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SCIENCE MEDICINES HEALTH

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Good Clinical Practice Inspectors Working Group (GCP IWG)

Procedure for reporting of GCP inspections requested by the Committee for Medicinal Products for Human Use (CHMP)

GCP Inspectors Working Group

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This procedure replaces procedure no. INS/GCP/4 (EMA/INS/GCP/197226/2005) and applies to the European Medicines Agency, EU/EEA Inspectorates and CHMP rapporteurs/co-rapporteurs.

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| Keywords | <i>GCP Inspection, report, IR, IIR, compliance</i> |
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1. Summary of scope

This procedure describes the content of GCP inspection reports (IR) and the process of their approval and the distribution to the European Medicines Agency (hereinafter the 'Agency') and the CHMP.

2. Introduction

Only GCP inspection reports relating to inspections requested by the CHMP are detailed in this procedure.

The duties of the involved parties (reporting inspector, lead inspector etc.) are provided in the "[Procedure for coordinating GCP inspections requested by the EMA](#)" (INS/GCP/1), the legal basis of which is to be found in Article 57(i) of Regulation (EC) No. 726/2004 and Article 78 of Regulation (EU) No. 536/2014. When a GCP inspection has been performed, the GCP inspection reports should be part of the documentation used for the assessment of the application.

Inspections are coordinated by the Agency's committees and inspections department and conducted by the European Union (EU)/ European Economic Area (EEA) national inspectors. The request for an inspection (IREQ) is made by CHMP in a document stating the grounds for the inspection, the scope, reporting deadlines and suggested sites as well as any other information relevant to the inspectors. Contact details of the rapporteur, co-rapporteur and clinical assessors concerned by each procedure selected for inspection should be included by the Agency's committees and inspections department in the announcement letter to the inspection team as well as the time table for the assessment of application inspected. The Agency's committees and inspections department should also notify the CHMP rapporteur and co-rapporteur of the contact details of the assigned inspectors to the inspection(s).

Direct communication is always encouraged and often required between the reporting inspector, the lead inspectors, rapporteur and co-rapporteur and the Agency's committees and inspections department as early as possible in the process of preparing and reporting CHMP requested inspections. After the reports are finalised and signed, the discussion on matters such as the potential implication of the findings described in the report, will continue.

3. Inspection reports

For each site inspected an individual inspection report ([Appendix 1](#)) will be prepared. This is prepared by the lead inspector of the inspection at that site.

In some circumstances it may be appropriate to generate one report for two or more sites, even though these represent separate inspections (e.g. where a particular process at a sponsor/marketing authorisation holder (MAH) is inspected at two or more sites globally, but it is more practical to combine the findings as they address elements of the same process). In this case it will be indicated in the CHMP adopted IREQ, that a single report is requested combining the results of a group of specified sites. The IREQ may be amended to reflect this decision following input by the inspectors. These remain separate site inspections nonetheless.

For multiple site inspections on a given application, and after the full cycle of responses by the sites and reply to those by the inspectors, the outcome of the individual inspection reports are summarised into one report, the integrated inspection report (IIR). This IIR ([Appendix 2](#)) is produced to summarise and evaluate the potential implications of any major and/or critical findings described within the IRs with respect to the impact on the integrity of the trial data, the rights, wellbeing and safety of the

subjects, the compliance of the trial with GCP (including ethical principles) and also clearly address any particular concerns or questions raised by the rapporteurs in the IREQ.

Where only one site is inspected an IR can fulfil the requirement for an IIR provided the objectives and content of both are addressed. It would have to be ensured that the IR in those cases incorporates the requirements contained in the IIR template. The IR template contains these elements to be used when applicable.

The target date for the availability of the IIR is agreed and stated in the IREQ adopted by the CHMP (refer to "[Procedure for coordinating GCP inspections requested by the CHMP](#)" (INS/GCP/1)).

4. Inspection reporting process

4.1. Lead inspector

The lead inspector must ensure that appropriate input from members of the inspection team is obtained by involving them in formulating feedback for the closing meeting at the inspection, asking them to provide their written observations/findings from the inspection (for the closing meeting, afterwards or writing them into the IR directly) and reviewing the draft IR.

