Integrating Transparency into a University Quality Management System

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About LSHTM

• LSHTM is a leading centre for research and postgraduate education in public and global health

• School has over 4000 students, 1200 staff and 20000 alumni working in 180 countries worldwide

• Income from research grants £110 million in 2015-2016, including:
  – £36.7 million from charities
  – £33.9 million from UK government, research councils and other
  – £23.2 million from EU
LSHTM is legal sponsor for 88 trials:

<table>
<thead>
<tr>
<th>Clinical Trial Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial of a public health intervention (eg health management, training)</td>
<td>48</td>
</tr>
<tr>
<td>Clinical Trial of an Investigational Medicinal Product (IMP) (eg drug)</td>
<td>26</td>
</tr>
<tr>
<td>Clinical Trial - Device</td>
<td>8</td>
</tr>
<tr>
<td>Clinical Trial - other</td>
<td>4</td>
</tr>
<tr>
<td>Clinical Trial of a non-IMP (vitamins etc)</td>
<td>2</td>
</tr>
</tbody>
</table>
Components of a QMS

- Quality System
- Equipment & Materials
- People, Training & Experience
- Processes
- Documents & Records
- Facilities

SOPs

RQA quality systems workbook
LSHTM audit programme

• Risk-based approach
  – Risk assessment conducted at sponsor review
  – Consider training, finances, adverse reaction likelihood, project management, care for participants

• Higher risk studies added to audit programme
  • reviewed quarterly

• Aim to conduct 8-10 audits per year

• Tissue holdings: 2 audits/year

• Also conduct for-cause audits
Instilling transparency in the QMS in academia
Concordat to Support Research Integrity

• Provides assurances that the UK research community works to the highest standards of rigour and integrity

• Assures that procedures are in place for dealing with allegations of misconduct.
  — Including public statement on website
Gap Analysis

• Reviewed Concordat against current practices, policies and procedures

• Highlighted areas of improvement
  – Particularly with regards to transparency of misconduct investigations

• Felt that audit results, as a key component of the School’s QMS, should be made more transparent
  – Falls within the spirit of the Concordat
Why transparency?

• To help ensure that all staff can learn from common discrepancies in trial conduct

• Allows the RGIO to
  – target training
  – clarify SOPs and templates
  – share knowledge across LSHTM
  – benchmark findings

• Promotes good practice and integrity in research
Building an audit database

- Over five years' worth of audits (2012-present) have been added to the database.
- Findings aggregated into excel spreadsheet from audit reports in word format.
- Used DIA TMF reference model as starting point for generating categories and sub-categories.
- To assure anonymity, audits are given a number.
  - Identifiable details (PI, title etc) are not on the findings database.
<table>
<thead>
<tr>
<th>A</th>
<th>Grade of finding</th>
<th>Finding Category</th>
<th>Finding sub-category</th>
<th>Core or recommended</th>
<th>ICH-GCP reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Minor</td>
<td>Data Management</td>
<td>Audit trail planning and testing</td>
<td>Core</td>
<td>5.5.3a, 5.5.3c, 5.5.3d</td>
</tr>
<tr>
<td>3</td>
<td>Minor</td>
<td>Data Management</td>
<td>Data Management Plan</td>
<td>Recommended</td>
<td>5.1, 5.5</td>
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<td>Minor</td>
<td>Data Management</td>
<td>Data Management Plan</td>
<td>Recommended</td>
<td>5.1, 5.5</td>
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<td>5</td>
<td>Minor</td>
<td>Data Management</td>
<td>Documentation of Corrections to Entered Data</td>
<td>Core</td>
<td>4.9.3, 5.5.3a, 5.5.3c, 5.5.3d, 8.3.15</td>
</tr>
<tr>
<td>6</td>
<td>Minor</td>
<td>Data Management</td>
<td>Documentation of Corrections to Entered Data</td>
<td>Core</td>
<td>4.9.3, 5.5.3c, 8.3.15</td>
</tr>
<tr>
<td>7</td>
<td>Minor</td>
<td>Data Management</td>
<td>System Account Management, eg each to have own log-in suitable to role</td>
<td>Core</td>
<td>5.5.3a, 5.5.3c, 5.5.3d</td>
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<tr>
<td>8</td>
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<td>Database</td>
<td>Data Entry Procedures</td>
<td>Core</td>
<td>5.1, 5.5</td>
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<tr>
<td>9</td>
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<td>Database</td>
<td>Validation Documents</td>
<td>Core</td>
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<tr>
<td>10</td>
<td>Minor</td>
<td>Essential documents</td>
<td>any document detailed in section 8</td>
<td>Core</td>
<td>8.1-8.4</td>
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<tr>
<td>11</td>
<td>Minor</td>
<td>Essential documents</td>
<td>any document detailed in section 8</td>
<td>Core</td>
<td>8.1-8.4</td>
</tr>
<tr>
<td>12</td>
<td>Minor</td>
<td>Essential documents</td>
<td>any document detailed in section 8</td>
<td>Core</td>
<td>8.1-8.4</td>
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<tr>
<td>13</td>
<td>Minor</td>
<td>Essential documents</td>
<td>Various missing</td>
<td>Core</td>
<td>2.8, 8.1-8.4, 8.2.3, 8.2.12</td>
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<tr>
<td>14</td>
<td>Minor</td>
<td>Ethics Committee</td>
<td>Amendments submitted and approved prior to implementation</td>
<td>Core</td>
<td>1.4.5, 8.2.2, 8.3.2</td>
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<tr>
<td>15</td>
<td>Minor</td>
<td>IMP</td>
<td>IMP Accountability Documentation</td>
<td>Core</td>
<td>4.6.2, 5.14.4, 8.3.23, 8.4.1</td>
</tr>
<tr>
<td>16</td>
<td>Major</td>
<td>IMP</td>
<td>IMP Accountability Documentation</td>
<td>Core</td>
<td>4.6.2, 5.14.4, 8.3.23, 8.4.1</td>
</tr>
<tr>
<td>17</td>
<td>Minor</td>
<td>IMP</td>
<td>IMP Accountability Documentation</td>
<td>Core</td>
<td>4.6.2, 5.14.4, 8.3.23, 8.4.1</td>
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<tr>
<td>18</td>
<td>Minor</td>
<td>IMP</td>
<td>IMP Instructions for Handling not followed or not accurate</td>
<td>Core</td>
<td>5.13.2, 5.14.3, 8.2.14</td>
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<tr>
<td>19</td>
<td>Minor</td>
<td>IMP</td>
<td>IMP Unbinding Plan</td>
<td>Core</td>
<td>5.13.4, 8.2.17, 8.4.4</td>
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<tr>
<td>20</td>
<td>Major</td>
<td>Informed consent</td>
<td>Consent not done per SOPs and GCP (general findings)</td>
<td>Core</td>
<td>4.8.1, 4.8.8, 4.8.9</td>
</tr>
<tr>
<td>21</td>
<td>Minor</td>
<td>Informed consent</td>
<td>Consent not done per SOPs and GCP (general findings)</td>
<td>Core</td>
<td>4.8.1</td>
</tr>
<tr>
<td>22</td>
<td>Minor</td>
<td>Informed consent</td>
<td>correct completion of informed consent forms</td>
<td>Core</td>
<td>2.3</td>
</tr>
<tr>
<td>23</td>
<td>Major</td>
<td>Informed consent</td>
<td>Inclusion of participant without capacity to consent</td>
<td>Core</td>
<td>4.8.5, 4.8.12</td>
</tr>
<tr>
<td>24</td>
<td>Minor</td>
<td>Informed consent</td>
<td>Incorrect completion of informed consent forms</td>
<td>Core</td>
<td>4.8.8</td>
</tr>
</tbody>
</table>
Audits

