ISPR as a Tool to Differentiate between Fraudulent and Non-fraudulent PK Profiles

Anders Fuglsang, PhD
Fuglsang Pharma, Denmark
anfu@fuglsangpharma.com

Flashback

(slide shown at Biobridges 2023)

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New flavours of trouble

Re-use profiles across studies for different sponsors. Especially straightforward when the number of samples per period is the same.
SaToWIB and Buster are clean.

I have unfortunately seen this happen!
Sponsors will not realise it.

Screening for this may require centralised trial data repositories (agencies!).

Of course no-one gave a tiny mouse dropping about any of that.

Earlier this year realities hit hard.

Real life situation

Your BE study passed. The dossier is submitted. The regulatory agency comes back with questions. They name e.g. three profile pairs which they think might be duplicates. PSRtPH does not require proof now. Grief, anger, sorrow and plenty whining.

What would you do?

Strategies that do not work well

Paying a famous independent academic $10000 to write a letter stating there is nothing wrong. Denial. Claiming that similar profiles are just proof that the volunteer selection process works well for selection of a uniform pool. Doing nothing. Taking out the affected profiles from ADaM / FAS / PP pool and re-running stats.

Today's menu

(Because in Canada they have a saying….)

Why ISPR – the background?

What is ISPR?

Performance of ISPR.

How to implement it?

And finally some good news :-)

Background

Around 2013/2014 rumours circulated that some CROs were capable of making any BE study pass through:

1. Interim analysis
2. Identification of (most) offending subjects
3. Re-analysis of those subjects under false identity and with T and R switched.

Background

- ”The switch”
- Software for detection
- Regulators (EU, elsewhere) accessed it.

Buster: ID’ing the statistical fingerprint of the switch.
SaToWIB: Measuring the “sameness“ of two profiles.

Both are entirely empirical.

The software was accessed by regulators for several years.

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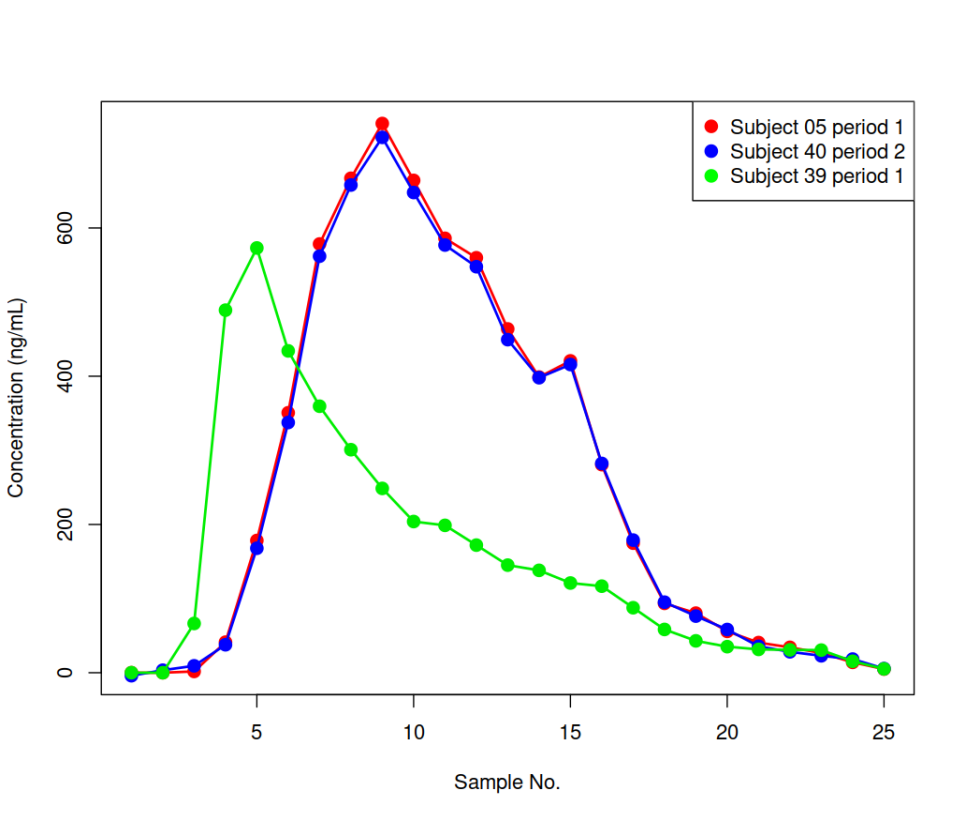
Detection of data manipulation in bioequivalence trials

Anders Fuglsang

Hiort Lorenzens Vej 6c, DK6100 Haderslev, Denmark

SaToWIB

Compare all profiles against each other. Derive a score for similarity. Sort all profile pairs according to similarity score, so that the most similar pairs are at the top of the sorted table. If we have a reasonable comparison function, then the top pairs are the most likely candidates for re-analysis (overlapping profiles).