4.2. Post inspection preliminary outcome report

The preliminary outcome report is to provide the rapporteur/co-rapporteur and the Agency's committees and inspections department with prompt feedback on the inspection before the IRs and IIR are issued. It provides an important early indicator to the rapporteurs and CHMP as to whether the sites inspected are likely to be seriously GCP non-compliant and/or do not follow the applicable local legislation and ethical requirements which impact on the acceptability of the data that may be of major concern to the CHMP.

Following the inspection, in cases where any serious GCP non-compliance has been identified, the lead inspector should complete a brief individual preliminary outcome report ([Appendix 4](#)), indicating the details of the non-compliance that might affect the credibility of the data or the rights, safety and wellbeing of the patients. It is accepted that as this is a preliminary report, that pre-dates any responses of the inspectee/sponsor, a final decision on compliance and/or the reliability of the data for assessment might not be possible at that time.

The lead inspector should collaborate with the other members of the inspection team and aim to prepare and submit the completed preliminary outcome report to the reporting inspector within 5 working days from the completion of the inspection. If there are two or more consecutive site inspections for the same requested inspection, then the lead inspector(s) could also prepare and aim to submit a combined preliminary outcome report to the reporting inspector within 5 working days from the completion of the last site inspection.

On receipt of any preliminary outcome report from lead inspector(s), the reporting inspector should promptly submit it to the Agency's committees and inspections department.

Where preliminary outcome reports have been issued communication between the reporting inspector, the rapporteur and co-rapporteur is encouraged. E-mail exchanges may be sufficient and if necessary a teleconference should be arranged with support from the Agency's committees and inspections department.

4.3. Inspection report content

The IR should be in line with the inspection procedures as described in the "[Procedure for conducting GCP inspections requested by the EMA \(INS/GCP/3\)](#)". The IR should include an evaluation of the compliance with EU and local regulations, the principles and guidelines of good clinical practice and applicable ethical and scientific standards. The outcome of an inspection should be evaluated in accordance with the scope of the inspection and issues identified in the IREQ, and all findings should be described. A response with corrective and preventive actions (CAPA)¹ (if applicable) for each numbered critical and major finding, will normally be required to be provided by the inspectee/sponsor. For minor findings a response will usually not be required unless stated otherwise. This request will need to be stated in the report as well as in the covering letter ([Appendix 3](#)).

Findings related to the ability to continue to evaluate the marketing authorisation application (MAA) (by the assessors) will always require a CAPA response, whereas findings relating to GCP quality systems may not. The specific instructions for a particular finding (for example provision of a document or need for any additional analyses) or where CAPA is decided by the inspector not to be required by the inspectee/sponsor, can be included directly in the finding written in the IR. There is no need for any response to be provided to "comments".

Items inspected should be described in the IR using the "summary of activities inspected" table following the instructions in the IR template. The completed table could therefore be a summary of the inspection activities and the main report restricted to reporting deficiencies.

The inspection findings should be classified as minor, major or critical as per the definitions in [Appendix 5](#) and each finding should be given a unique reference number. All findings must refer to the requirements described in the legislation/guidance for which they are non-compliant. The IR should clearly state which findings are related to the application (i.e. the trial conduct and data) that may directly impact on the rapporteur/co-rapporteur benefit/risk assessment, i.e. "application related" and those which do not have such a direct impact but have been identified as system deficiencies (e.g. standard operating procedures and processes), i.e. "GCP systems related". The inspector may also make comments, which could include recommendations for best practice, but there is no need for a reference for these.

An evaluation of the significance of the findings should be presented. An overall conclusion should be included on whether the conduct, recording and reporting of the trial is acceptable/non-acceptable according to the principles of GCP; this would be the form of an interim and final conclusion as per the IR template. A separate statement should be included on whether, based on the procedures assessed, the trial was considered to have been conducted in accordance with internationally accepted ethical standards or not. A recommendation should be given on whether the quality of the reported data is suitable for the assessment by the CHMP. The preliminary conclusion in the IR may change dependent upon the assessment of the inspection responses and in this case, this would be documented in addendum 2 (see section 4.6). Serious ethical misconduct, should substantially affect the recommendation on the use of the reported data in the assessment by the CHMP.

