MEETING THE BIOANALYTICAL CHALLENGES OF GLOBAL MULTI-CENTRE TRIALS : OBSERVATIONS AND EXPECATIONS

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Overview…

- What's in a trial, some history and what about now
- Where is the problem and who has it
- Why, How, What (Design, Operations, Assays)
- Some concluding thoughts

GLOBAL MULTI-CENTRE CLINICAL TRIALS

- Most typically : later phase of development (2b or 3)
  - Substantial knowledge of drug behaviour

- Multiple subjects (patients)
  - Combination treatments and other co-medications
  - Disease state subjects : effect on samples

- Multiple clinical sites (>1)

- Multiple doses

GLOBAL MULTI-CENTRE CLINICAL TRIALS

- BA almost always involved to some extent
  - Relatively few samples (for PK) per subject
  - Soluble Biomarker sampling often complex
  - Immunogenicity testing requirements

- Samples spread across time within subject, within trial (weeks/months)

- Blinded design, placebo dosing

Overall study aim is to deliver:
"an adequate well controlled study to provide substantial evidence of efficacy"

A BIT OF HISTORY …

1948: first randomised controlled trial 109 patients recruited (107 randomised)

1987-2001: 200 to 400 patients (*pivotal trial antihypertensives*)

1994 : 4,400 patients (*pivotal simvastatin*)

Recent (2010 onwards): 30,000 patients (*cholesterol modulating agent used as adjunct to simvastatin*)

Taken from, Scannell et al, Nature reviews Drug Discovery (11) Mar 12

AND NOW…

- Recent analysis [1] of later stage studies has shown
  - 1 in 5 procedures are run for secondary, tertiary and exploratory endpoints
    - Approx. 22% of all procedures are non-core (doubled from 10 years ago)
    - About half of procedures support primary and secondary
    - Typical protocol has average of 13 endpoints
  - Adds $1.1 million per trial for "extraneous data"
  - HOW MUCH OF THAT IS BIOANALYTICALLY RELATED?

[1] November/December 2012 Tufts CSDD Impact Report

THE SOURCE OF THE CHALLENGES…

TRIAL DESIGN

Should the assay lab be blinded ?

Assay samples from placebo dosed subjects ?

Collect and/or assay pre-dose samples

Soluble Biomarkers

Follow on studies

TRIAL DESIGN … ASSAY LAB BLINDED ?

YES

Prohibits bias

Prevents accidental unblinding

Less in-study resource required for sample identification

Properly investigate data anomalies and reconciliation

Reduces costs without significant loss of benefit

Bias by study team still eliminated - data delivered only after study unblinding

NO

TRIAL DESIGN … PLACEBO SAMPLES ASSAYED

- My experience is that most often placebos are not measured (what arguments persuade… ?)
- For PK ?
  - YES : Confirms that no placebos dosed
  - NOT NECESSARY :No actual study reason other than some way of confirming non-dose compliance (post hoc).

- For soluble Biomarkers -- will or often may be required for comparator or baseline measures.. esp. if efficacy marker decreases on treatment.

TRIAL DESIGN … PRE DOSE SAMPLES ASSAYED

- Measure pre-dose or not?
  - More contentious, our experience is that difficult to persuade not to.
  - Same arguments on compliance “just to check”
  - Alternative: no analysis until needed (assuming acceptable stability)
  - What to do with positives !!