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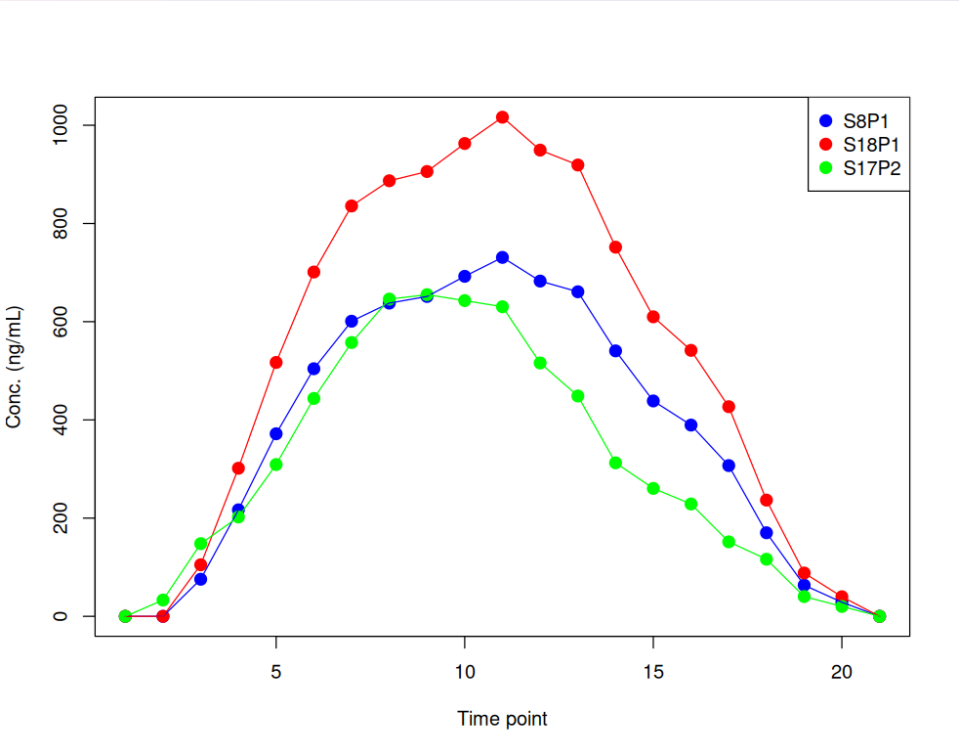
Need to detect diluted and re-analysed profiles