4.4. IR format

A standard format has been developed for the IR. The template is provided in Appendix 1 and should be used for a sponsor site or investigator site or BE/BA trial IR according to the instructions contained

¹ Corrective actions: Any action designed to rectify a detected non-conformity or other undesirable situation.

Preventive actions: Any action which is intended to eliminate the cause of non-conformity or other undesirable situation and prevent them from happening in the future.

within it. The IR template, pre-populated with the trial(s) and inspection site details etc., will be provided to the inspection team by the Agency's committees and inspections department as soon as the inspection dates will be defined.

The IR should be produced with the appropriate national authority logo (the EU/EEA Member State leading the inspection at the site for which the IR is prepared) on the cover.

The IR should be written in English.

4.5. Inspection report issue and request for responses

The lead inspector should send the draft IR to the inspection team conducting that inspection and also to the reporting inspector for review and input. Once all comments have been addressed by the lead inspector, the IR is declared as final. This process should be undertaken such that the IR is usually prepared within 15 calendar days² of the end of the inspection. Where multiple sites are inspected in sequence, the IR may be prepared within 15 calendar days³ from the last day of inspection of the last site inspected.

The final IR should be appropriately signed by all the inspectors in the inspection team and sent securely to the inspectee and sponsor (where site inspected is not the sponsor) by the lead inspector with an accompanying covering text in the e-mail/letter, with the suggested text contained in Appendix 3.

The response to the IR should be requested within 15 calendar days⁴ of receipt of the IR. The lead inspector should also send a copy of the final IR to all inspectors / experts participating in the inspection and also the reporting inspector (if they have not participated in the inspection).

4.6. Responses to inspection report

Upon receipt of the responses, the inspection team, but pre-dominantly the respective lead inspector will review the responses, whether or not they are acceptable and what impact, if any, they have on the original inspection findings. Any changes as a result of factual errors in the original IR should be addressed in the addendum 2.

The responses provided by the inspectee/sponsor should form addendum 1 to the final IR – "Response from the sponsor or inspectee". Where there are attachments to the responses, the lead inspector should decide whether they need to be included in the addendum or not. The IR should not be amended and re-issued as a result of the review of the responses.

A summary of the evaluation should be written by the lead inspector, indicating the final number of critical, major and minor findings, then reviewed and appropriately signed by the inspection team. The final document will be addendum 2 to the final IR - "Evaluation by the inspectors of the response to the inspection report". This should be sent to the inspectee and/or the sponsor by the lead inspector and by the Agency's committees and inspections department to the applicant, where they are not the sponsor, if the IR is acting as the IIR or upon specific request by the sponsor. Additionally, the addendum 2 should give any recommendations for further actions (e.g. re-inspection) and where it is acting as the IIR, the specific sections in addendum 2 in the template should be completed.

² This should be considered as an indication and can be modified if necessary as per the Reporting Inspector's plans

³ This should be considered as an indication and can be modified if necessary as per the Reporting Inspector's plans

⁴ This should be considered as an indication and can be modified if necessary as per the Reporting Inspector's plans

If there is no response from the inspectee within the 15 calendar days' time frame, the absence of a reply should be recorded in addendum 2 of the report "Evaluation by the inspectors of the response to the inspection report" by the lead inspector.

The final signed IR, including any appendices and addenda 1 and 2, should be prepared as one pdf document (in exceptional cases, some additional files may be required where converting to a pdf would not be feasible, for example, Excel® files of data, which the assessor may wish to review) and sent by the lead inspector to the reporting inspector within 10 calendar days⁵ after the inspection responses deadline stated in the covering letter to the inspectees/sponsor.

Where the IR is the only inspection report (no requirement for an IIR), then this should be sent to the Agency's committees and inspection department by the reporting inspector by secured e-mail (Eudralink) as would be the case for an IIR (see section 5.2).

