Machine
Readable Data
Not Required for
EMA – Really?

David C. Izard
PhUSE 2019
– EMA does indeed have a mechanism for pulling in machine readable data to their review process!

– Provided to support GCP Inspection during review cycle

– Deployment of CDISC standards to these EMA deliverables is encouraged
GCP Inspection Process

**BIMO Deliverables**
- Standardized Study Data
- US FDA NDA Filing
- Identify Sites for GCP Inspection
- Notify Sponsor of GCP Audit (sites identified)
- GCP Audit Sites & Sponsor
- Data as TLFs
- EMA Marketing Application Filing
- Identify Sites for GCP Inspection
- Notify Sponsor of GCP Audit (sites identified)
- GCP Audit Sites & Sponsor

Data...

**US FDA NDA Filing**
- eCTD

**EMA Marketing Application Filing**
- eCTD
Notice of EMA GCP Inspection Request

- The individual patient data listings for the patients. These may be restricted to the selected investigator site, but confirmation should be sought from the lead inspector prior to sending the documentation (including discontinued patients, protocol deviations, patients excluded from the efficacy analysis, demographic data, compliance and/or drug concentration data (if available), individual efficacy response data, adverse event listings, listing of individual laboratory measurements, etc.).

- Excel ® work book containing data listings for patients recruited at the selected site(s) (see EMA Q&A for further details –
Notice of EMA GCP Inspection Request

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- Excel ® work book containing data listings for patients recruited at the selected site(s) (see EMA Q&A for further details -
Notice of EMA GCP Inspection Request

Please note that no data should be provided until contact has been established with the reporting/lead inspector and the requirements for data listings have been discussed. Source data location list, see also Q&A: Good Clinical Practice on EMA homepage:


EMAP Website: Q&A for GCP

Navigation to Presenting Data to a GCP Inspection Team

Q&A: Good clinical practice (GCP)

GCP matters

7. How should data be presented when they are sent to the inspection team prior to a GCP inspection requested by the CHMP?
In connection with centralised applications, the Committee for Medicinal Products for Human Use (CHMP) often requests a good clinical practice (GCP) inspection of one or more sites to be performed. Prior to such GCP inspections, the European Medicines Agency (EMA) sends an announcement letter to the applicant in which – among others – a list of documents to be provided to the inspection team is presented. The data are used by inspectors for review in order to select patients and data to inspect. Among the requested documents are the individual patient data listings for the patients recruited at the sites to be inspected. Based on past experience, this request for data listings poses a significant number of problems and subsequently costs a lot of time for companies and inspectors, quite often resulting in listings of suboptimal quality.

The aim of this Q&A is to standardise and clarify the format of the data listings to be provided.

It is important to emphasise that the following guidance is the expected standard for most inspections; however, for some trials different, specific requests may be warranted. Consequently, no data should be provided until contact has been established with the reporting inspector and the requirements for data listings have been discussed.

In general, the following is expected:

a. All data for the selected sites (and if requested for all sites in the trial) should be provided to the inspectors. That includes all case report form (CRF) data and in addition data which are not necessarily part of the CRF such as data provided to the sponsor by vendors (laboratory data, data from central evaluation of electrocardiograms (ECGs), imaging etc.), data from electronic patient-reported outcomes (ePROs) etc.

b. Data should be provided as Excel spreadsheet line listings following the proposed formats and naming detailed below.

c. All listings must have raw CRF data and any data derived or imputed from it that forms part of the data analysis.

d. Both the CRF data set and the data set used for analysis, for instance as Excel exports from statistical analysis system (SAS), should be provided. They should be provided as exported to Excel document. Any process from raw data to analysed data should be explained if not explained in the statistical analysis plan.

e. Paper copies should not be provided unless specifically requested by the inspection team.

f. There should be a statement from the sponsor to confirm that the data provided is exactly the same as that submitted in the clinical study reports (CSRs) in the application (this will be checked at the inspection).
"Do you want data for just the selected sites or do you want it for all sites (the full set of study data)?"

"Yes, please provide the full set of study data, not just the sites being audited."

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Provide collected data as well as analysis (derived) data.

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Specification of formats and names:

a. Naming of all files and Excel spreadsheets should be meaningful and self-evident. Columns/names of variables in Excel worksheets could be called adverse event (AE), concomitant medications (CM), vital signs (VS) preferably in accordance with clinical data interchange standards consortium (CDISC) terms. Alternatively a 'translation' document should be provided to explain abbreviations.

b. Data should be presented formatted, for example category values 1 and 2 as "yes" and "no" etc. If this isn’t done then the format assignment to the data code must be provided.

c. The data listings in Excel should ideally be consistent with the layout in the Clinical Study Report CSR, such that cross referencing the data is straightforward.

d. Data types and field types should be appropriate for the specific data, for instance numerical data should always be numeric type and not character type, formats can be applied to the numeric data (e.g. dates). This is to allow the inspectors to do their own calculations.

e. A copy in PDF format of the CSR listings per patient, for just the particular investigator site to be inspected should generally also be provided. The inspection team may also request to have paper copies brought to the investigator site for source data verification (SDV) purposes. The electronic data should not be an image, such that it is not possible to search, for example by date. There should be a statement from the sponsor to confirm that the data provided as copies in PDF format is exactly the same as that submitted in the CSR(s) in the application (this will be checked at the inspection).

f. The data provided in PDF format and Excel worksheets should be set up for printing (e.g. print areas defined and suitable page arrangements set).
“Are you familiar with CDISC SDTM & ADaM data formats?”