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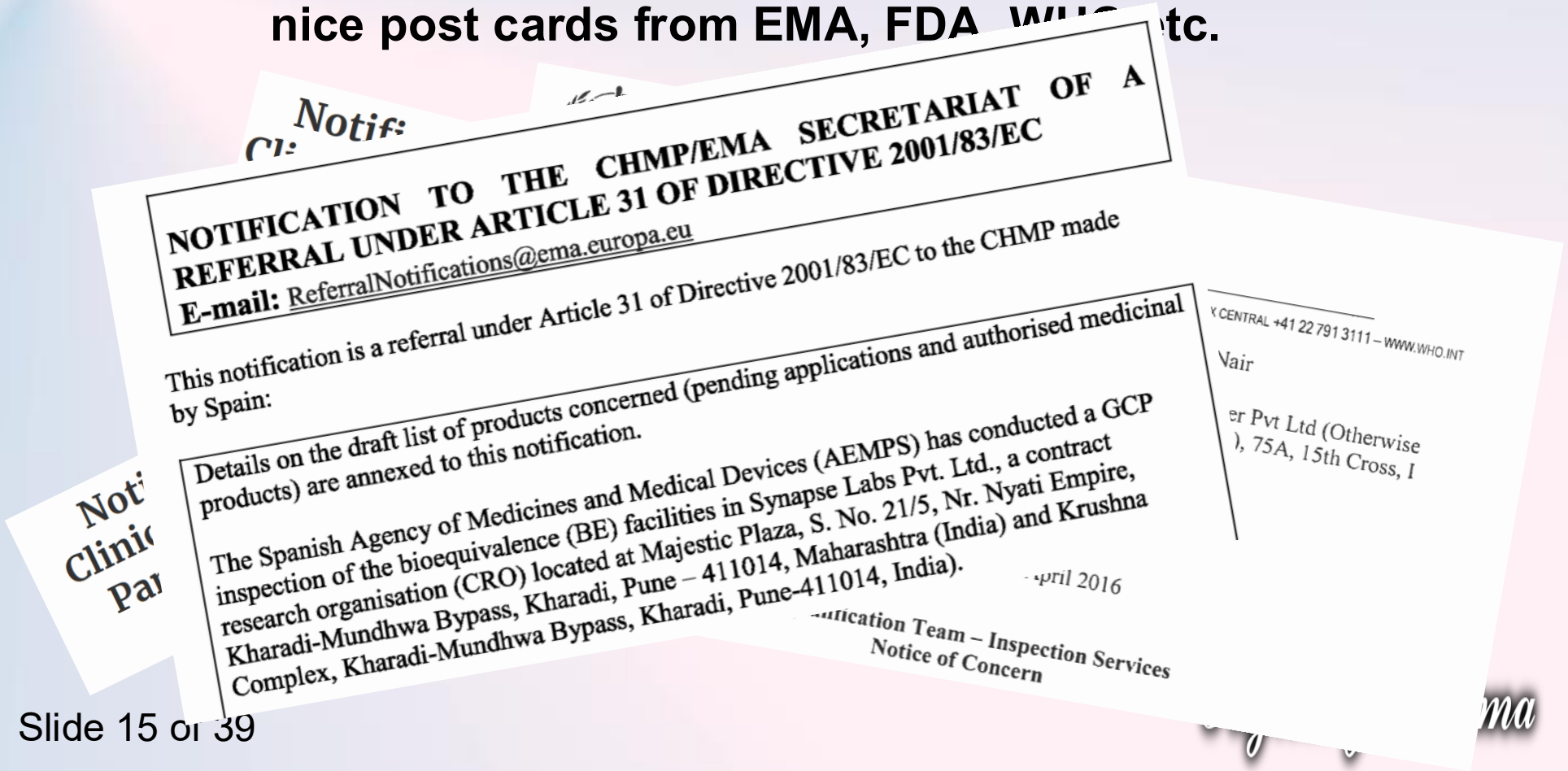
Profile1	Profile2	Score	Rank	Ratio
S18P1	S27P2	0.03891	1	0.9561
S21P1	S28P2	0.03990	2	1.0051
S5P1	S25P2	0.04041	3	0.9901
S2P2	S33P2	0.04182	4	0.9639
S9P2	S30P1	0.04187	5	1.0264
S4P1	S26P2	0.04239	6	1.0189
S2P1	S33P1	0.04487		273
S15P2	S34P1	0.04557		024
S7P2	S31P1	0.04609		282
S10P1	S35P1	0.04671	10	2.0087
S23P2	S36P1	0.04716	11	0.9593
S19P2	S29P2	0.04827	12	1.0492
S21P2	S28P1	0.04924	13	1.0083

But where is the limit ??

In recognition of their high level of creativity -and without actual proof of duplication- a series of CROs (Sponsors) were sent some nice post cards from EMA, FDA, WHO etc.



NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Spain:

Details on the draft list of products concerned (pending applications and authorised medicinal products) are annexed to this notification.

The Spanish Agency of Medicines and Medical Devices (AEMPS) has conducted a GCP inspection of the bioequivalence (BE) facilities in Synapse Labs Pvt. Ltd., a contract research organisation (CRO) located at Majestic Plaza, S. No. 21/5, Nr. Nyati Empire, Kharadi-Mundhwa Bypass, Kharadi, Pune – 411014, Maharashtra (India) and Krushna Complex, Kharadi-Mundhwa Bypass, Kharadi, Pune-411014, India).

April 2016

Notice of Concern

And today

Dossiers are being scrutinized and screened.
FDA use Dabers, and authorities in EU and elsewhere have access to it. It tries -aot- to detect overlapping profiles with or without “the switch”.