4.7. Publishing IRs

Once implemented, Regulation 536/2014 will require IRs to be published to the EU CT system. The lead inspector will be responsible for this submission together with an evaluation of the responses of the inspectees (addendum 2). Guidance for this will be available, for example, relating to redaction requirements.

5. Integrated inspection reporting process

5.1. Reporting inspector

The reporting inspector is nominated by the reporting inspectorate. It is the duty of the reporting inspector to circulate any post-inspection preliminary outcome reports (see section 4.2) and to monitor the timely production of the IRs. The reporting inspector is also responsible for the production of the IIR and the communication with the Agency's committees and inspections Department.

Any questions related to the IIR are handled by the reporting inspector, who is responsible for the necessary communication with the lead inspector(s), the Agency' committees and inspections department, CHMP members and rapporteur/co-rapporteur.

5.2. Integrated inspection report production and availability

The IIR should be written in English and the template in Appendix 2 should be used. The IIR template, pre-populated with the trial(s) and inspection site details etc., will be provided to the inspection team by the Agency's committees and inspections department together with the individual inspection reports. The IIR document should be produced with the appropriate national authority logo (the EU/EEA Member State acting as reporting inspector in the inspection) and the Agency logo on the cover.

The reporting inspector compiles the IIR based on the IRs received by the lead inspector(s). The IIR is intended as a summary document and not a compilation of the individual IRs. The IRs should be appended to the IIR, (including their appendices and addenda 1 and 2).

The IIR should summarise and indicate the total number of major and critical findings from all the IRs and by reference to the findings in the IRs, not repeating the findings as a cut and paste operation.

⁵ This should be considered as an indication and can be modified if necessary as per the Reporting Inspector's plans

Any finding(s) that is/are system(s) related not impacting on the application should be highlighted in the IIR. These need to be clearly separate from the findings that are more specifically related to the individual site or the application (i.e. the trial conduct, ethical conduct and data) and thus may impact on the rapporteur/co-rapporteur assessment.

The IIR should contain an overall evaluation of the quality of the data submitted, compliance with the principles of GCP and ethical standards, based on the findings at all inspected sites. The IIR should clearly address any concerns or questions raised in the original inspection request(s) from CHMP.

The IIR should also contain a conclusion on whether the ethical conduct of the trial was acceptable and therefore whether the data may be used for the evaluation by the assessors. Furthermore, the conclusion should state whether the quality of the data inspected as a whole or in parts was adequate such that the data may be used for the evaluation by the assessors regarding acceptance/non-acceptance of the trial data. The report should be clear concerning whether the inspection findings affect the primary endpoints of the inspected clinical trial. The data which are not considered acceptable for assessment need to be detailed.

The IIR conclusions should recommend any follow-up to be requested from the applicant, for example additional analyses for the MAA or any further actions or a further inspection if considered necessary and any other follow-up as outlined in section 6.2.

The draft IIR should be circulated to the lead inspectors (authors of the IRs)/participating inspectors/experts for review. Once all comments have been addressed, the final IIR will be approved and appropriately signed by the RI and all the lead inspectors who have contributed with an IR.

The reporting inspector sends the final signed IIR with the individual IRs received from the lead inspector(s) to the Agency's committees and inspection department by secured e-mail (Eudralink) within 10 calendar days⁶ and copy in all of the participating inspectors. The individual IRs/IIR sent, should not be password controlled and documents should not be embedded. Only the IIR, including the final individual site inspection reports, should be provided to the Agency's committees and inspection department (however data may be provided as an additional file, see section 4.6); otherwise the Agency's committees and inspections department will request the reporting inspector the proper assembly of the reports for its submission to the Agency.

The reporting process, from completion of the last site inspection to the circulation of the IIR and related appendices to the Agency's committees and inspections department should be normally be completed within 50 calendar days⁷.

Any potential issues or problems with meeting timelines should be communicated to the Agency's committees and inspections department by the reporting inspector in a timely manner.