As an integral part of the School's Quality Management System, the RGIO manage a comprehensive audit programme whose aim is to assure compliance with Good Clinical Practice (GCP), regulations and standards of good practice. Since 2009, the School has conducted 75 audits in clinical trials where we have taken the role as legal Sponsor.

To help ensure that all staff can learn from common findings, the RGIO have developed an audit findings database. Over five years’ worth of audits (2012-present) have been added to the database. The database will allow the team to target training, clarify SOPs and templates and share knowledge across LSHTM so that all researchers can learn from each other. It also allows the RGIO to benchmark findings in current audits against those performed previously to ensure consistency of findings.

Overall:

- 94 audit finding topics in total:
  - 66 were classed as minor
  - 25 were classed as major
  - 3 were classed as critical

30% of findings involved informed consent:

- Re-consent not done appropriately following waiver/PrlR (35%)
- Informed Consent Form not written per SOP with all required elements (35%)
- Incorrect completion of informed consent forms (18%)
- Incorrect use of impartial witness (7%)
- Inclusion of participant without capacity to consent (4%)
GCP Categories

- Informed consent: 30%
- Site Management: 16%
- Laboratory: 14%
- Safety Documentation: 6%
- Data Management: 6%
- IMP: 5%
- Essential documents: 4%
- Protocol: 4%
- Monitoring / QC: 4%
- Protocol Management: 2%
- Database: 2%
- Ethics Committee: 1%
- QA / QMS: 1%
- Trial Management Team: 1%
- QA/QMS: 1%
- Regulatory Authority Approval: 1%
Drilling down: consent

<table>
<thead>
<tr>
<th>Informed consent</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-consent not done appropriately following waiver/PrLR</td>
<td>10</td>
</tr>
<tr>
<td>Informed Consent Form not per SOP with all required elements</td>
<td>10</td>
</tr>
<tr>
<td>Incorrect completion of informed consent forms</td>
<td>5</td>
</tr>
<tr>
<td>Incorrect use of impartial witness</td>
<td>2</td>
</tr>
<tr>
<td>Inclusion of participant without capacity to consent</td>
<td>1</td>
</tr>
</tbody>
</table>

*Total 28*
Next steps
What next?

• Add further years to the findings database
• Move from excel to a relational database
  – To be queriable by PIs
• Incorporate into GCP teaching, newsletters
• Trial CAPA plans to be amalgamated to ensure robustness of PI’s response
Concluding thoughts

- Undertaking this exercise was beneficial:
  - PIs can see common findings
  - Targeted messages to PIs on key areas of improvement
  - Allows benchmarking of audit findings to ensure consistency
- Continuous review of the audit programme by all staff
- Greater awareness of issues in research integrity and conduct
Thank you
References & Further Reading

- UKRIO
  - www.UKRIO.org
- Office for Research Integrity
  - http://ori.hhs.gov/
- Research Integrity Concordat
  - www.universitiesuk.ac.uk/highereducation/Documents/2012/TheConcordatToSupportResearchIntegrity.pdf
- European Code of Conduct for Research Integrity
  - www.esf.org/fileadmin/Public_documents/Publications/Code_Conduct_ResearchIntegrity.pdf
- Concordat to support the career development of researchers
  - www.vitae.ac.uk/policy/concordat-to-support-the-career-development-of-researchers
- DIA Global TMF model v3