“Yes”

“Should we provide our sets of SDTM & ADaM data to satisfy this requirement?”

“Yes”

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**EMA Website: Q&A for GCP**

**Patient Data Listings in Excel Format**

- **“Are you familiar with the data definition file (define.xml) for SDTM & ADaM?”**
  - “Yes”

- **“Can we provide this file in PDF format to serve as the ‘translation’ document?”**
  - “Yes”

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- f. The data provided in PDF format and Excel worksheets should be set up for printing (e.g., print areas defined and suitable page arrangements set).
Preserve data types (character versus numeric), particularly when creating Excel version of ADaM

Make sure define.xml / pdf provides complete decodes / controlled terminology

Provide Excel workbooks with printing controls in place
“Can we repurpose data listings from the CSR for this requirement?”

“Yes”

“Can we provide a single listing per domain (e.g., AE or VS) for each site?”

“Yes”

Specification of formats and names:

a. Naming of all files and Excel spreadsheets should be meaningful and self-evident. Columns/name of variable in Excel worksheets could be called adverse event (AE), concomitant medications (CM), vital signs (VS) preferably in accordance with clinical data interchange standards consortium (CDISC) terms. Alternatively, a ‘translation’ document should be provided to explain abbreviations.

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EMA Website: Q&A for GCP

Patient Data Listings in Excel Format

Report format of the patient data listings

Unless otherwise agreed with the inspection team, the data should be collected in the groups defined below - each to be presented in a different Excel spreadsheet. The columns “study site ID”, “subject ID” and “treatment group” and where applicable “visit ID” and/or “visit date” should be in all spreadsheets. Some data listings may – depending on the trial – belong to different groups, for instance “vital signs/physical exam” usually belongs in the safety data group; however, in a hypertension trial it is likely to be an efficacy parameter. If in doubt, please ask the lead inspector:

1. **Study populations & conduct data** – recruitment dates, analysis populations, protocol/GCP non-compliance (deviations/violations), withdrawals/completed and reasons for withdrawing/not completing/not being randomised and outcome.
2. **Subjects’ data** – demographic/covariate data (birth date, age, gender, ethnicity, race), medical history (general and related to trial objectives, e.g. tumour details, disease history/measurements), eligibility (inclusion/exclusion), consent date(s).
3. **Treatment data** – stratification group, randomisation, treatment given (including kit number and batch number), dosing dates, dose, dose adjustments, data concerned with compliance with treatment, non-medicinal co-treatments as part of trial protocol (e.g. radiotherapy).
4. **Specific efficacy** – raw data, repeated assessments related to efficacy, imputed values presented such that their determination from raw data can be seen (changes in parameters compared to baseline, categorisation of data to form new endpoint, clarity on last observation carried forward (LOCF) when used).
5. **Safety data** – adverse event (AE) / serious adverse event (SAE) – data from CRF log and also from SAE forms, repeated assessments related to safety, side effects captured in CRF (not AEs) with severity grading etc. Both data entered by site and coded data should be listed.
6. **Laboratory type data** – sample/scan/measurement date/time (nominal and actual from CRF)/settings and other necessary details, report data time, result (from laboratories), investigator review.
7. **Concomitant medication data** – both data entered by site and coded data should be listed.
8. **Subject questionnaire data** (if not part of efficacy) (e.g. quality of life (QoL)).
“Are you familiar with the Study & Analysis Data Reviewers Guides?”

“Yes”

“Can we provide those documents in order to communicate study data groupings?”

“Yes”

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Complete Set of Deliverables to GCP Auditor

Patient Data Listings in Excel format
- Full SDTM & ADaM data as Excel
- Define.xml/pdf for SDTM & ADaM
- Study Data Reviewer’s Guide
- Analysis Data Reviewer’s Guide

Traditional PDF Patient Data Listings
- PDF data listing by domain for each site
- Complied into single PDF file w/ bookmarks
- Readme file that grouped listings by data type
Parting Thoughts

• These deliverables are not all you will do…
  …many queries from the GCP Inspector in advance of the site level inspection

• Site inspections followed by Sponsor inspection
  …and everything it stands for
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Thank you!