  - Soluble biomarkers different case

TRIAL DESIGN … SOLUBLE BIOMARKERS

Pre-Clinical → Phase I → Phase II/ III/IV

Translation of Biomarker assays

Methodology Studies

Clinical feasibility assessments / training

Initial validation and on going re-validation for changes in patient groups, assay range or intended use (exploratory becomes pivotal) etc

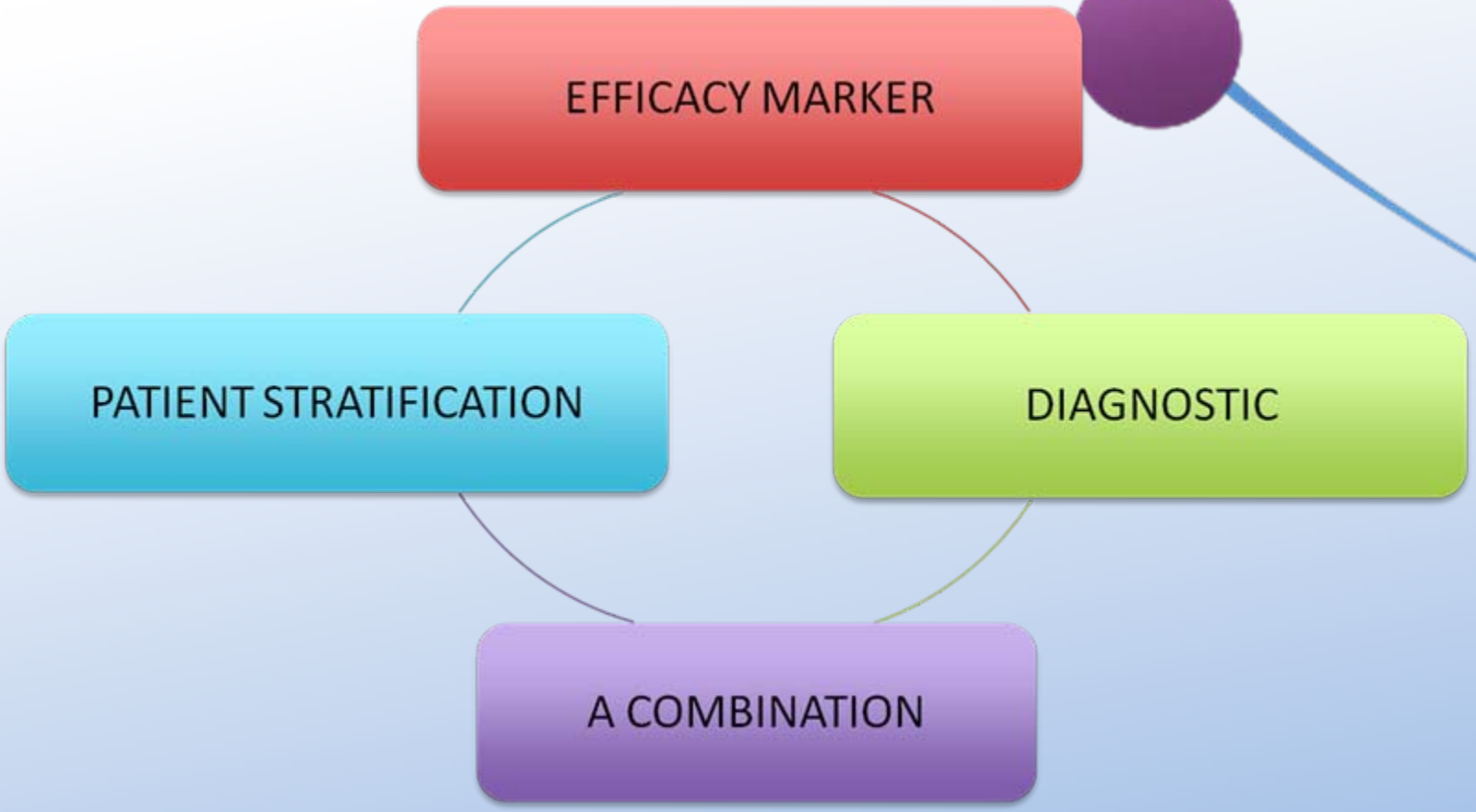
Fast turn round analysis of FIH, SD, MD studies

Batch analysis of later studies

Partnering for use of biomarker assay as companion diagnostic / patient stratification /product differentiation /"routine" marker