And that’s why those questions about potential duplicates appear.

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S2P1	S33P1	0.04487		273
S15P2	S34P1	0.04557		024
S7P2	S31P1	0.04609		282
S10P1	S35P1	0.04671		087
S23P2	S36P1	0.04716		593
S19P2	S29P2	0.04827		492
S21P2	S28P1	0.04924	13	1.0083

The limit may vary with assay, molecule, phenotype, genotype and myriads of unknown factors.

ISPR – the idea

We do not have a model that establishes a limit, generally speaking. I believe we won't get one any time soon.

But what if the CRO re-analyses a handful of profiles in a given study?
ISPR = incurred subject period re-analysis.

The ISPR hypothesis

Presented at a conference in 2023.

If we have a good scoring function, then the true ISPR pairs should come out on top of the sorted SaToWIB list.

If this is true then the score threshold should be between the last true ISPR pair and the first non-pair.

The ISPR hypothesis - example

Profile1	Profile2	Rank	Score	Ratio
S6P1	S6P1.ISPR	1	0.0293	0.981
S10P2	S10P2.ISPR	2	0.0331	1.057
S11P2	S11P2.ISPR	3	0.0359	1.008
S4P2	S4P2.ISPR	4	0.0357	1.021
S21P1	S21P1.ISPR	5	0.0382	
S7P2	S11P1	6	0.1086	
S1P1	S9P2	7	0.1232	0.795
S13P2	S14P2	8	0.1235	1.541
S5P1	S15P1	9	0.1384	1.108

Approx. threshold !

If ISPR would not work - hypothetically

Profile1	Profile2	Rank	Score	Ratio
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S7P2	S11P1	4	0.0357	1.021
S1P1	S9P2	5	0.0382	0.976
S13P2	S14P2	6	0.0493	1.277
S5P1	S15P1	7	0.0551	0.795
S4P2	S4P2.ISPR	8	0.0611	1.541
S21P1	S21P1.ISPR	9	0.0643	1.108

The AAPS Journal (2025) 27:15
https://doi.org/10.1208/s12248-024-01000-x

RESEARCH ARTICLE

Evaluation of Incurred Subject Period Re-analysis (ISPR) as a Tool to Distinguish Fraudulent Pharmacokinetic Profile Pairs from Non-fraudulent Pairs

Anders Fuglsang[1] · Anshul Dogra[2] · Naveen Sharma[2]

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ISPR tested in Four studies w. five analytes

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Results, method 101

Table I SaToWIB Table Showing the first 20 Ranks from Study C1B03661 (analyte Voclosporin) where Method 101 was Employed. There are in Total 5 ISPRs in this Study and the True ISPR Pairs all Come out on Top of this Table (Green Lime Color); Non-pairs all Have Higher Scores (Reddish Color)

Rank	Series1	Series2	Dilution	Score
1	S8P1	S8P1.ISPR	1.03	0.000088
2	S1P1	S1P1.ISPR	1.02	0.000126
3	S10P2	S10P2.ISPR	1.10	0.000222
4	S12P2	S12P2.ISPR	1.06	0.000251
5	S5P1	S5P1.ISPR	1.05	0.000275
6	S3P2	S12P2	1.77	0.001200
7	S3P2	S12P2.ISPR	1.87	0.001644
8	S2P2	S5P1.ISPR	1.81	0.002064
9	S2P2	S5P1	1.73	0.002096
10	S2P1	S12P1	2.31	0.003400
	S3P1	S12P1	1.84	0.003721
		S7P2	1.00	0.004270
		S10P2.ISPR	1.42	0.004665

It works !!

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In that paper

The outcome is perfect for the three current SaToWIB scoring methods (101, 36, 205): The true pairs come out on top of the sorted list across all studies/analytes/scoring methods. Not necessarily in the same order, though.

Wait a moment…..

