Sponsor duties: Auditing and monitoring of BE studies

BioBridges, Prague, 2018.

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My background

Former EU regulator: Norwegian M
Clin. assessor, PK, BE, TE. So
WHO PQ.

As BE inspector
+ BE trainer

Now freelance consultant: Present and past clients include companies, agencies, WHO/UN, and USP.

Discussion with client, 2018

Me: *“What do you see as the risk in your trials?”*

Client: *“The risk is that you audit them and have findings. ICH E6 tells us to minimize the risks.”*

ICH E6

5.18 Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s) with GCP, and with the applicable regulatory requirement(s).

Plasma concentrations are definitely data.

Extent and nature

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Perspective on Centralized Monitoring

Much phase III data is now collected electronically, often on smartphone. Direct upload to a central server or pseudo database. The wording in ICH E6 R2 may indeed reflect this fact and explore the opportunities offered by novel technology.

Conclusion so far:

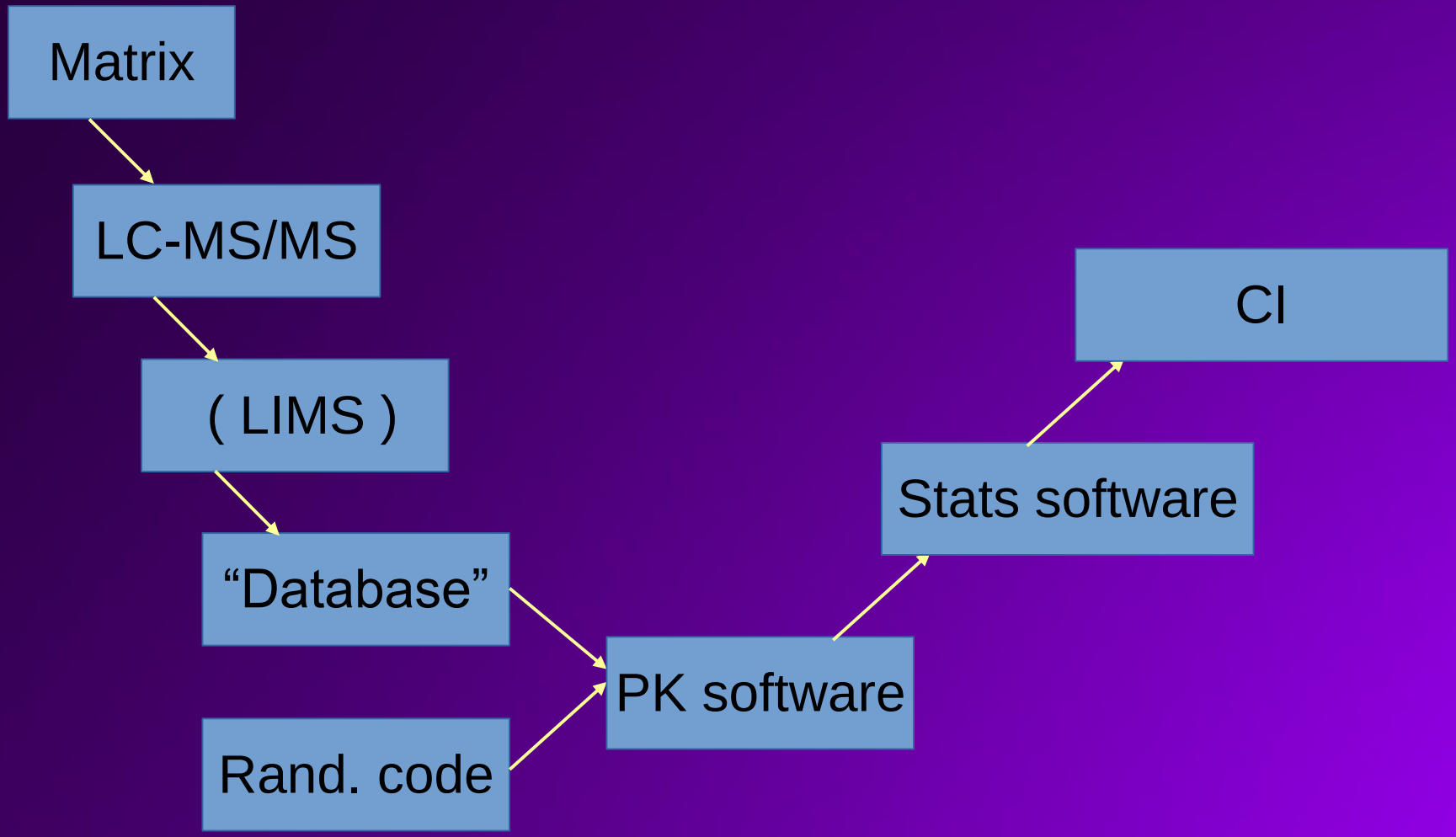
ICH E6 explains why monitoring of the bioanalytical portion of BE trials is as important as any other part of the trial.

Note also that most CRO warning letters (NOCs) map directly to the bioanalytical work. So naturally it has priority.

