Acknowledgements

- Lola Awoyale
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- Emma Bedson
- Rachel Breen
- Helen Hickey
- Helen Hill
- Hannah Short
- Cath Spowart
Clinical Trials Directive 2001

- Regulation of clinical trials addresses two distinct risks:
  - the risk to patient safety
  - the risk to data reliability.
- Heavily criticised as being a barrier to conduct of clinical trials
  - Increased costs and time to launch clinical trial
  - Variations in the way the Directive was transposed in to law across member states led to difficulty for multinational trials
  - 25% decrease in applications for clinical trials 2007-2011
Clinical trials in emergency situations

- Informed consent corner stone of the Directive
- No provision for trials where this was not possible
- Member states forced to accept restriction or operate at variance
- UK amendments made in 2006 for adults and in 2008 for paediatrics to allow deferred consent
UK amendment 2008

Informed consent can be deferred whilst

(i) the minor requires urgent treatment;

(ii) urgent action is required for the purposes of the trial;

(iii) meeting the requirements of informed consent is not reasonably practicable, provided that an ethics committee has given its approval.
Practicalities of deferred consent

- It makes research in emergency life threatening conditions possible
- Researchers
  - How to approach parents when seeking deferred consent?
  - What should we do in the situation that a child dies prior to discussions about the trial?
- Recruit study highlighted practitioners concerns that an approach for informed consent could ‘exacerbate the emotional impact of the child’s illness’ and personal anxiety about the approach. PLoS ONE 2011;6(7):e21604
Deferred consent: Parental survey

**PLoS ONE 2012; 7(5):e35982**

- Investigate parents’ views about:
  - Acceptability of deferred consent
  - Timing of requesting consent
  - Trial disclosure after a child’s death.

- Postal survey of members of the MRF UK charity whose child had suffered bacterial meningitis and been admitted as an emergency within 5 years

- Postal survey outlined the proposed trial which if running at the time of the child’s illness they would have received one of the treatments without prior consent
Deferred consent survey

220 families sent questionnaire (29% bereaved)
68 (31%) families responded (28 % bereaved)

Parents understood the need for medical research but
- The word ‘trial’ frightening
- Equating medical uncertainty with lack of expertise of clinical team

“If we thought [...] that the staff did not fully know what they were doing or administering fluids they did not know would work, we would have been horrified”
Deferred consent survey

- I would be willing for my child to be included without the trial being explained to me beforehand (68% agreed)

- I would like to be asked for consent as soon as their condition stabilised (70% agreed).

- I would not want to be told about the trial at anytime so long as both fluids considered safe (33% agreed, 55% disagreed)
If a child of mine had a serious infection and needed emergency fluid treatment:

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1)</strong> I would <strong>not want</strong> my child to be included in a clinical trial of these two commonly used fluids under any circumstances.</td>
<td></td>
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<tr>
<td>Bereaved</td>
<td>40</td>
<td>50</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Recovered</td>
<td>28</td>
<td>37</td>
<td>31</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>2)</strong> I would be willing for my child to be included in a clinical trial <strong>without the trial being, explained to me beforehand</strong>.</td>
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<tr>
<td>Bereaved</td>
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<td>33</td>
</tr>
<tr>
<td>Recovered</td>
<td>8</td>
<td>10</td>
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<td><strong>3)</strong> I would like to be asked for consent as soon as their condition stabilised.</td>
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<td>11</td>
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<td>45</td>
<td>33</td>
</tr>
<tr>
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<td>0</td>
<td>12</td>
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</tr>
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<td>6</td>
</tr>
<tr>
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</tbody>
</table>
If a child of mine had a serious infection and needed emergency fluid treatment:

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1) I would **not want** my child to be included in a clinical trial of these two commonly used fluids under any circumstances.

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2) I would be willing for my child to be included in a clinical trial **without the trial being explained to me beforehand**.

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<th>39</th>
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</table>

3) I would like to be asked for consent as soon as their condition stabilised.

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<th>0</th>
<th>11</th>
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<th>45</th>
<th>33</th>
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</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>0</td>
<td>12</td>
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<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

4) I would **not want** to be told at any time, as long as both fluids considered safe.

<table>
<thead>
<tr>
<th>Bereaved</th>
<th>33</th>
<th>33</th>
<th>11</th>
<th>17</th>
<th>6</th>
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<td>14</td>
<td>23</td>
</tr>
</tbody>
</table>
Qualitative responses

My understanding is that both treatments are currently used and there is genuinely no established right or wrong. Therefore I don’t think parents would need to know [B]

I would have sued anyone that moved if he had died in a trial that we knew nothing about [R]

They will not “hear” or understand the fact that both fluids are safe [...] grief makes people irrational [...] people would consult legal advisors, and in general it would cause more distress [R]
If a child could not be resuscitated and unfortunately died in the emergency department we would want to tell the parents that their child had been given the fluid as part of a clinical trial of emergency treatments.

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
</table>

Statement 5: It would be better **not to tell** the bereaved parent/carer about the trial at any time.