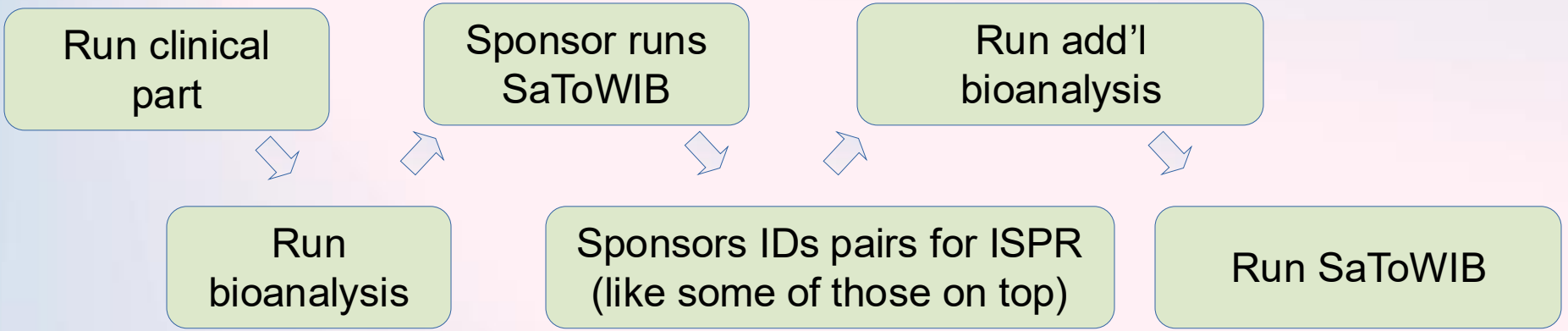
Which profiles should be selected for ISPR?
When are they selected?
Who selects them?

ISPR mode 1: Simple

The CRO selects the profiles. They do so at random. Before or after the ordinary bioanalysis.

ISPR mode 2: More advanced

might require a change in the QMS with certain CROs



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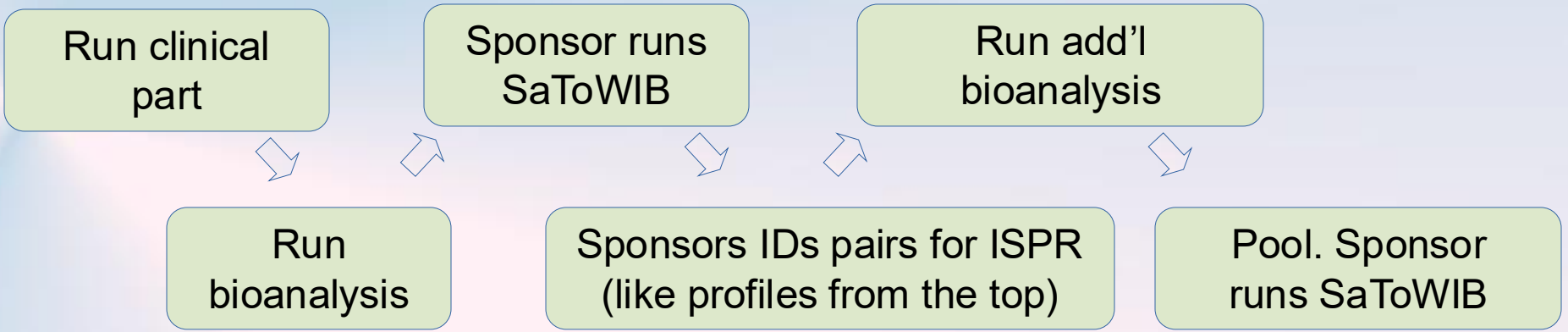

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S2P2				9639
S9P2				0264

If we re-analyse S27P2 and S28P2 and the score of (S27P2 vs S27P2.ISPR) and (S28P2 vs S28P2.ISPR) is e.g. ~0.006 then we would have a very good argument for saying S27P2 and S28P2 are not re-analyses.

Can the CRO play tricks using ISPR?

Would imply: There are duplicates (reanalysed profiles) but the true ISPR pairs are on top.

How could a CRO achieve that in practice ???

Bear in mind

ISPR bioanalysis happens after ordinary bioanalysis. If selection of the ISPRs is not in the hands of the CRO, and only known after ordinary bioanalysis, then it becomes difficult to know how to rig the ordinary bioanalysis.

Could a CRO re-use profiles and add a bit of scatter (sloppy pippetting etc) in profiles -the ordinary ones- to increase sameness score?

Theoretically yes. But this addition of scatter would also increase the CV. Which would either drive sample sizes up or increase risk of failure. Low sample size is a direct and hugely important competition parameter as it directly drives trial cost.

Moreover, they'd need to only add scatter / be sloppy with analysis of those profiles not selected for ISPR (otherwise the corresponding pairs would not be on the top of the SaToWIB list).