Part I

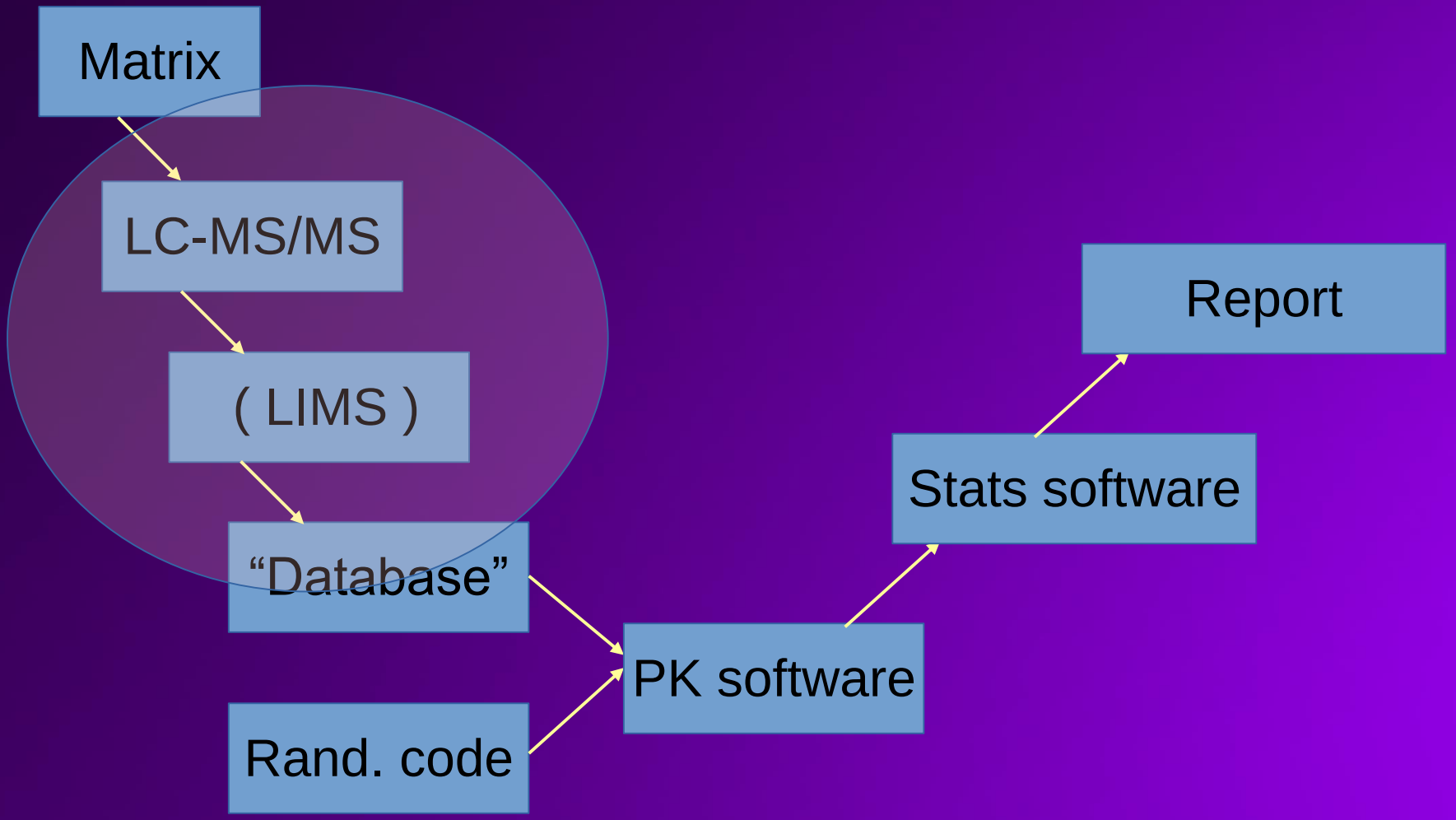
A CM proposal for the
bioanalytical parts of BE trials

Essential flow in a nutshell, sorta.



Spot the “accumulating data”

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).



Nature of the accumulating data

“Result tables”
e.g. Analyst ™ or MassHunter ™

Index	Sample Name	Sample Type	Acquisition Date	File Name	Analyte Pea	Analyte Co	Area Ratio	IS Peak Area	Use Record	Record Mod	Calculate	Accuracy (%)
1	Std Blank 1	Double Blank	08/08/18 12:00 AM	AbxD01.wiff	0	0	#DIV/0!	0		0	N/A	N/A
2	Std Zero	Blank	08/08/18 12:04 AM	AbxD02.wiff	0	0	0	122415		0	N/A	N/A
3	ESCIT_J8_STD1	Standard	08/08/18 12:08 AM	AbxD03.wiff	6531	0.2	0.04941	127054	1	0	0.206	103.00
4	ESCIT_J8_STD2	Standard	08/08/18 12:13 AM	AbxD04.wiff	13461	0.4	0.10864	131738	1	0	0.383	95.75
5	ESCIT_J8_STD3	Standard	08/08/18 12:17 AM	AbxD05.wiff	32009	1	0.28494	123500	1	0	0.9304	93.04
6	ESCIT_J8_STD4	Standard	08/08/18 12:22 AM	AbxD06.wiff	66391	2	0.58194	118239	1	0	1.9842	99.21
7	ESCIT_J8_STD5	Standard	08/08/18 12:26 AM	AbxD07.wiff	149472	4	1.02724	115485	1	0	4.5388	113.47
8	ESCIT_J8_STD6	Standard	08/08/18 12:31 AM	AbxD08.wiff	257203	8	2.32261	115887	1	0	7.7638	97.05
9	ESCIT_J8_STD7	Standard	08/08/18 12:35 AM	AbxD09.wiff	527641	16	4.64908	118193	1	0	15.589	97.43
10	ESCIT_J8_STD8	Standard	08/08/18 12:40 AM	AbxD010.wiff	771933	20	5.69453	133365	1	0	20.204	101.02
11	Std Zero 2	Double Blank	08/08/18 12:44 AM	AbxD010.wiff	0	0	#DIV/0!	0		0	N/A	N/A
11	ESCIT_J8_S18_P1_Smpl001	Unknown	08/08/18 12:49 AM	AbxD011.wiff	0	N/A	0	137860		0	No Peak	N/A
12	ESCIT_J8_S18_P1_Smpl002	Unknown	08/08/18 12:53 AM	AbxD012.wiff	0	N/A	0	136714		0	No Peak	N/A
13	ESCIT_J8_S18_P1_Smpl003	Unknown	08/08/18 12:58 AM	AbxD013.wiff	0	N/A	0	129496		0	No Peak	N/A
14	ESCIT_J8_S18_QCLOW	Quality Control	08/08/18 01:02 AM	AbxD014.wiff	21082	0.6	0.16897	121368	1	0	0.6324	105.40
15	ESCIT_J8_S18_QCHIGH	Quality Control	08/08/18 01:06 AM	AbxD015.wiff	519390	16	2.66063	123000	1	0	14.747	92.17
16	ESCIT_J8_S18_P1_Smpl004	Unknown	08/08/18 01:11 AM	AbxD016.wiff	107864	N/A	1.26546	113762		0	2.223	N/A
17	ESCIT_J8_S18_P1_Smpl005	Unknown	08/08/18 01:15 AM	AbxD017.wiff	17121	N/A	0.19965	136356		0	0.362	N/A
18	ESCIT_J8_S18_P1_Smpl006	Unknown	08/08/18 01:20 AM	AbxD018.wiff	52687	N/A	0.58804	128992		0	1.04	N/A
19	ESCIT_J8_S18_P1_Smpl007	Unknown	08/08/18 01:24 AM	AbxD019.wiff	144870	N/A	1.8125	133475		0	3.177	N/A
20	ESCIT_J8_S18_P1_Smpl008	Unknown	08/08/18 01:29 AM	AbxD020.wiff	154405	N/A	1.84175	134430		0	3.228	N/A

