Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Mrs Zirka Yousaf
H&H Consultancy (UK) Ltd
Lawrence House
37 Normanton Road
Derby
DE1 2GJ

MHRA

151 Buckingham Palace Road
London
SW1W 9SZ
United Kingdom

www.gov.uk/mhra

Sent by special delivery

01 July 2016

INFRINGEMENT NOTICE
Served pursuant to regulation 48 of the
Medicines for Human Use (Clinical Trials) Regulations 2004

GCP non-compliances in relation to monitoring activities conducted during the period from September 2012 to September 2015 in relation to the clinical trials listed below.

Eudract Number	CTA Reference
[redacted]	[redacted]

The Secretary of State for Health is serving this Infringement Notice on Mrs Zirka Yousaf under regulation 48 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) (the Regulations).

The Secretary of State considers that Mrs Yousaf has contravened regulation 28(1) of the Regulations which prohibits any person from conducting a clinical

trial otherwise than in accordance with the conditions and principles of good clinical practice. The conditions and principles of good clinical practice are set out in Schedule 1 to the Regulations and, in particular, include-

- At Part 2, paragraph 4, that the necessary procedures to secure the quality of every aspect of the trial must be complied with; and
- At Part 2, paragraph 9, that all clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while confidentiality of records of the trial subjects remains protected.

The Secretary of State's grounds for considering that regulation 28(1) has been contravened are based on the identification of 18 occasions where trial monitoring activity recorded by Mrs Yousaf in the trial master file or investigator site file has not taken place as described or at all. A table setting out the 18 occurrences is attached (table 1). This demonstrates shortcomings in the processes adopted by Mrs Yousaf in relation to monitoring the trials and recording the outcome which jeopardises the quality of the trial. Additionally, it puts into question the accuracy of the clinical information given the systemic nature of the shortcomings in the monitoring process.

Preventative measures are required to be put in place by Mrs Yousaf to ensure that these breaches do not recur, and that any future clinical trial activity in the UK in which Mrs Yousaf participates is conducted in a manner fully compliant with the Regulations.

As such, Mrs Yousaf must implement effective mechanisms to ensure all trial data is collected and recorded in accordance with regulation 28(1), read with Schedule 1, Part 2 paragraphs 4 & 9. In particular:

- It is expected that any information that can verify the conduct of the trial and quality of the data is accurately recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified from the master file.

- It is expected that as author Mrs Yousaf takes responsibility for her work and the accuracy of the full information detailed in the visit report and on any other essential GCP documentation (e.g. site visit logs). In addition all changes made to any trial documents must be contemporaneous.

A written response is required within 21 days of the date of this Notice. The response should confirm that the preventative measures set out above will be implemented to prevent a reoccurrence of the issues outlined in this Notice. A

failure to implement the measures may result in further action against Mrs Yousaf, including criminal prosecution.

This Notice, along with any responses, will be provided to the European Medicines Agency and the Health Research Authority (for distribution to the relevant ethics committees) and may be published on the MHRA website.

Yours sincerely

[redacted]

A person authorised to sign on behalf of The Secretary of State for Health
Email: IAGSecretariat@mhra.gsi.gov.uk

[redacted]

Table 1: Trials and associated dates with monitoring discrepancies

Number	Date	EudraCT Number	CTA Reference	Issues
1	26 November 2012	[redacted]	[redacted]	The visit report stated that you conducted an on-site monitoring visit, however, there was no corresponding entry in the site visit log that the visit occurred at site. In your response you stated this was in fact a remote visit. Therefore, the detail of the type of visit in the report (and also contained within the trial master file) was incorrect. In addition, as this was not an on-site visit some of the activities stated in the visit report could not have occurred. For example, signing the visit log, source data verification (SDV), checklist completion, availability of source data, IMP accountability and temperature monitoring checks). Therefore, you failed to complete this report as required; as a result the trial master file was inaccurate.
2	3 December 2012	[redacted]	[redacted]	The visit report stated that you conducted an on-site monitoring visit, however, there was no corresponding entry in the site visit log that the visit occurred at site. In your response you stated this was in fact a remote visit. Therefore, the detail of the type of visit in the report (and also contained within the trial master file) was incorrect. In addition, as this was not an on-site visit some of the activities stated in the visit report could not have occurred. For example, signing the visit log, source data verification (SDV), checklist completion, availability of source data, IMP accountability and temperature monitoring checks). Whist this was a draft report, it was still prepared by you with information pertaining to the monitoring visit and containing information about what had