5.3. Procedure for review of acceptability of IIR, the Agency's committees and inspections department, European Medicines Agency

A review of the report is conducted on behalf of the CHMP by the Agency's committees and inspections department that will check the IIR (with the appended IRs) (or the IR for single site inspections) for adherence to:

- the procedures established by the GCP IWG;
- the IREQ adopted by the CHMP;

⁶ This should be considered as an indication and can be modified if necessary as per the Reporting Inspector's plans

⁷ This should be considered as an indication and can be modified if necessary as per the Reporting Inspector's plans

- the citation of applicable regulations and guidelines.

The Agency's committees and inspections department will validate the IIR received within 5 working days. Any difficulties encountered during this review will be notified to the reporting inspectorate in writing and without delay, with a deadline for revision or other remedial action.

If the reporting inspectorate does not agree with the Agency's committees and inspections department, the reasons should be explained. If the Agency's committees and inspections department still considers there is a problem with the content of the report, the rapporteur/co-rapporteur and CHMP will be sent the report and a document describing the point(s) of disagreement.

In the event of outstanding disagreement, the report and problems identified will be circulated to the GCP IWG, for peer review, by written procedure. The responses should be provided within 15 calendar days⁸ after which they will be collated and appended to a final recommendation made by the Agency's committees and inspections department which will be communicated to the rapporteur/co-rapporteur, CHMP and the reporting inspectorate.

5.4. IIR submission to rapporteur/co-rapporteur and CHMP

The Agency's committees and inspections department will submit the final IIR (or IR in case of a single site inspection) to the rapporteur/co-rapporteur and CHMP as soon as it has been validated. The rapporteur/co-rapporteur and CHMP consider the content and findings of the IIR (or IR) and may ask for clarification or additional information to be provided by reporting inspector (and referral to the inspection team where necessary).

The Agency's committees and inspections department will submit the IIR (or IR) to the applicant after obtaining a corresponding authorisation from the sponsor or other owner of the data if it is a different organisation and after having consulted the rapporteurs concerned.

6. Interaction between inspectors and rapporteurs/co-rapporteurs

6.1. Discussions between inspectors and rapporteur/co-rapporteur

The classification of GCP findings as minor, major and critical does not directly correspond to the overall benefit-risk evaluation performed by the assessors. Some critical findings may not be relevant to the overall evaluation, but may be relevant to single individual patients' safety. Other findings, that do not meet the criteria to be classified as critical, may be of significant concern to the CHMP in their evaluation of the data. Also, multiple issues that are individually not especially serious could collectively indicate a trial of such poor quality that the conclusions might be unreliable. GCP inspection findings, even if not directly influencing the benefit-risk balance, may still affect the acceptance or not of a trial submitted in a MAA, if they raise serious questions about the rights, safety and well-being of trial subjects and hence the overall ethical conduct of the trial.

If the GCP inspection does not identify any issues considered to potentially impact on the benefit-risk evaluation or the ethical conduct of the trial(s), then little or no interaction will be required between the inspectors and the rapporteur/co-rapporteur.

⁸ This should be considered as an indication and can be modified if necessary as per the Reporting Inspector's plans

The outcome of the GCP inspection is an important part of the assessment forming part of the benefit/risk discussion and it needs to be properly reflected in the CHMP assessment report (AR) and in the European public assessment report (EPAR).

Where there are significant issues, the Agency's committees and inspections department will be responsible for ensuring that timely interaction between rapporteur/co-rapporteur and the reporting and lead inspectors to discuss findings that are identified as possibly impacting on the benefit/risk evaluation or major issues regarding ethics and/or patient safety, will take place. E-mail exchanges with assessors may suffice, but if necessary the Agency will provide support through organisation of teleconference or presentation by the inspector(s) at CHMP. In case CHMP comes to a positive opinion on a MAA even though a pivotal trial had serious GCP non-compliance identified, the discrepancy should be explained in the AR and EPAR.

Any documentation referring to the outcome of the interaction between inspectors and assessors should be archived in the inspection file. The reporting inspector and lead inspectors should ensure, to the extent possible, that deputies are nominated to provide input where they are not themselves available. In some cases the reporting inspector may need to provide the evaluation alone if the lead inspector(s) are not available in the timeframe required.