Columns (here Analyst)

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12	ESCIT_J8_S18_P1_Smpl002	Unknown	08/08/18 12:53 AM	AbxD012.wiff	0	N/A	0	136714		0	No Peak	N/A
13	ESCIT_J8_S18_P1_Smpl003	Unknown	08/08/18 12:58 AM	AbxD013.wiff	0	N/A	0	129496		0	No Peak	N/A
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Chromatolophystique in a nutshell

Chromatolophystic software will (should):

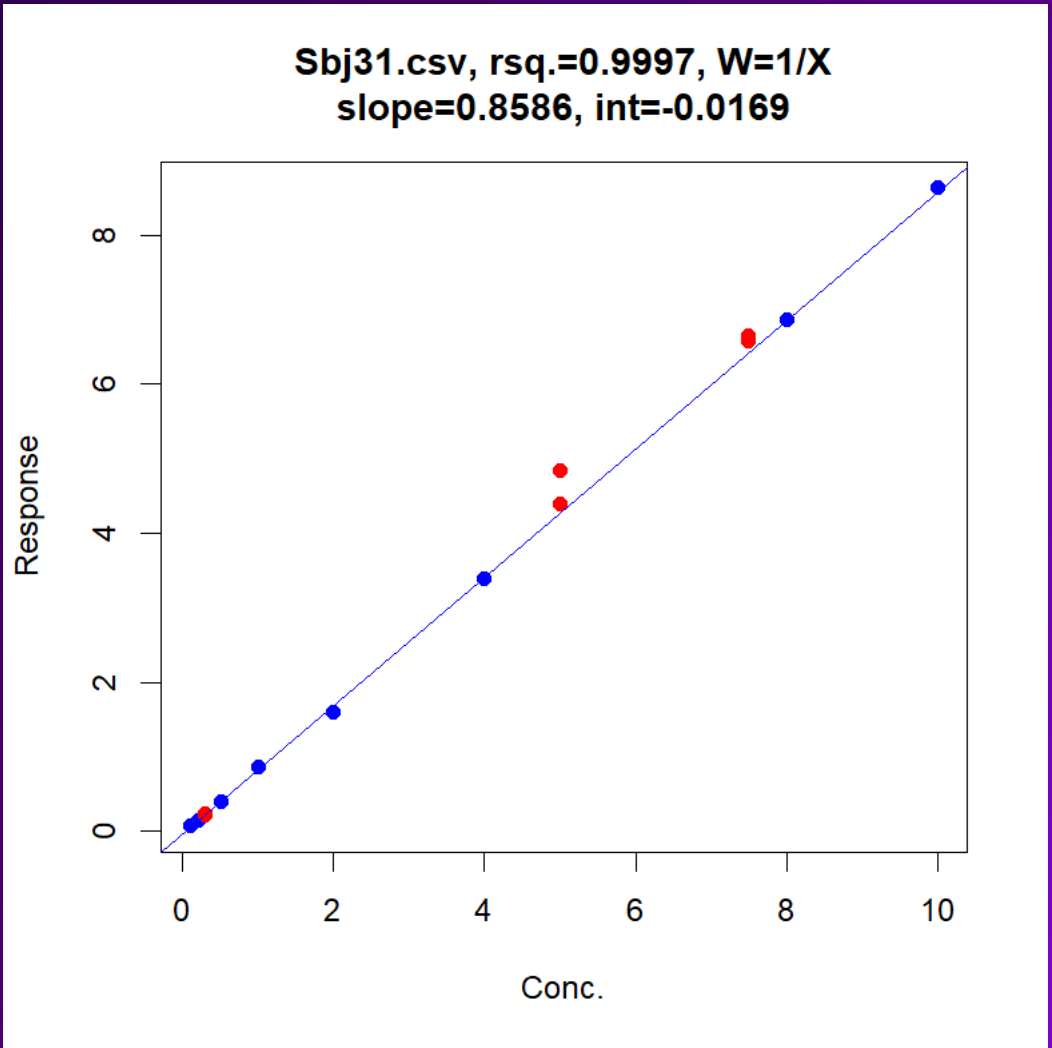
1. Extract analyte peak, IS peak areas for standards.
2. Construct a standard curve.
3. Extract unknown peaks and back-calculate the concentrations.
4. Back-calculate QCs and calibrator accuracies to check for runs acceptance (discard individuals).

We can do all that too
=centralized monitoring!