Revision of assay number and method of analysis

FUNCTIONAL USE OF SOLUBLE BIOMARKERS



TRIAL DESIGN … BIOMARKER CHALLENGES

- Various “uses” can result in sub optimal approach

- By clear pre study definitions of use and BM scope opportunities to

  - Reconcile and investigate appropriately data anomalies
  - Use appropriate level of validation “ Tiered approach”
  - Define the limits on data “quality” and delivery

TRIAL DESIGN … FOLLOW ON STUDIES

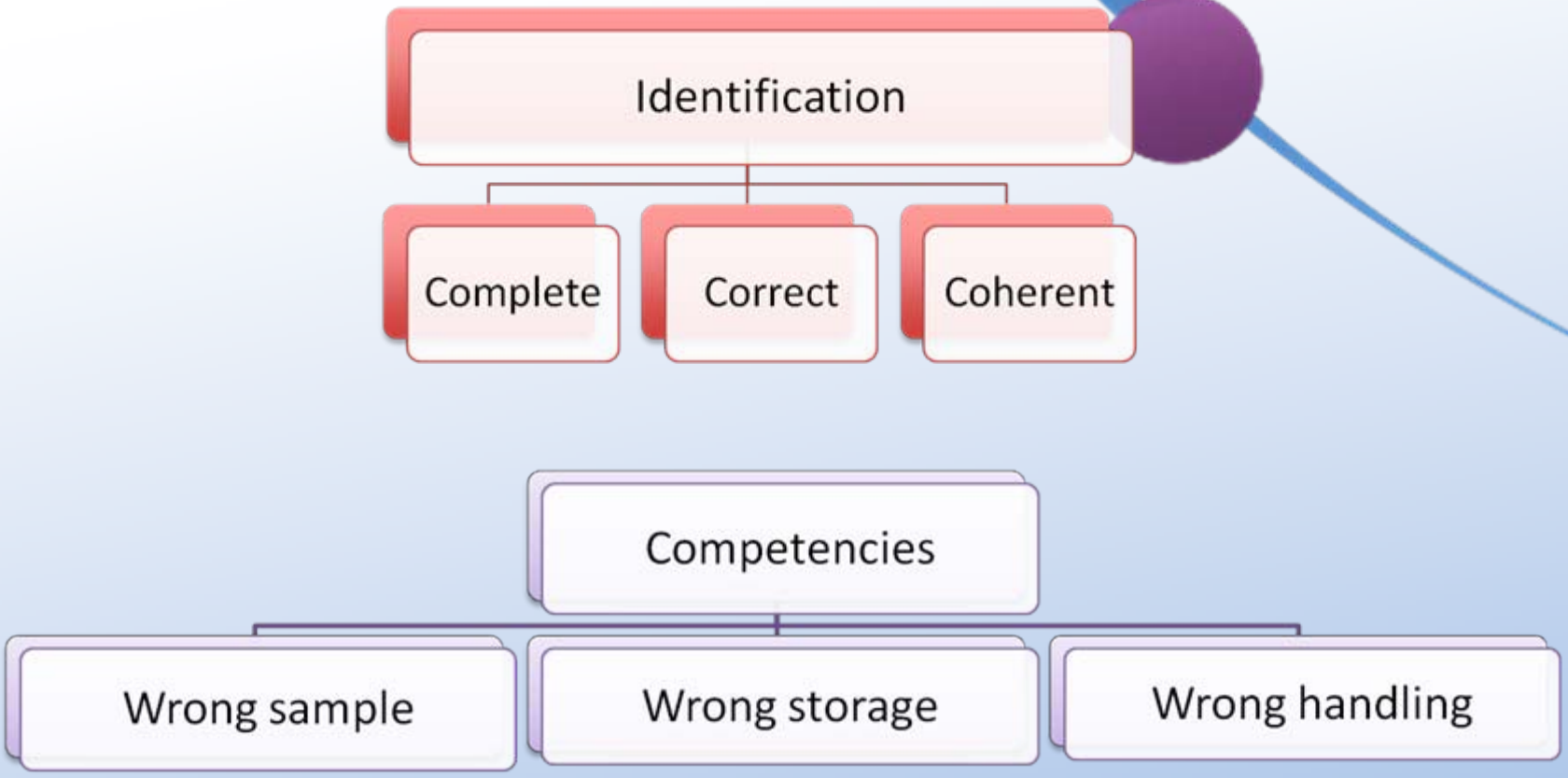
- Sampling in follow up phases can be problematical