The purpose of the discussion, between inspectors and rapporteurs/assessors, is to agree on any issues that need to be put in the list of questions (LoQ) or list of outstanding issues (LoOI) by the rapporteur/co-rapporteur assessors. The discussions should consider at least the following:

- Whether and to what extent the trial in question should be accepted for consideration in the benefit/risk assessment.
- Measures to be taken to clarify any areas of uncertainty (e.g. re-analyses of data). It is not expected that there will normally be any measures additional to those already being dealt with by the GCP inspection process.
- Recommendations for post-inspection follow up (described below).

Additionally, the document "[Points to consider on GCP inspection findings and the benefit-risk balance](#)" should be consulted in undertaking this assessment (EMA/868942/2011).

Following the issue of the preliminary outcome report, discussion between the inspectors and assessors will continue regarding the findings that could have an impact on benefit/risk evaluation or serious ethical misconduct.

6.2. GCP trial/application findings related follow up

The LoQ/LoOI should be copied to the inspection team by the Agency's committees and inspections department once adopted by CHMP. When there are follow-up documents to be reviewed and/or generated as a result of the inspection (e.g. sensitivity analyses or new analyses with corrected errors), the review should be led by the rapporteur/co-rapporteur, if applicable in conjunction with the reporting inspector, the Agency's committees and inspections department and Agency product leader (EPL).

The Agency's committees and inspections department will ensure that the reporting inspector (cc inspection team) is provided with the applicant's responses and, when required by the rapporteurs, with a deadline for providing an assessment of these responses to the rapporteur/co-rapporteur. The reporting inspector's assessment of the applicant's responses should be sent by e-mail directly to the

rappporteur/co-rappporteur as well as to the Agency (Agency's committees and inspections department and the Agency product leader).

In order to achieve this in an effective way the following steps are taken for each inspection, or follow-up:

- The letter announcing the inspection to the applicant, from the Agency, will make clear that any responses to the trial specific or application specific issues raised by the inspection(s) must be addressed by the applicant to the rapporteur/co-rappporteur, CHMP, and the Agency product leader (EPL) and the Agency's committees and inspections department who will be responsible to inform the inspection team as appropriate. This in particular means any responses submitted as part of a response to a LoQ or LOI, and/or any written comments related to the inspection, GCP compliance, ethical conduct and/or validity of the data.
- The rapporteur and co-rappporteur may request a review of the applicant's responses by the inspection team; this has to be done in writing to the reporting inspector (cc the Agency's committees and inspections department and Agency product leader).
- Where an evaluation of the responses by the inspection team is required, the points and the timelines for such review will need to be agreed on a case-by-case basis with the rapporteur and co-rappporteur, the reporting inspector and the Agency (its committees and inspections department and Agency product leader).
- The inspection team, through the reporting inspector, may decide in any event to make a written comment to the responses. In this case, the reporting inspector should inform the rapporteur/co-rappporteur and the Agency (its committees and inspections department and Agency product leader and agree on the timelines).
- The written evaluation will be provided by the reporting inspector to the rapporteur/co-rappporteur and the Agency (its committees and inspections department and Agency product leader) in parallel.
- The rapporteur/co-rappporteur integrates the inspectors' assessment/comments into the relevant assessment report.

6.3. GCP systems findings related follow up

Follow up on findings that relate to potential issues of data integrity, as recommended in the IR and/or IIR, may be important outside of the MAA procedure. This should be done in order to ensure the future quality of the inspected entity since, for example, some major GCP deficiencies affecting the systems of a contract research organisation or the sponsor, might have implications for the data integrity of subsequent regulatory submissions. In response to the inspection reports, the inspectees may have provided CAPA for such findings if requested in the IR. In such case the committees and inspection department will review the reports with a view to assess whether any additional actions are needed, these could include:

- Where the inspected organisation is within a Member State (MS), then the inspectorate of that MS is made aware of the inspection report (if their inspectors did not participate in the inspection). At MS level an inspection of the organisation as part of a new CTA, a 'for cause' inspection or follow up of the CAPA could be incorporated in the national inspection programme. Any follow-up actions would be the responsibility of the concerned Member State.

