**Breach Report**

**1 April 2016 - 31 March 2017**

1. **Introduction**

It is a requirement that all breaches of the standards of Good Clinical Practice or of the study protocol are reported to the reviewing REC for the purpose of keeping the favourable ethical opinion under review in light of significant developments in the research. Breach notifications are managed centrally by the HRA and classified as a violation, serious breach, or (allegation of) fraud or misconduct. All breaches are managed individually but general data is also collected for the purpose of identifying themes and trends to enable the sharing of learning outcomes.

The following data fields are recorded for all breaches:

1. Whether the breach notification relates to one or multiple breaches for the same study or more than one study.
2. Whether it was a REC breach (REC not adhering to SOPs)
3. UK or non-UK breach
4. Whether recruitment was halted in response to the breach
5. (For CTIMPs) Whether there was an MHRA inspection, either triggered or routine
6. Study details (title, REC reference, EudraCT number etc.)
7. Sponsor, site & Chief Investigator details.
8. How the breach was initially identified (e.g. routine audit or monitoring)
9. Study type (CTIMP or Other)
10. Breach type (violation, serious breach, alleged fraud or misconduct)
11. **Breach notifications**

The breach notifications received during the reporting period 1 April 2015 - 31 March 2016 are broken down in the following sections:

* 1. **Breach classification**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **2016 -2017** | **2015 - 2016** | **2014 -2015** |
| **Category** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| Serious breach | 143 | 56.08 | 135 | 53.36 | 86 | 41.75 |
| Violation | 108 | 42.35 | 115 | 45.45 | 118 | 57.28 |
| Fraud or misconduct | 4 | 1.57 | 3 | 1.19 | 2 | 0.97 |
| ***Total*** | **255** | **100.00** | **253** | **100.00** | **206** | **100.00** |

Table 2.1

* 1. **Type of study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **2016 -** | **2017** | **2015 -2016** | **2014 -2015** |
| **Study Type** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| CTIMPs | 145 | 56.86 | 166 | 65.61 | 147 | 71.36 |
| Other | 106 | 41.57 | 87 | 34.39 | 59 | 28.64 |
| Healthy Volunteers (Phase 1) | 4 | 1.57 | 0 | 0.00 | 0 | 0.00 |
| ***Total*** | **255** | **100.00** | **253** | **100.00** | **206** | **100.00** |

Table 2.2

* 1. **Other factors**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **2016 - 2017** | **2015 - 2016** | **2014 – 2015** |
| **Factor** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| Multiple breaches\* | 16 | 6.28 | 10 | 3.95 | 9 | 4.37 |
| REC breach\*\* | 1 | 0.40 | 2 | 0.79 | 2 | 0.97 |
| Study halted\*\*\* | 8 | 3.14 | 2 | 0.79 | 11 | 5.34 |

Table 2.3

\*Where one breach notification contains a number of individual breaches

\*\*Where the REC has breached Standard Operating Procedures:

Advice was sought from a referee in respect of the first dose for the trial but this advice was not taken into account in the REC decision. An unfavourable opinion was given and the application received a favourable opinion on resubmission.

\*\*\* Study halts:

Device study – PI used component used in standard practice instead of component listed in the protocol – study ended at this site.

Non-CTIMP qualitative study – consent not obtained from one patient in accordance with protocol – study halted pending re-training and audit

CTIMP – non-serious adverse event of mild blurring of vision – research site refused to continue unless potential participants were given this information up-front. Sponsor said this would impact the integrity of the trial and terminated it.

CTIMP in emergency situation – one of four ambulance services involved found a number of treatment packs unaccounted for – study halted temporarily pending investigation. Corrective And Preventive Action (CAPA) accepted by MHRA

CTIMP – PI miscalculated scores for one patient who was recruited in breach of inclusion criteria. Recruitment was halted temporarily and a substantial amendment was submitted to clarify. MHRA had no concerns re the PI or safety.