				occurred during that visit. If the report was pre-populated in advance of the visit, as you stated in your response, it could not contain information about what had occurred during the visit. This information could only have been known and completed after the visit. Therefore, you failed to complete this report as required; as a result the trial master file was inaccurate.
3	7 September 2012	[redacted]	[redacted]	The visit report stated that you conducted an on-site pre-study visit to Worcester on 7 September 2012. However, in your response you confirmed the visit on 7 September 2012 was in fact conducted by someone else [redacted] and you have provided documented evidence to this effect. This means that a key essential document (visit report) held in the trial master file was misleading. The visit report can be edited to document who performed the visit, and there are adequate free text areas within which this could have been recorded. However, the visit report stated nothing about the person who actually performed the visit, and was written in a manner that implied you performed it. So, the trial master file contained no information about this other person. Therefore, you failed to complete this report as required; as a result the trial master file was inaccurate. In addition, the sub-contract and training documentation for [redacted] (which you provided as evidence with your response) are considered essential documents to be able to reconstruct the trial. Sponsor responsibilities must be transferred in writing (ICH GCP 5.1 and 5.2). Therefore any agreements relevant to delegated sponsor activities must be in the trial master file. Also, the

				sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial (ICH GCP5.5.1). Therefore, all staff involved in the trial must be identified, and evidence of their qualifications, training and experience must be documented in the trial master file. You failed to submit these essential documents; as a result the trial master file was incomplete.
4	17 September 2012	[redacted]	[redacted]	As you were visiting a sponsor office in [redacted] on the 17 September 2012, a site evaluation visit to Gloucester was not feasible. Your response stated this visit actually occurred on 18 September 2012. However, there was no entry in the site visit log to verify the date of the visit at the site, so the only formal evidence provided in the trial master file was the visit report. Therefore, you failed to complete this report as required; as a result the trial master file was inaccurate.
5	17 May 2013	[redacted]	[redacted]	As you were visiting a sponsor office in [redacted] on the 17 May 2013 the monitoring visit to Manchester was not feasible. Your response stated this visit actually occurred on 16 May 2013. However, there was no entry in the site visit log to verify the date of the visit at the site, so the only formal evidence provided in the trial master file was the visit report. This was a routine monitoring visit, therefore should have had a corresponding date completed in the site visit log. Therefore, you failed to complete this report as required; as a result the trial master file was inaccurate.

6	14 November 2013	[redacted]	[redacted]	As you were visiting a sponsor office in [redacted] on the 14 November 2013, the monitoring visit to Birmingham was not feasible. Your response stated this visit actually occurred on 19 November 2013. However, the site visit log signed by both the site and yourself to verify the date of the visit at the site is documented as 14 November 2013 (corresponding with the visit report). Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.
7	18 November 2013	[redacted]	[redacted]	As you were visiting a sponsor office in [redacted] on the 18 November 2013, the monitoring visit to Birmingham was not feasible. Your response stated this visit actually occurred on 19 November 2013. However, the site visit log signed by both the site and yourself to verify the date of the visit at the site is documented as 18 November 2013 (corresponding with the visit report). Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.
8	19 December 2012	[redacted]	[redacted]	A visit report and site visit log signed by site and yourself confirmed a pre-selection visit occurred in Cardiff on 19 December 2012. However, a second visit report and site visit log signed by site and yourself confirmed a monitoring visit in Nottingham also on the 19 December 2012 for a different trial and sponsor. Your responses stated that the visit to Nottingham occurred in the morning of the 19 December 2012 and also on 20 December 2012. However, you only provided evidence (as a parking receipt) for the Nottingham visit on 20