- MC study (>100 subjects, 2 years to complete)

- Double blind phase : 12 weeks subjects on A or B
- After 12 weeks into follow on part for **n** weeks on A with pre dose samples at this point

- Data set for A: some +ve predose samples : team now confused, concerned
- Needed resource intense investigation post study finish
- Confusion at certain sites on timing of pre dose sample and dosing of A in follow up part :
- Better site monitoring, more clarity in protocol and rationale in why measuring pre-dose may have prevented

OPERATIONAL … THE SAMPLES



OPERATIONAL … sample identification issues

- BA process reliant on third party information
- No analysis until resolved
- Blinding : reconciliation may be delayed until first attempt at data release
  - Reconciliation complex, time consuming, pressured if at study end, resource intensive, historical data and knowledge needed
- Can mean missing data
- Just letting the “lab sort it” is not acceptable
- **BA needs help**, technological, pre-planning and “what if” decisions made ahead of events

OPERATIONAL … competencies

- Wrong sample (a/c, tube, matrix)
- Wrong storage temperature for wrong time duration

- Significant delay in discovering error most usual
- Problem can be only uncovered post study : worst case !

- May require more assay validation
  - Extend stability, widen conditions tested, confirm different a/c has no effect on p/a and selectivity

- Delay or rework of data; rejection of subset may be better ROI

OPERATIONAL … competencies

- Incorrect handling or preparation
  - Recommend increase monitoring, re-training at sites

- For complex handling comprehensive pre study training is a real cost/time saver investment

- Example of study procedural training investment led by BA
  - Needed near patient sample work-up at clinical sites for BM
  - Invested in video training, monitoring, competency testing on dummy samples
  - Delivered reliable data set; enabled clear unambiguous decisions

OPERATIONAL… OFF PROTOCOL SAMPLES

- "accidentally" taken
  - Breach of IC and protocol deviation thus reporting to study team
  - Generally not to be assayed if identified as such in advance
  - If identified as such after assayed … what to do with the data?

- Need a procedure on what will be done if this happens *

- Request to assay for non protocolled endpoint or different analyte
  - Don't … unless IC allows .. BA must confirm this *..
  - ISR should be a protocolled endpoint (in BA plan if not in Clinical protocol)
  - Unless for safety (documented request)

* EMA/INS/GCP/532137/2010 Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples

ASSAYS CHALLENGES …HOW MUCH VALIDATION

For non-primary (tertiary or exploratory) endpoints, how much validation is truly necessary ?

Extension of stability data for a very small subset of subjects	Co-medication analysis checks (assay selectivity)	Comparator assays "fully validated" ?

ASSAYS CHALLENGES …PERFORMANCE

DECISIONS .. DECISIONS … DECISIONS

- How often should you batch analyse
  - Clearly driven by stability
  - Driven by data use
  - Otherwise as convenience (cost) dictates
- How to re-establish the assay

  Re-establish by P/A batch check if assay dormant for a period of time … time limit arbitrary.. Are there any criteria or evidence to base interval on
- What if you <u>have</u> to run the assay at more than one location
  - Cross validation or method establishment ?
  - Establish data "equivalence" or demonstrate lack of bias

ASSAYS CHALLENGES …REGULATORY SPACE

Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples : EMA GCP

It is always appropriate to consider the need to expedite the reporting of results regardless of the nature of analysis or evaluation that is being conducted.