CTIMP – failure to follow procedures regarding lab reports and other reporting. Stud halted at site concerned. MHRA satisfied with CAPA.

Tissue bank – licence for the collection of autologous blood was incorrect. Processes halted pending investigation. MHRA satisfied with action taken.

Non-CTIMP – missing consent form and report form for one participant. Study halted temporarily and restarted once corrective measures in place.

* 1. **Type of breach**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **2016 - 2017** | **2015 - 2016** | **2014 – 2015** |
| **Type of breach** | **No.**  | **% of total**  | **No.**  | **% of total**  | **No.**  | **% of total**  |
| IMP | 38 | 14.90 | 54 | 21.34 | 51 | 24.75 |
| Recruitment/informed consent | 81 | 31.76 | 85 | 33.60 | 75 | 36.41 |
| Record keeping | 3 | 1.18 | 9 | 3.56 | 11 | 5.34 |
| Safety reporting | 6 | 2.35 | 8 | 3.16 | 13 | 6.31 |
| No approval | 28 | 10.98 | 19 | 7.51 | 17 | 8.25 |
| Tissue | 8 | 3.14 | 10 | 3.95 | 6 | 2.91 |
| Data protection | 27 | 10.59 | 28 | 11.07 | 17 | 8.25 |
| Other | 64 | 25.10 | 75 | 29.64 | 71 | 34.47 |

Table 2.4

1. **Summary of actions taken**

The HRA maintains close liaison with the MHRA when managing breaches for CTIMPs. It follows the lead taken by the MHRA which considers breaches on the basis of their impact on patient safety and validity of trial data. However, the REC is asked to consider any ethical implication of the breach, particularly in relation to the information provided to participants and ensuring that any consent was, and continues to be, informed.

This generally involves a review by a Sub-Committee of the reviewing REC, which may request further information/action in the interests of participants. For research other than CTIMPs, the REC is asked to consider all aspects of the breach to ensure that the favourable ethical opinion which was issued remains valid.

* 1. **Examples of further information/action requested by RECs**
* Assurances that adequate action has been taken to rectify the problem and prevent recurrences for future participants in the research
* Confirmation that samples taken without appropriate consent for research have been destroyed.
* Confirmation that an amendment has been submitted to rectify the cause of the breach
* Confirmation that appropriate steps are in place to ensure patient confidentiality
* Reassurances about training, revisions to safety protocols etc.

Additional action is taken exceptionally where deemed necessary in the interests of participants.

Note is taken of multiple transgressions\*, whether occurring at a particular site or in association with a particular individual, and information is shared with the MHRA on such matters where appropriate.

*\*It is noted that effective monitoring and reporting procedures will inevitably result in the proactive sponsors and sites appearing more often than the sponsors and sites with the inadequate reporting procedures. It is therefore important to take a proportionate approach and ensure that proactive monitoring and reporting is not being penalised. The HRA is also keen to provide support and assistance when issues are highlighted rather than taking a heavy handed approach.*

Due to the relatively low number of breach notifications received, RECs review breaches infrequently. An information sheet was therefore produced and sent out to REC members to support them in their role when dealing with breaches.

1. **Position at end of year**

At the end of the year under review, the position of breaches received was as follows:

|  |  |
| --- | --- |
|  | **2016 - 2017** |
|  | **Open** | **Closed** |  |
| **Study type** | **No.** | **%** | **No.**  | **%** | **Total** |
| CTIMPs | 17 | 6.67 | 128 | 50.20 | 145 |
| Other | 3 | 1.17 | 103 | 40.39 | 106 |
| Healthy Volunteers | 1 | 0.40 | 3 | 1.17 | 4 |
| ***Total*** | **21** | 8.24 | **234** | 91.76 | **255** |