				December 2012. The visit report and site visit log for Nottingham make no mention of a visit on 20 December 2012, only 19 December 2012. This was a routine monitoring visit, therefore should have had a corresponding date completed in the site visit log for each date attended. Therefore, you failed to complete the visit log and the report for the Nottingham visit as required; as a result the trial master file was inaccurate.
9	22 July 2013	[redacted]	[redacted]	As you were conducting an accompanied monitoring visit in Nottingham on 22 July 2013 a monitoring visit to Cardiff was not feasible. Your response stated this visit occurred on 19 July 2013. However, the site visit log signed by both the site and yourself to verify the date of the visit at the site is documented as 22 July 2013 (corresponding with the visit report). Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.
10	22 June 2012	[redacted]	[redacted]	The visit report for the monitoring visit to Cambridge documented this visit as having occurred on 22 June 2012. This was corroborated in your response. However, there was no entry in the site visit log to verify the date of the visit at the site. This was a routine monitoring visit, therefore should have had a corresponding date completed in the site visit log. Therefore, you failed to complete this log as required. In addition, a visit in Bradford 161 miles away (as documented in line 11), plus 8 hours non-project training was billed for on 22 June 2012.

11	28 June 2012	[redacted]	[redacted]	The visit report for the selection visit to Bradford documented the visit as having occurred on 28 June 2012. In your response you stated this visit was actually performed on 22 June 2012. However, there was no entry in the site visit log to verify the date of the visit at the site, so the only formal evidence provided in the trial master file was the visit report. Therefore, you failed to complete this report as required; as a result the trial master file was inaccurate.
12	19 November 2012	[redacted]	[redacted]	The visit report documented that an on-site pre-study visit occurred on 19 November 2012. In your response you stated that this visit was actually performed on site on the 8 November 2012 with a follow up telephone visit on 19 November 2012. The visit report dated 19 November 2012 documented it as an on-site visit and made no mention of the on-site visit being on 8 November 2012, or a telephone visit on 19 November 2012. You mention in your response this was not picked up by the management team, however, it is the monitor's responsibility to ensure the records of site visits are accurate. Therefore, you failed to complete this report as required; as a result the trial master file was inaccurate.
13	4 June 2013	[redacted]	[redacted]	The visit report for the close out visit to Wolverhampton documented the visit as having occurred on 4 June 2013. In your response you confirmed this visit was actually performed on 24 April 2013. The entry in the site visit log signed by you to verify the date of the visit at the site was recorded as 24 April 2013.

				Therefore, you failed to complete this report as required; as a result the trial master file contained discrepancies.
14	25 July 2013	[redacted]	[redacted]	The visit report documented a monitoring visit as having occurred on 25 July 2013 in Birmingham. Your response stated this visit occurred on 23 July 2013. However, the site visit log signed by both the site and yourself to verify the date of the visit at the site is documented as 25 July 2013 (corresponding with the visit report). Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.
15	12 December 2013	[redacted]	[redacted]	The visit report documented a close out visit as having occurred on 12 December 2013 in London. Your response stated this visit occurred on 5 December 2013. However, the site visit log signed by both the site and yourself to verify the date of the visit at the site is documented as 5 December 2013 (corresponding with the visit report). Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.
16	6 January 14	[redacted]	[redacted]	The visit report documented an on-site monitoring visit starting on 3 January 14 and completing on 6 January 14 in Preston. Your response stated this visit only occurred on 3 January 14 and that the 6 January 14 was a remote visit. However, the site visit log signed by both the site and yourself to verify that visits occurred has a record of visits on both 3 and 6 January 14 (corresponding with the visit report). In addition the visit report makes no mention of the 6

				January 14 being a remote visit. Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.
17	23 January 14	[redacted]	[redacted]	The visit report documented a monitoring visit as having occurred on 23 January 14 in Birmingham. The site visit log signed by you and the site staff was dated 23 January 14 (corroborating the visit report date). However, in your response supporting your visit to Hull on the 23 January 14 (as detailed in the row below) you advised this visit actually occurred on 20 January 14. You also provided a copy of the site's own diary showing an entry for this visit on 20 January 14. Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.
18	23 & 24 January 14	[redacted]	[redacted]	The visit report documented a monitoring visit as having occurred on 23 and 24 January 14 in Hull. In your response you advised this visit only occurred on 23 January 14 and the visit on the 24 January 14 was cancelled. There was no entry as evidence of either a visit on 23 or 24 January 14 in the site visit log. This was a routine monitoring visit, therefore should have had a corresponding date completed in the site visit log. Therefore, you failed to complete the visit log and the report as required; as a result the trial master file was inaccurate.