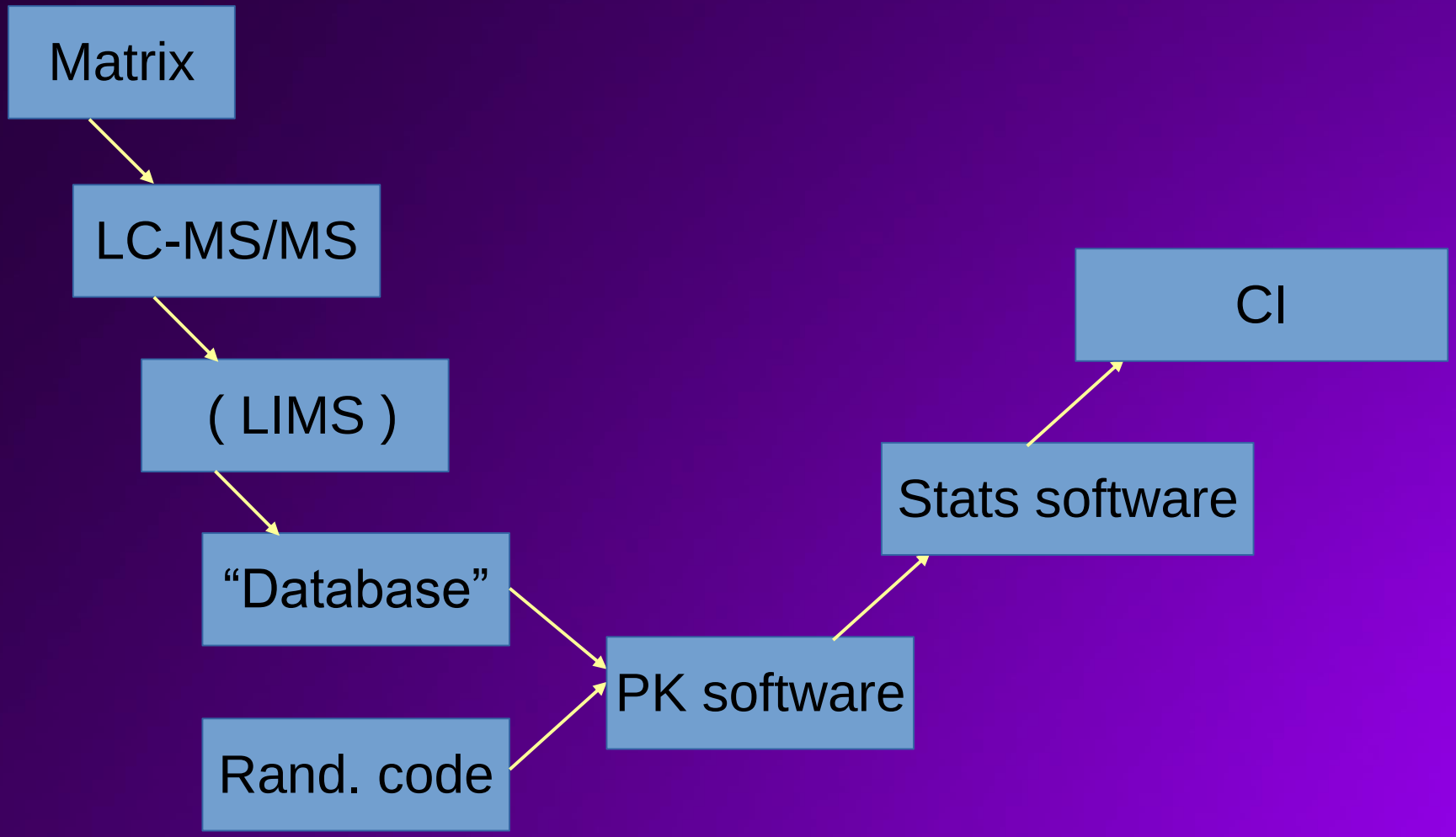
CM opportunity

- Re-calculate calibration curves (slope, intercept, r^2)
  - What do we also need to do that?
- Verify runs acceptance and calibrator inclusion
- Verify unknown concentrations
  - This gives us Cmax and AUC by subject and period through further calculation.
  - What do we also need to work out AUCs?
- Check for manual integrations.
- IS plots (note Analyst vs MassHunter difference)
- Check for aberrant observations, repeat flags.