<table>
<thead>
<tr>
<th>Bereaved</th>
<th>6(33)</th>
<th>6(33)</th>
<th>0(0)</th>
<th>1(6)</th>
<th>5(28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>7(14)</td>
<td>11(23)</td>
<td>3(6)</td>
<td>8(16)</td>
<td>20(41)</td>
</tr>
</tbody>
</table>

- No overall consensus about the right time to tell.
- 57% wanted the information provided in both written and consultation formats.
- Time to ask questions and follow up
Deferred consent: practitioners survey
Proposed EU Regulation

- Will replace the Directive
- Expected to come into effect 2016
- Makes a provision for trials emergency in emergency situations
- Explanatory memorandum states:

Directive 2001/20/EC does so far not address the specific situation where, because of the urgency of the situation, it is impossible to obtain free and informed consent from the subject or the legal representative (‘clinical trials in emergency situations’). To address this, specific provisions on clinical trials in emergency situations have been added in line with existing international guidance documents on this issue.
Informed consent may be obtained after the start of the clinical trial to continue the clinical trial and information on the clinical trial may be given after the start of the clinical trial provided that **all** of the following conditions are fulfilled:

(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;

(b) no legal representative is available;

(c) the subject has not previously expressed objections known to the investigator;

(d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information;

(e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.
Lessons from the CRASH Trial


- International RCT of a time critical treatment in adults with head injuries
- Variation in consent processes
- Informed consent delayed treatment by 1.2 h (95% CI 0.7–1.8)
- CRASH2:
  - RR of death in CRASH2 0.85 (95% CI 0.76–0.96)
  - RR with a 1-h delay is 0.96 (0.86–1.08)
- Informed consent may not be in patients best interest
- Potential to obscure a real treatment benefit
Risk Proportionate approaches

- Academy of Medical Sciences report 2011
  - A new pathway for the regulation and governance of health research

The broad scope and ‘one-size-fits-all’ approach of the EU Clinical Trials Directive (CTD) places an unnecessary regulatory burden on clinical trials of both new products and established drugs.

- Highlighted within proposed EU regulation
  - ‘measures will better differentiate the obligations according to the risk-profile of the trial
Risk proportionate approaches

- Joint working group
  (http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf)

- Develop a risk assessment that gives practical guidance on risk adaptations.

- Considered in relation to what is known about the IMP and standard medical care (Brosteanu et al. Clinical Trials 2009:585-596)

- Identify lower risk trials where simplification is possible for regulatory approvals and trial conduct
Risk categories

- Considered in relation to what is known about the IMP and standard medical care
  (Brosteanu et al. Clinical Trials 2009:585-596)

- **Type A**: no higher than that of standard medical care

- **Type B**: somewhat higher than that of standard medical care

- **Type C**: markedly higher than that of standard medical care
### Risk adaptations

(http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf)

<table>
<thead>
<tr>
<th>Are risk adaptations possible?</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced MHRA role for approval</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Content of application</td>
<td>Yes</td>
<td>(Yes)</td>
<td>No</td>
</tr>
<tr>
<td>Labelling</td>
<td>Yes</td>
<td>(Yes)</td>
<td>(Yes)</td>
</tr>
<tr>
<td>Safety Surveillance</td>
<td>Yes</td>
<td>(Yes)</td>
<td>No</td>
</tr>
<tr>
<td>IMP management</td>
<td>Yes</td>
<td>(Yes)</td>
<td>(Yes)</td>
</tr>
<tr>
<td>Documentation</td>
<td>Yes</td>
<td>(Yes)</td>
<td>No</td>
</tr>
<tr>
<td>GCP Inspections</td>
<td>Yes</td>
<td>(Yes)</td>
<td>(Yes)</td>
</tr>
</tbody>
</table>
On going pilot

- Examples published on MHRA web site

- TINN trial-
  - To evaluate the PKs, tolerability and short-term safety of ciprofloxacin in neonates with suspected (or proven) Gram Negative infection.
  - Phase I, open-label pilot PK Study

- Conducted a risk assessment
  - Classified as Type B
  - Argue for classification as Type A
Type A

- Medicinal products licensed in any EU Member State if they relate to the licensed range of indications, dosage and form