Added value of ISPR

Adding ISPR data in the CDISC package would benefit FDA (and thus agencies accessing Dabers) tremendously as it might, in the long run, help them develop a model to determine a way to define a natural threshold.

Regulators are also looking for the threshold

“Indeed, the current practice offers no practical guidelines regarding how similar PK profiles from different subjects can be in order to be considered valid. This makes it difficult to assess the adequacy of data to be accepted for an ANDA and requires additional information requests to applicants.”
https://www.hhs.gov/sites/default/files/hhs-ai-use-cases-2023-public-inventory.csv

Submission of ISPR data as part of e.g. the CDISC package to e.g. FDA would in the long run help regulators develop a valid model / threshold.

AI ?

Conclusion I

After submission, sponsors / CROs are occasionally hit with requests to justify that similarity between select profiles is natural.

ISPR can be built into the trial at the planning stage (not after receipt of the deficiency letter) and will to some degree tell if an overlap is natural or not. **It is the CRO's/Sponsor's way to deliver reasonable evidence that the conduct is not fraudulent.**

It is difficult to rig studies where ISPR is employed, especially if "mode 2" is used. Minimal cost/timeline impact.

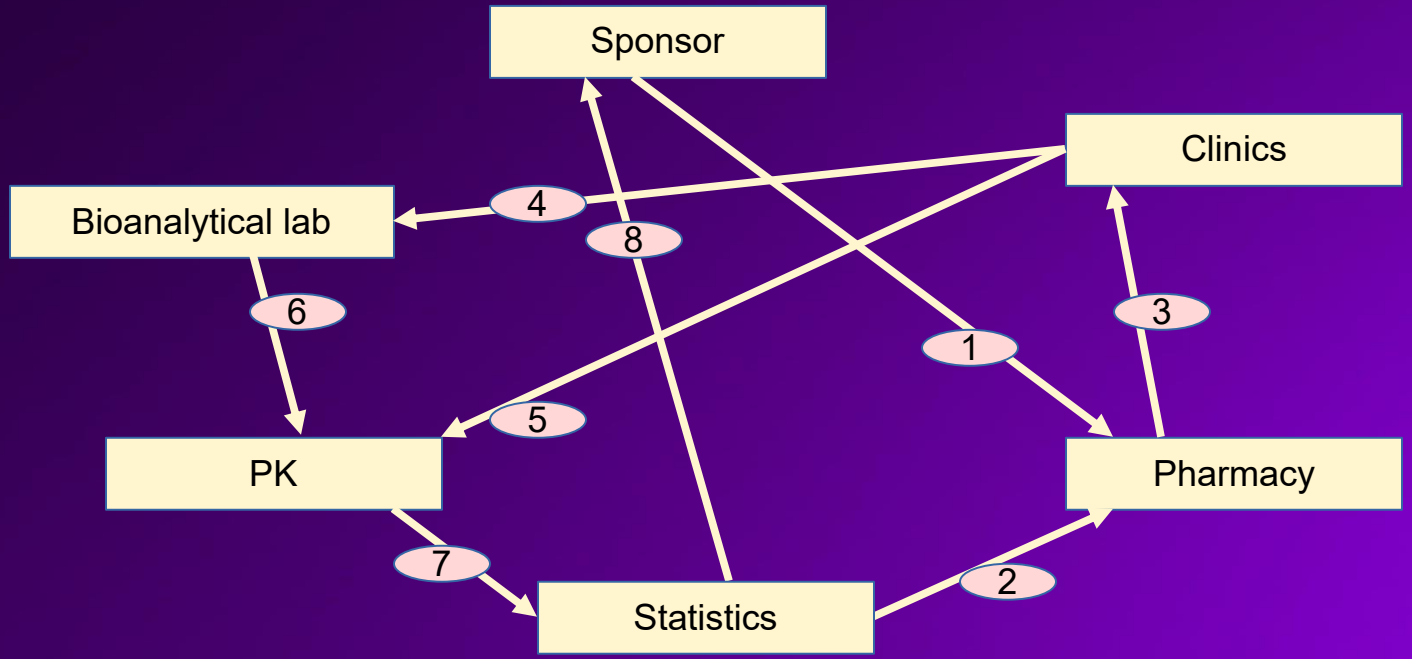
Proof of ISPR viability is backed by in vivo data.

What if we want to act?

Act where the problem is. Act in proportion to the risk.