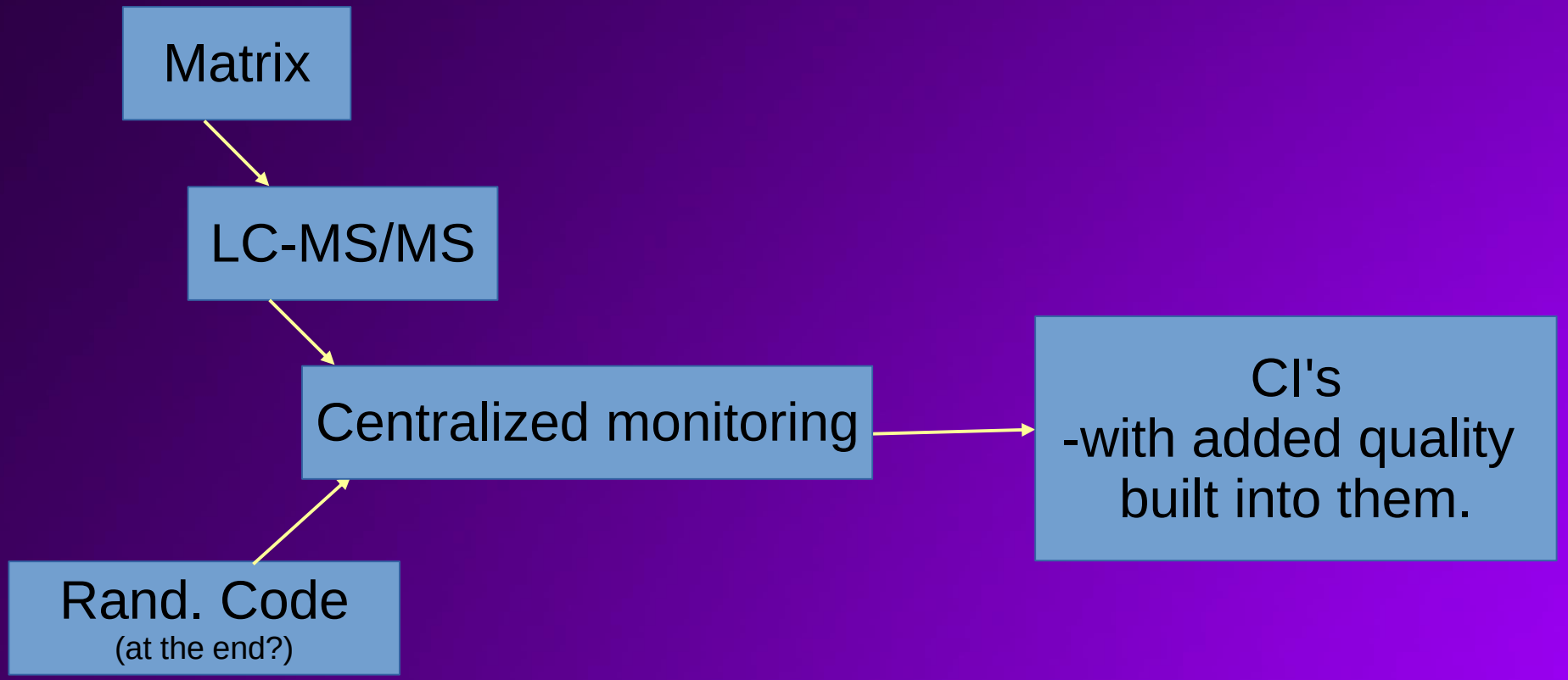
Example


Sbj31.csv, rsq.=0.9997, W=1/X
slope=0.8586, int=-0.0169
Response
Conc.
0
2
4
6
8
10

Essential flow in a nutshell, sorta.



CM achieves this, in principle



Example of CM finding

Case 1

In a trial with N=26 completers I had 3 runs which had deviations on the accuracies.

Wrong weights applied in three runs which passed with r^2>0.99xx. When applying the proper regression weights the r^2's for these three runs were 0.98xx. And guess what?

EMA grading

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

01 December 2014
INS/GCP/46309/2012
Compliance and Inspections

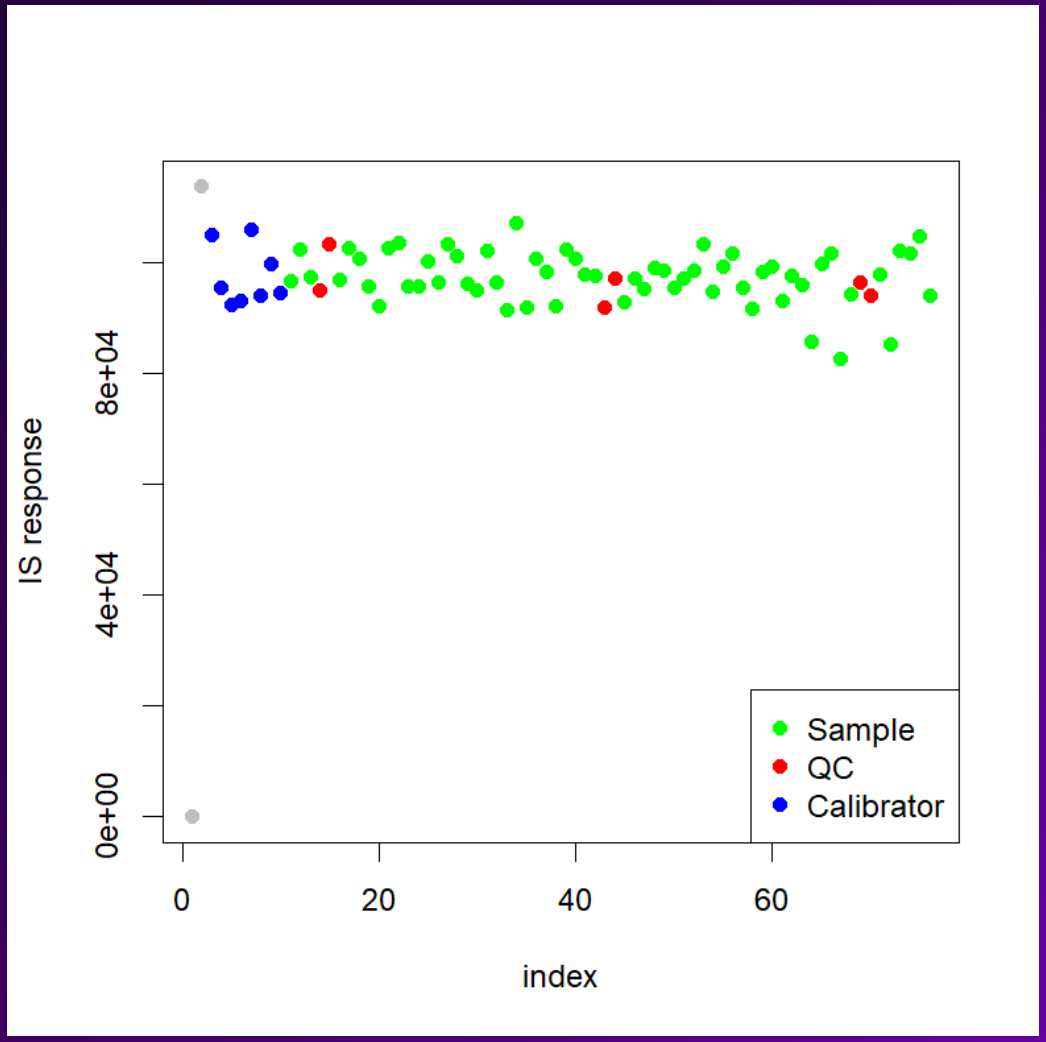
Classification and analysis of the GCP inspection findings of GCP inspections conducted at the request of the CHMP