|  |  |  |
| --- | --- | --- |
|  | **2015 - 2016** | **2014 - 2015** |
|  | **Open** | **Closed** |  | **Open** | **Closed** |  |
| **Study type** | **No.** | **%** | **No.**  | **%** | **Total** | **No.** | **%** | **No.**  | **%** | **Total** |
| CTIMPs | 5 | 1.98 | 161 | 63.64 | 166 | 2 | 0.97 | 145 | 70.39 | 147 |
| Other | 17 | 6.72 | 70 | 27.66 | 87 | 3 | 1.46 | 56 | 27.18 | 59 |
| ***Total*** | **22** | 8.70 | **231** | 91.30 | **253** | **5** | 2.43 | **201** | 97.57 | **206** |

Table 4.1

1. **Significant cases**
2. Misconduct 1

An Investigator claimed to have conducted mouse experiments as preparatory work for a number of trials - allegations of violations of research integrity were upheld following extensive and rigorous investigation. It was concluded that he had not conducted a number of experiments (5 of 11) and in 2 other cases, data presented was of unknown origin. He ran an independent research group at an NHS site. The researcher reports were presented between 2009 and 2011. The investigator resigned on 03/09/2014 and signed his report on the findings on 20/01/2016. His case went to the Medical Practitioners’ Tribunal, at which the GMC was present; this considered the allegations of fabrication of scientific data bearing upon research into pancreatic cancer. The investigator did not attend and was not represented. An order to suspend his registration was implemented immediately and his licence to practice was withdrawn. The MHRA investigated and concluded that the failures did not impact the human research or patients.

1. Misconduct 2

The Trial Coordinator at a site was found to have completed and signed prescriptions (71), reviewed laboratory results (72) for significance and signed the eligibility criteria for 1 patient. The Trial Coordinator was not a medically qualified doctor and according to Trust policy should not have been conducting either of these activities. All prescriptions and lab reports have been reviewed by the PI and no patient harm has occurred. Issues with PI oversight were identified and the PI was instructed to undertake retraining. The Trial Coordinator has since left the Trust and the MHRA confirmed that she will receive a letter informing her that she should not have undertaken the activities in question. The REC required confirmation from the Trust that any other research undertaken by the PI is checked for adherence to GCP.  On receipt, the matter was considered closed.

Recruitment to the trial has ended and no patients suffered any harm.

3. Update on breach included in this report in 2014/15 – Care Oncology study

This study initially came to the attention of the HRA in 2015 due to an article in the Telegraph newspaper which referred to a clinical trial which was being run in a private clinic and involved prescribing a ‘cocktail’ of 4 drugs, which were licenced for other conditions, to patients with cancer where previous treatment options had been exhausted. As this was a private clinic, there was a cost associated with receiving this treatment. No Clinical Trial Authorisation or REC approvals were in place. The MHRA visited the site and determined what they were doing to be a CTIMP and therefore should come under the CT Regulation.

An application was submitted to the MHRA for a CTA which, after responses to grounds for non-acceptance, a CTA was granted. An application was subsequently submitted to a REC in September 2016 and received an unfavourable opinion. The main issues were in relation to the payment and the vulnerability of the participant group. A further submission was made to the same REC but these issues had not been sufficiently addressed and a further unfavourable opinion was issued in December 2016.

The HRA communications team was contacted in January 2017 from a journalist who was planning to run an article on behalf of the Care Oncology Clinic which was quite critical of the Research Ethics Service and suggested that the REC process prevented valuable research. The HRA responded that there was an appeals process available which had not been accessed by the Care Oncology Clinic and therefore options were still available to proceed. The following day, the Care Oncology Clinic contacted the Appeals Manager to discuss possible options.

Considerable work was then undertaken to support the applicants to develop an application which would address the ethical issued raised by the REC. This essentially required the decision to consent to the treatment being separated from, and to always precede, the decision to have data collected for the clinical trial. The further application was submitted to the same REC for a third time. A favourable opinion has now been confirmed.