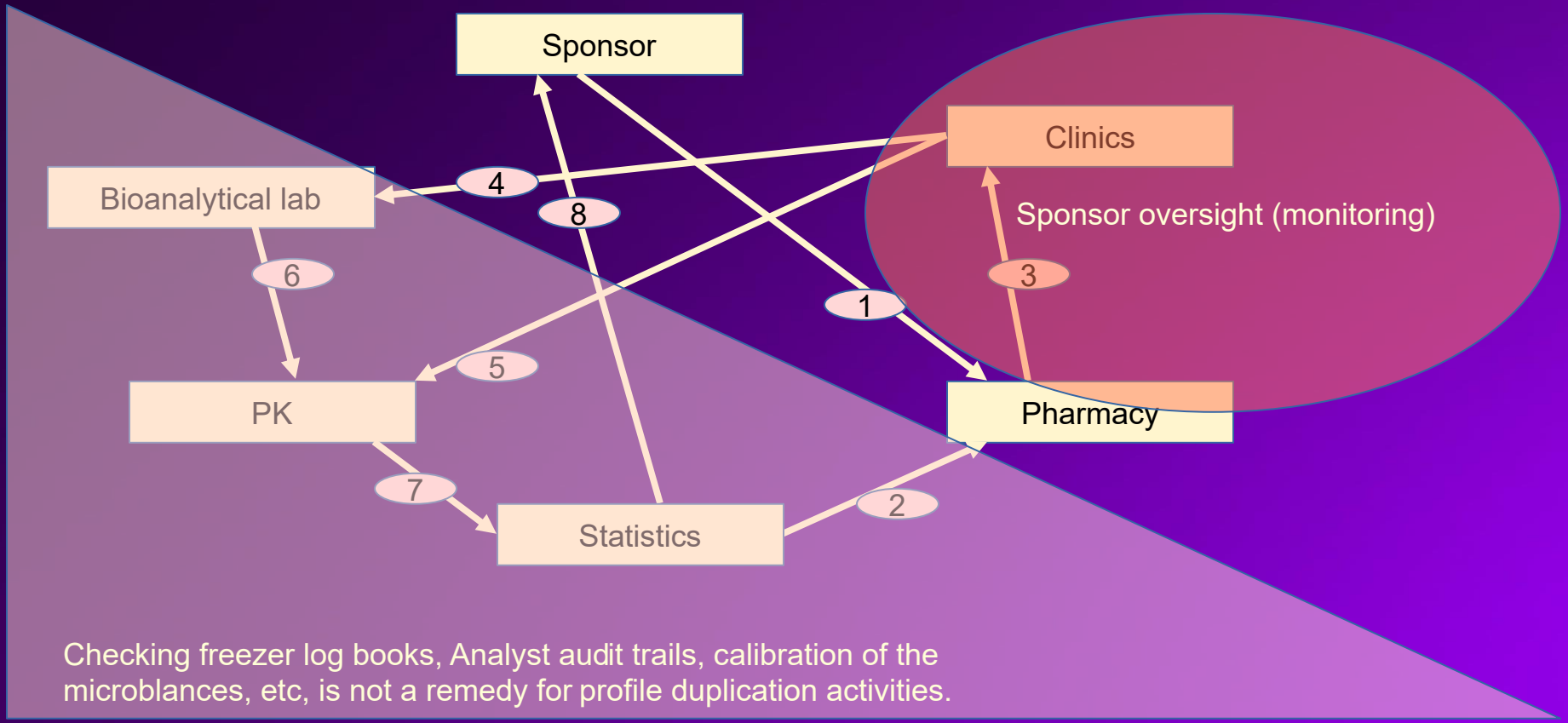
Flow in BE, common themes

Local variations exist



1. IMP
2. Rand. code
3. Labeled IMP
4. Plasma
5. TPDs
6. Blinded PK data
7. Blinded NCA outcome
8. Results

Oversight … where, how?



Checking freezer log books, Analyst audit trails, calibration of the microblances, etc, is not a remedy for profile duplication activities.

Conclusion II

The good news is:

If we want this mess to continue,
then all we have to do is
NOTHING. Ain't that great?

Credits

Thank to Anshul Dogra & Naveen Sharma from Cliantha

Plus:

Olivier Le Blaye, Stephanie Croft, Veeda, Helmut Schütz and many more with whom I have had discussions over the years.

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