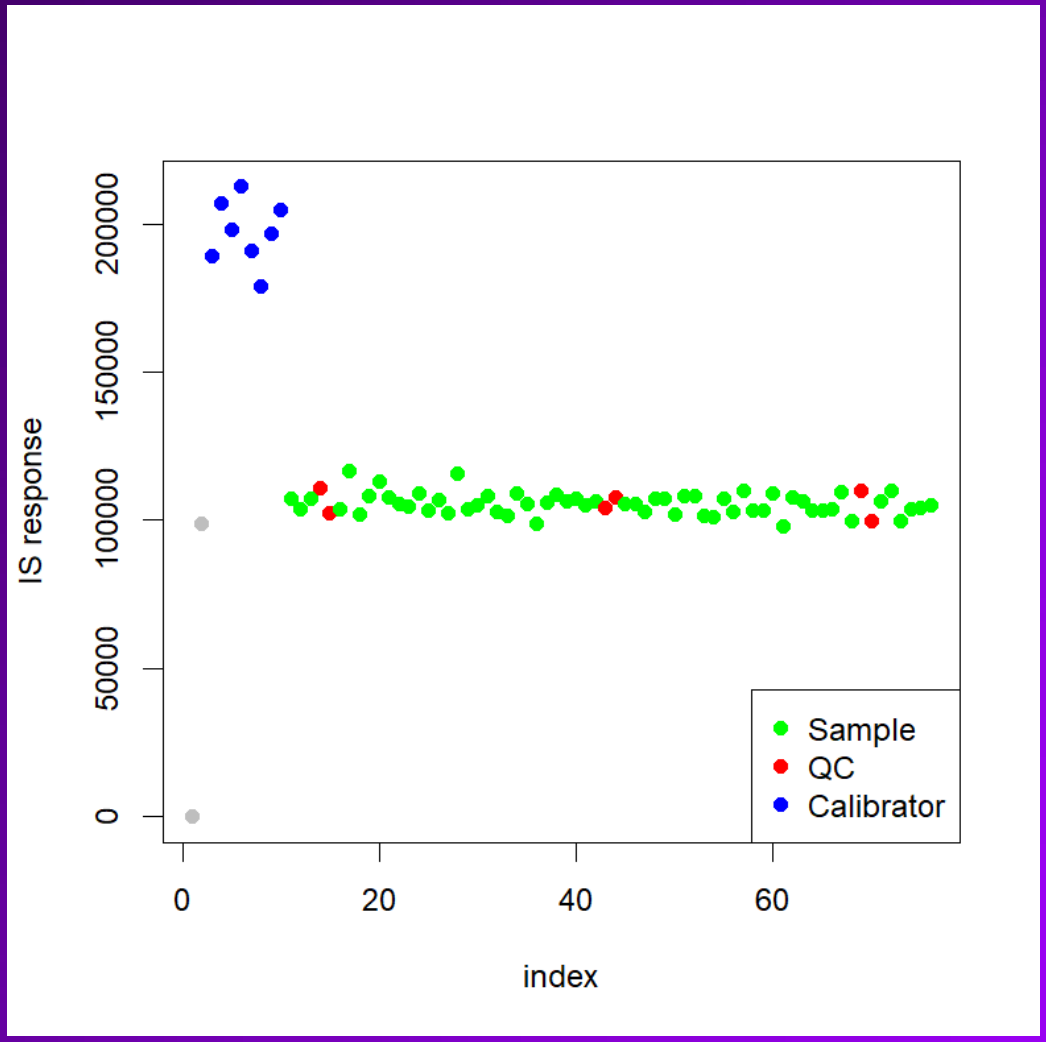
(Inspection reports to EMA 2000-2012)

- **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.
  - Remarks: 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 findings and are direct violations of GCP principles.
  - Possible consequences: data may be rejected and/or legal action required.
  - Remarks: observations classified as major, may include a pattern of deviations and/or numerous minor observations.

Which grading, if this had been observed during an inspection ?

Example 2: IS plot from CM





A complication re. IS variation, FDA

- For CCs, the IS response should be monitored for var… An SOP should be developed a priori to address issues with IS variability.

By the way:
It is quite common that CROs forget to add IS

What? How? Why is that sente… with only CC's?

I believe CROs should have an SOP to deal with IS variation in runs, not just IS-variation for CCs. What the requirements should be is not defined. It is my impression onsite inspectors enforce it this way.

A sore issue: Repeats

Can a CRO repeat a sample without a root cause?

Yes, say some: Samples can be repeated as part of an investigation if the value looks strange. We distinguish between recording a repeat and reporting a repeat. No reporting with a root cause.

No, say others: No root cause, no repeat.

Bear in mind: Recording vs reporting repeats

EMA:

For bioequivalence studies, normally reanalysis of study samples because of a pharmacokinetic reason is not acceptable, as this may affect and bias the outcome of such a study. In this case, reanalysis might be considered as part of laboratory investigations, to identify possible reasons for results considered as abnormal and to prevent the recurrence of similar problems in the future.

FDA:

- An SOP or guideline describing the reasons for a repeat analysis should be established a priori. Repeat analysis is acceptable only for assignable causes (e.g., the samples are above the ULOQ, there are sample processing errors, there is an equipment failure, the chromatography is poor). The SOP should include the acceptance criteria for re-analysis, and the sponsor or applicant should report final values. The specific recommendations

Repeat Analysis	• No re-analysis of individual calibrators and QCs is permitted.	• No re-analysis of individual calibrators and QCs is permitted.	• Re-analysis should be based on reasons described in a pre-existing SOP • No re-analysis of calibrators and QCs • At least the same number of replicates for repeats as originally tested • No confirmatory repeats for BE studies

Case 3: NCA

At the level of draft report:

Two times I checked the NCA I generated during CM versus the NCA reported by the CRO after the study.

Some AUCt differences noted.

Turned out the CRO had used the wrong _____ ?