- Triggering GCP inspections of later trials from the same source (applicant/sponsor) or from information received from elsewhere e.g. FDA, EudraCT /new EU CT system database. The Agency will use the information available in corporate GxP in order to create, on a regular basis, a report of inspections where GCP non-compliance issues were identified (inspections resulting in CAPA /request for re-inspection) and circulate it to the GCP IWG. In this way, all EU Member States will be systematically aware of site or organisation specific problems which would be taken into account in future assessments.
- At the Agency level a re-inspection of the concerned organisation could be requested as part of a MAA.
- Issues identified at third country level should be flagged by the Agency to the local authorities whenever possible and depending on the confidentiality arrangements in place. Any follow-up actions would be the responsibility of the third country authorities.

APPENDIX 1 – Individual inspection report template

Click here for the [template](#).

APPENDIX 2 – Integrated inspection report template

Click here for the [template](#).

APPENDIX 3– Suggested covering letter text for submission of individual inspection report to the inspectee and sponsor

Address

With regard to the GCP inspection conducted DD/MM/YY to DD/MM/YY at <inspectee>, please find enclosed the inspection report.

The following advice is provided regarding report responses.

1. One person should assume overall responsibility for the responses. This individual should sign and date the document that includes the responses.
2. You should respond to the inspection findings. The inspection report will be clear on those findings that concern the application and these must be responded to otherwise the application may not be progressed. Inspection responses should cross-reference the finding number detailed in the report.
3. Responses should detail a brief summary of planned corrective and preventive actions and estimated timeframe for completion.
4. Responses are NOT required for minor findings or comments (unless specifically indicated in the report).
5. Indicate clearly if there is any major disagreement or factual errors with any inspection finding.
6. Photocopies of documentary evidence should NOT be submitted unless specifically requested in the report.
7. Please provide the responses in electronic format (by e-mail to the inspector, via Eudralink or on CD) and a paper copy (inspector to amend this as required).

We look forward to receiving responses to the findings listed in the report by DD/MM/YY. (Amend date as appropriate)

Yours sincerely

Name

APPENDIX 4– Preliminary outcome report

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|---|
| To: |
| From: |
| Re: <EMA Procedure Number>, <Product>, <Protocol number>, <site type 1>,<site name 1>, <site address 1> |
| EMA Inspection reference number: |
| Number of pages: 1 |

THIS IS A PRELIMINARY INDIVIDUAL* OUTCOME REPORT

These observations should be considered as preliminary pending the circulation of the inspection report to the inspectee and, if applicable, to the sponsor and the evaluation of their response by the inspector(s). The response may result in some of the findings being removed from the report or their grading being modified.

Dear Colleague,

Following the inspection(s) carried out at the above mentioned site(s), please be informed that the inspection team made the following preliminary observations:

Issues which require further follow-up were observed. A decision regarding compliance and/or the use of clinical trial data for the assessment by the CHMP cannot be taken at this very moment, as the responses of inspectee/ sponsor might have an impact on the overall evaluation.

Non-compliance that could affect the rights, safety and wellbeing of the patients or the credibility of the data was observed.

<Furthermore the inspectors would like to bring the following issues to your attention:

The final evaluation of the inspection outcome will be provided in the final*/integrated* inspection report which will be sent to you*/the European Medicines Agency* **before <deadline for reporting>**.

Kind regards,

Name

* Delete as appropriate

Instructions for completion:

Lead inspector completes the preliminary outcome report, following consultation with the inspection team/reporting inspector, within 5 working days from the completion of each individual inspection (this can be extended in case of consecutive inspections). The completed form should then be sent to the reporting inspector.

Once received the preliminary report from the lead inspector, the Reporting inspector should forward it to the Agency's committees and inspections department who is responsible to inform the rapporteurs.

APPENDIX 5– Grading of inspection findings

Critical

Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action required

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.

Major

Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Major observations are serious deficiencies and are direct violations of GCP principles.

Possible consequences: data may be rejected and/or legal action required

Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

Minor

Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practises and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Comments

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.