIGHT (2)

PTC should maintain records of the following for each shared care centre:

1) Site signature & Delegation Logs
   - Clinical Collaborator
   - Pharmacist
   - Admin support (if applicable)
   - Log to be signed by PI at the PTC and stored in ISF

2) Written R&D approval

3) Copies of IMP accountability logs
PTC OVERSIGHT (3)

- PTC required to ‘activate’ each shared care centre
- No patients will be permitted to be treated at a shared care centre until formally activated by the PTC
- All documents to be filed in shared care section of Investigator Site File (ISF) at the PTC.
TRIAL FILES FOR SHARED CARE CENTRES

ISF:
- A ‘mini’ Investigator Site File (ISF) will be send to each shared care centre by the CRCTU
- Contain essential documents for trial conduct at shared care centre

PHARMACY FILE:
- Full pharmacy file for shared care centre

Shared care centres to fax confirmation of receipt of ISF and pharmacy file to PTC and Trial Office.
SHARED CARE CENTRE ACTIVATION PROCESS

1. CRCTU send pharmacy file and mini ISF to shared care centre
2. CRCTU initiate shared care centre pharmacy via telephone
3. PTC must ‘activate’ each shared care centre
4. PTC fax CRCTU ‘Shared Care Site Activation Form’
5. CRCTU acknowledge activation to PTC
6. CRCTU will notify IMP supplier to activate shipment
This form should be completed by the primary treatment centre once a shared care centre is activated

**PRIMARY TREATMENT CENTRE:**

<table>
<thead>
<tr>
<th>SHARED CARE CENTRE DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shared care centre name:</td>
</tr>
<tr>
<td>Address:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Collaborator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
</tr>
<tr>
<td>Tel:</td>
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<td>E-mail:</td>
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<th>Main Pharmacist:</th>
</tr>
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<tbody>
<tr>
<td>Name:</td>
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<tr>
<td>Tel:</td>
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<tr>
<td>Fax:</td>
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<td>E-mail:</td>
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**ACTIVATION CHECKLIST**

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<thead>
<tr>
<th>R&amp;D approval received on (date of approval letter):</th>
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<tr>
<td>DD/MON/YYYY</td>
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</table>

<table>
<thead>
<tr>
<th>Written agreement in place between PTC and shared care centre?</th>
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<tbody>
<tr>
<td>No ☐ Yes ☐</td>
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</tbody>
</table>

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>DD/MON/YYYY</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Date Pharmacy File received by shared care centre?</th>
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<tr>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mini Investigator Site File (ISF) received by centre?</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD/MON/YYYY</td>
</tr>
</tbody>
</table>

**SIGNATURE & CONTACT DETAILS**

<table>
<thead>
<tr>
<th>Form completed by:</th>
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</thead>
<tbody>
<tr>
<td>Signature:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tel:</th>
<th>Fax:</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
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</tbody>
</table>

Please fax form to UKALL 2011 Trial Office on 0121 414 9520 or e-mail ukall2011@trials.bham.ac.uk

**FOR CRCTU USE ONLY:**

<table>
<thead>
<tr>
<th>Stockport pharmaceuticals notified (for release of MTX oral suspension):</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ☐ Yes ☐</td>
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</table>

<table>
<thead>
<tr>
<th>Signature:</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD/MON/YYYY</td>
</tr>
</tbody>
</table>

The UKALL 2011 Trial Office will acknowledge confirmation by faxing completed form back to PTC.
PTC OVERSIGHT (4)

- PTC responsible for sending all subsequent documents to shared care centre e.g. updated protocols
- PTC must track receipt of documents sent to shared care centre and maintain version control records
- The CRCTU will not perform any on-site monitoring at shared care centres
- CRCTU will perform quality checks on the PTC oversight of shared care centres
  - Appropriate procedures in place for trial activities
  - Relevant documents in ISF
ADVERSE EVENT (AE) REPORTING

- AEs should be reported to the CRCTU from the PTC
- PTC to ensure process in place for receiving SAEs within required timeframes from shared care centres
- CRCTU will monitor reporting rates to ensure SAEs are being reported appropriately.
- Follow-up requests will be sent to the PTC
DATA COLLECTION

- Electronic data capture system used for collecting UKALL 2011 data
- Delegated staff at PTCs only will have access system
- PTCs to arrange procedures to collect required data from shared care centre for entry onto system
R&D/REC APPROVAL PROCESS

- CRCTU will complete a single generic SSI form with details of all shared care centres and activities undertaken at each.

- SSI for shared care centres will be sent to R&D departments via the Central & East London CLRN.

- PTC must inform CRCTU of any changes to shared care centres.
RISK-ADAPTED APPROACH

- UKALL 2011 is a Type A trial (no higher than the risk of standard medical care)
- Potential to:
  - Remove IMP accountability logs for IMPs in maintenance phase of treatment
  - Ability to define expected adverse events
- Risk-adapted approach plan being worked on and will need to be approved by MHRA
SUMMARY

- PTC has overall responsibility for oversight of shared care centres
- CRCTU will initiate each shared care centre pharmacy
- Mini ISF and pharmacy file sent to shared care centre from CRCTU
- Each shared care centre requires formal activation by PTC before trial-related activity can commence