Repeats and CM

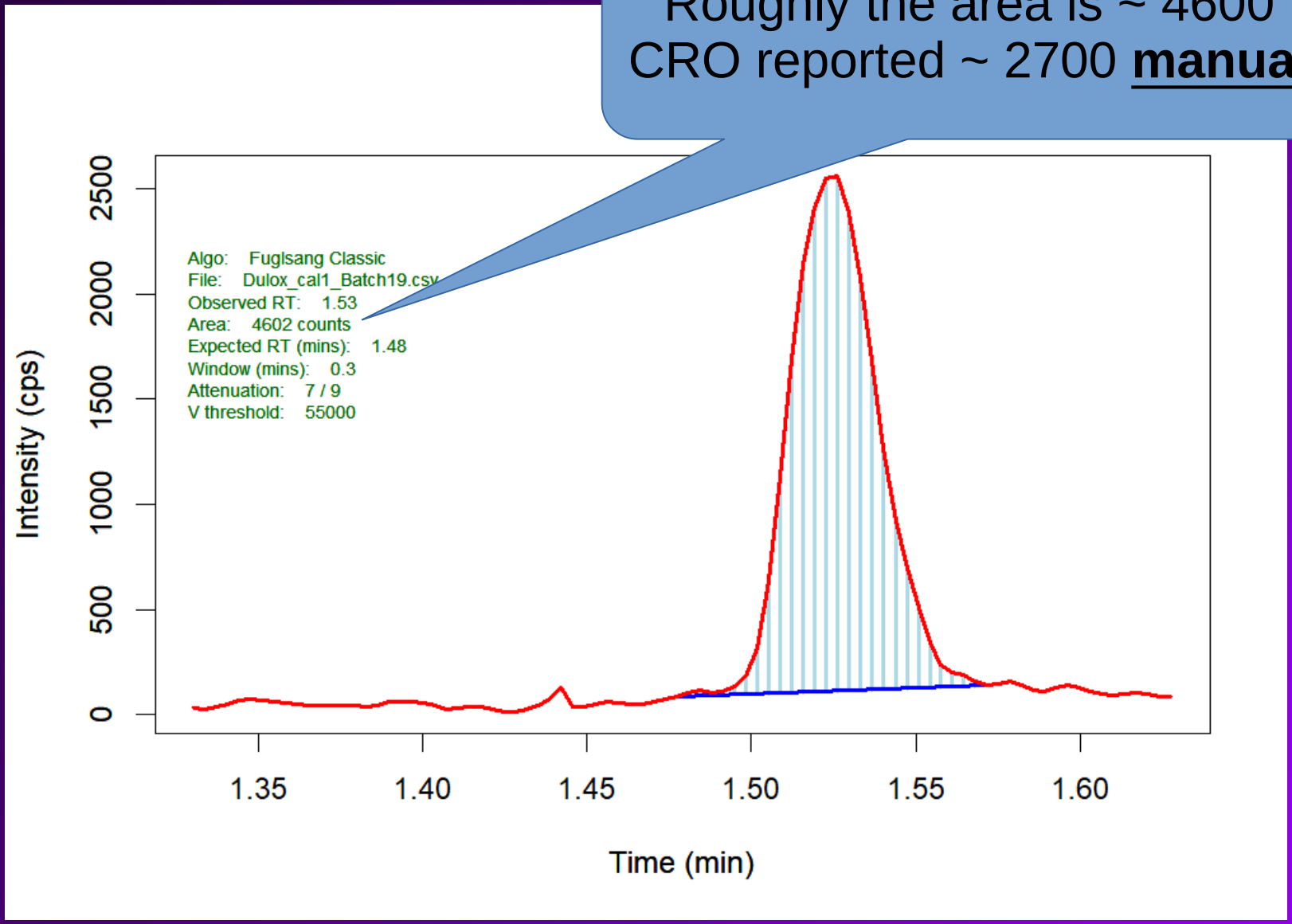
We can ask for the CROs repeat SOP and check the re-calculated accuracies for repeat triggers (whether we like them or not).
Or absence of same!

For the hardcore number crunchers.

- Sciex Analyst can export raw chromatographic data.
- Data file containing rows with time and signal.
- This is in fact all we need to re-integrate a chromatogram to verify the concentration or area if need be. Reproduced areas will not be 100% reproductions of result tables since the integration algos of Analyst are not published.
- When to use?

Case 3

Roughly the area is ~ 4600
CRO reported ~ 2700 **manual**



What I occasionally do (audits or home)

Ask for
low calibrators
+
low QCs
then reintegrate them and compare with Results Tables.

I never figured out a way to extract signal versus time for Waters/ThermoFischer systems. If someone knows how to do that then let me know, please, thanks.

Conclusion, Part I

Accumulating bioanalytical data include the data

5.18 Monitoring

5.18.1 Purpose

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(b) The reported trial data are accurate, complete, and verifiable from source documents.