- Off-label use if this off-label use is established practice (such as is paediatrics or oncology) and supported by published evidence/guidelines
<table>
<thead>
<tr>
<th>Type A: no higher than that of Standard medical care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-label use is established practice and supported by sufficient published evidence and/or guidelines</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Intervention</th>
<th>Ciprofloxacin is being prescribed as part of standard medical care (not for research)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Practice: Neonatal Sepsis Policy Bannon et al 1989</td>
<td>The Neonatal Policy includes Ciprofloxacin – Published evidence of use in neonates for 20 years+</td>
</tr>
<tr>
<td>SmPC Dated 2/2011</td>
<td>Children and Adolescents Other severe infections 10 mg/kg body weight three times a day with a maximum of 400 mg per dose. According to the type of infections</td>
</tr>
<tr>
<td>British National Formulary for Children 2011</td>
<td>Licensed for use in Children over 1 year age for severe infections Neonatal dose 10mg/kg /12 hourly intravenously</td>
</tr>
<tr>
<td>European Survey of usage:</td>
<td>25% Neonatal Units use Ciprofloxacin</td>
</tr>
<tr>
<td>Paediatrics: a systematic review Abiodun Adefurin et al 2010</td>
<td>105 articles met the inclusion criteria and involved 16 184 paediatric patients.</td>
</tr>
<tr>
<td>Neonatal Systematic Review Kaguelidou, et al 2011</td>
<td>In total, 32 reports met all eligibility criteria and were included in the review. Of these, 5 were cohort studies20–24 and 27 were single case reports (n _ 14)25–38 or series of 2 to 29 patients (n _ 13)39–51 treated with ciprofloxacin.</td>
</tr>
<tr>
<td>Conroy et al 1999</td>
<td>55% drugs are used off label in neonates - 90% of neonates in hospital receive an off label drug</td>
</tr>
<tr>
<td>Russell et al 2012</td>
<td>Table 3 propose Ciprofloxacin is 3rd line antibiotic for neonates</td>
</tr>
</tbody>
</table>
Decision

- Type A
  - Important to establish an example that used off-label drugs in neonates/paediatrics as low risk
- An Investigator Brochure is replaced by the SmPC.
- As the IMP is used off label, the trial will require authorisation by MHRA, rather than notification to MHRA.
  - Notifications can be made for certain Type A trials
  - Inconsistent with press release and joint project table
SCIP1 trial

- Compare two methods of insulin delivery via CE marked devices used for their intended purpose
  - Not a clinical investigation under the Medical Devices Regulations 2002
- Methods used different insulins
  - Not licensed across full age range
- Contacted MHRA Clinical Trial helpline to identify if:
  - SCIP1 came under the definition of a CTIMP
  - Waive labelling requirements
    - Provision in SI2004 1031 to for Market Authorised products used in a CTIMP prescribed by Health Care Professional
  - Waive formal accountability of IMP
    - Compliance recorded in patient diaries & CRFs
    - Local procedures used in event of a manufacturer recall
  - Reduced pharmacovigilance
TORPEDO trial

- Comparison of IV and oral antibiotics for the treatment of pseudomonas in CF patients.
- Contacted the MHRA July 2010 to establish if we could:
  - Waive labelling requirements ✓
    - Provision in SI2004 1031 to for Market Authorised products used in a CTIMP prescribed by Health Care Professional
  - Waive formal accountability of IMP ✓
    - Compliance recorded in patient diaries & CRFs
    - Local procedures used in event of a manufacturer recall
  - Prescribe and administer IV treatment as per routine practice ❌
    - Trained patients could self administer
    - Provided by a registered IV homecare provider
TORPEDO trial

- Proposal appears sensible and to reflect the nature and low risk of the trial
- Homecare provider must have an MIAIMP license to reconstitute the IV centrally and supply the reconstituted injectables in IV bag and syringe to patients
- Trial struggled to recruit
- We tried again via Clinical Trial Helpline and received the same response, requested a face to face meeting.
- Agreed MIAIMP not required, registered pharmacy
GCP training

- Requirement that clinical trials conducted in accordance with GCP principles
- Persons involved with CTIMPs should be trained in GCP
  - timing of training is not specified in legislation or guidance
- Barrier in settings such as PICU and emergency settings
- SLEEPs trial
  - Train the trainer
  - Only trainer need GCP training, could train others in trial procedures relevant to them
  - Proposal approved by MHRA
The Health Research Authority has issued the following statement about researcher training:
For research, training should be appropriate and proportionate to the type of research undertaken, and should cover the responsibilities of researchers set out in relevant legislation and standards. **There is no set requirement for the frequency of such training.** Researchers are expected to maintain awareness of current standards through reference to published guidance and relevant policies. **Training should be updated when legislation has changed, new policies or practice have been implemented, different research activities are to be undertaken, or a significant period of time has elapsed since research activities have been conducted.**
For research involving CTIMPs, there is a requirement for GCP training. However, the timing of this training is not specified in legislation or guidance but should be appropriate and proportionate. See the MHRA website for further details.
• HRA statement unlikely to help CTUs
• Need for clear systems to be developed to provide researchers with regulatory news/changes
• This is not happening yet.
• Example from Deferred consent
  • Feasibility study of emergency departments for a new trial using deferred consent
    • 30 expressions of interest received. 7 raising concerns with deferred consent
      “I am not aware of any legal recognition for deferred consent”
      “What is deferred consent?”
  • GCP trainers unaware of deferred consent provision
What are trialists doing?

- Challenging Regulations that are barriers to research

- Working with the competent authorities as stakeholders to benefit the delivery of trials

- Outlining risks inherent in trial and challenging disproportionate applications of the regulations

- Conducting research to identify the best ways to deliver that research for patient benefit