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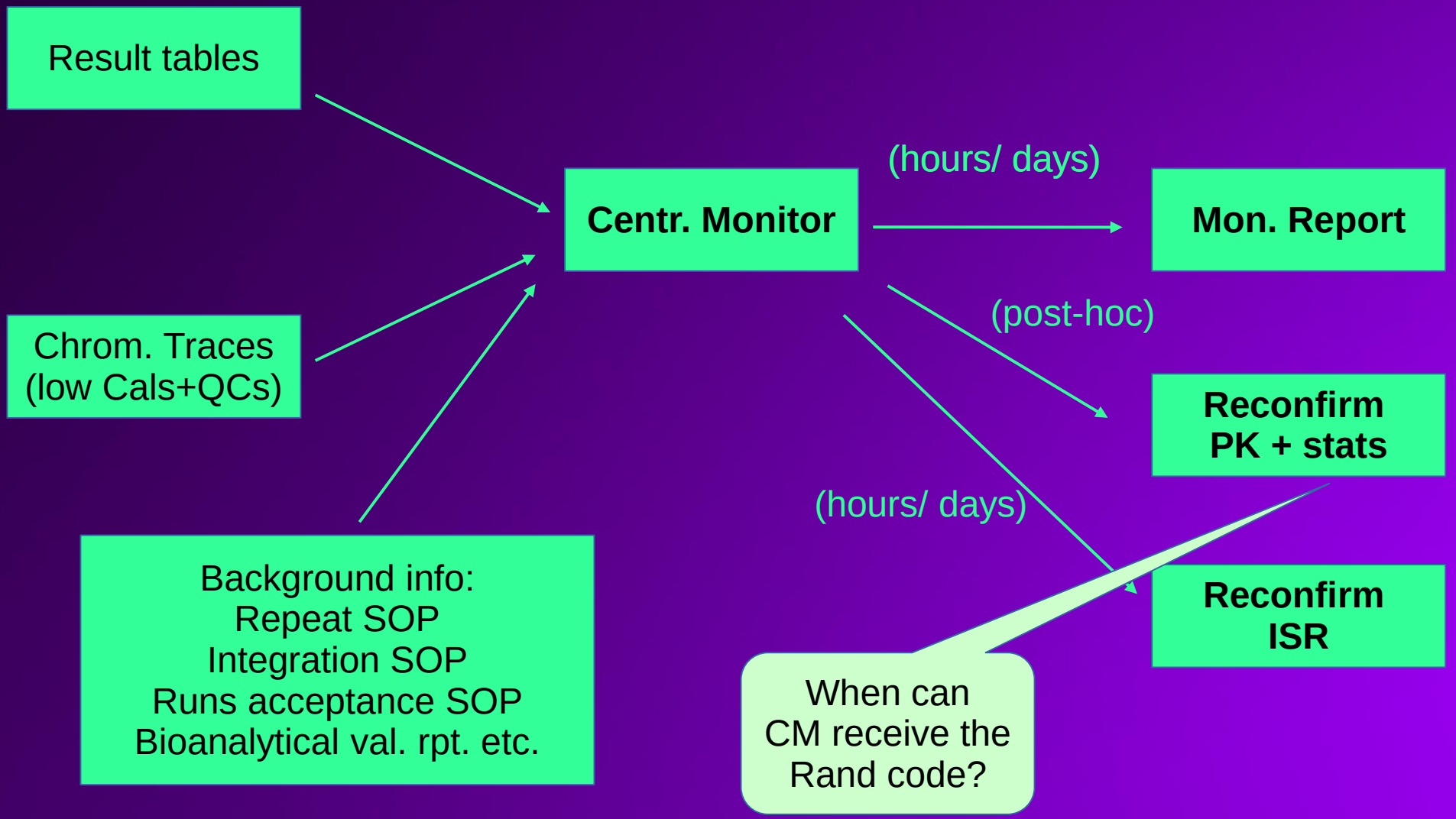
We ual

=via CM we can form a decent opinion on whether the analysis is progressing as per protocol and as per guidelines.

How it works


Result tables
Chrom. Traces
(low Cals+QCs)
Background info:
Repeat SOP
Integration SOP
Runs acceptance SOP
Bioanalytical val. rpt. etc.
Centr. Monitor
(hours/ days)
Mon. Report
(post-hoc)
Reconfirm
PK + stats
(hours/ days)
Reconfirm
ISR
When can
CM receive the
Rand code?

Part II

A CM proposal for the
clinical parts of BE trials

Accumulating data, clinic

Screening and enrollment.

And note: Even though sponsors/auditors/monitors/we never see much going on in this phase this is very much a race against the clock where the accumulating data is the availability of subjects.

One trial a little South and East of here

Not necessarily anemic.
Cleared by PI.

N=50 enrolled.

t-3 days: 14 enrolled. 1 had low hemoglobin.

t-2 days: 20 enrolled. 6 had low hemoglobin.

t-1 day: 16 enrolled. 11 had low hemoglobin.

True or false ?

a. We do not interfere with PI's decision.
b. 5% are expected to be outside the normal/ref. range.
c. If more than 5% of enrolled subjects are outside then the study does not enroll from the population stipulated by the protocol.

n behalf of, subjects
hysician or, when

1. The PI can clear a subje low hemoglobin if the subject is deemed fit fo rticipation ?

2. The PI can do that for many/all of the subjects?

- (perspective: analytical runs with many manuals)

WHO, March 2017

News

Health assessment testing of human subjects in bioequivalence studies

22 MARCH 2017

Applicants and Contract Research Organizations (CROs) performing bioequivalence studies are reminded that all studies with human subjects must be conducted in compliance with Good Clinical Practices (GCP), which requires that the rights, safety, and well-being of trial subjects be given top priority in every trial conducted. The eligibility and prospective health of trial subjects is assessed through numerous pre-study, in-study, and post-study tests, including the assessment of serum biochemistry and haematology parameters. The measured values for these parameters are compared to a pre-defined set of site normal values, which have been established as a "normal range" for each parameter at the study site in question.

The enrolment of a subject with measured values for the health verification parameters that fall outside the pre-defined site normal values should not occur, except on a rare, exceptional basis. On the rare occasion where a subject is enrolled in a study despite having a measurement outside the site normal range, the study physician should have a clearly documented and medically rigorous justification for making that exception.

CM, clinical screening/enrollment

1. Define a list with all screening parameters and their reference ranges.
2. Keep a list of all screened subjects and enrollment status through the values (M/F).
3. We'lk eep track of “cumulative” percentage of subjects with e.g. aberrant hemoglobin (subject needing PI clearance in one **or more** cases).
4. Dosing when sponsor approves the table?

Conclusions

- “Accumulating data” in a BE trial are e.g. screening/enrollment data and bioanalytical data.
- ICH E6 R2 paves a way for risk-based QM of this data. Risks are real.
- Verify some/most of the primary data [illegible]eration (incl. std. curves, completeness, [illegible] integration, runs acceptance. IS [illegible]epeat reasons).
- Verify ethical
- Verify **accurate** and **complete**. What if…?

Cost, ease, speed, power.
Over time we learn the weak areas of the CRO. Signal value.

Thank you.

Please get in touch.

anfu@fuglsangpharma.com