For example, anomalous results or unexpected values associated with pharmacokinetic analysis may indicate incorrect dosing or marked differences in a subject's ability to metabolise an investigational medicinal product which may potentially have safety implications.

In all cases, results and observations should be reviewed by an appropriately qualified person to identify any anomalous or out of specification data. This review should be performed in a timely manner.

ASSAYS CHALLENGES …Anomalous results

- How do you manage this when blinded and have sparse samples (maybe weeks apart)
- Expected range of concentrations ?
- Who is the qualified person(s)
- May require expert input (pharmacometricians/ clinical pharmacologist)
- How to make this work effectively in an increasingly outsourced environment

THE ACCUMULATION OF SMALL ISSUES

The less good news

At least one or more of these "minor" issues arise in every trial. At what cost, and accumulation

It is not getting easier unless..

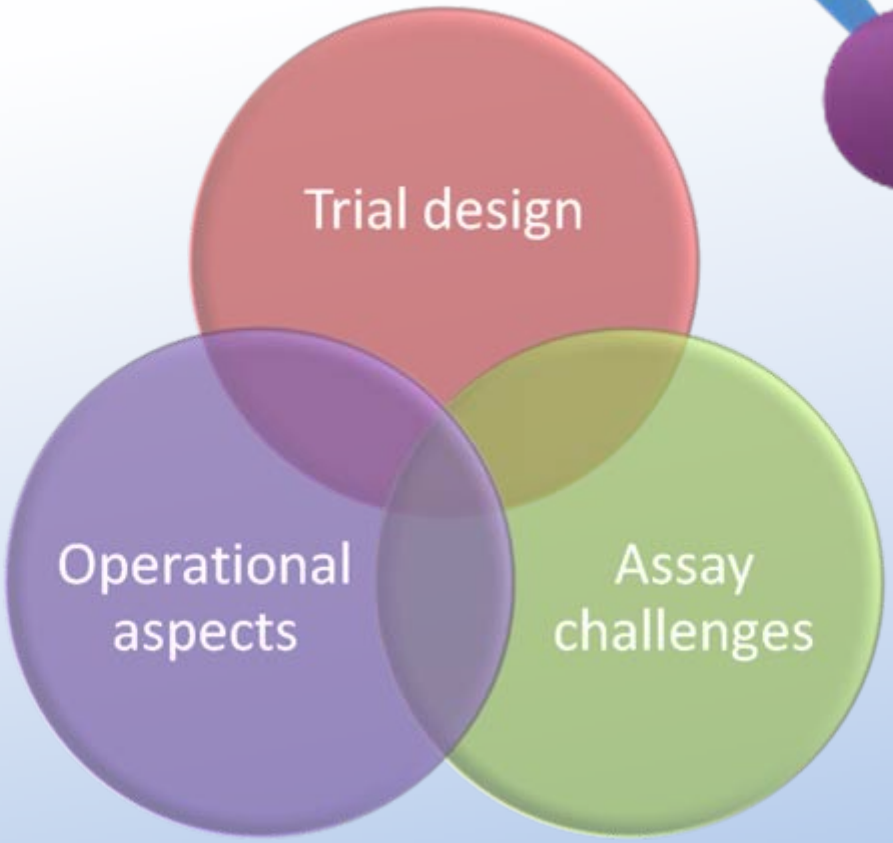
The good news

PK assays (usually) well characterised and validated

PK Assay challenges mainly about planning and procedures to cope with "what if"

Soluble BM assays : not so clear-cut if multiple tertiary/exploratory endpoints introduced

THE SOURCE OF THE CHALLENGES…



TO SUMMARISE…

MC trials are complex undertakings and BA is affected by that complexity

- Decline in R&D efficiency is leading to increased scrutiny in their design, rationale, objective & performance

The barriers to BA quality and control are most often accumulated small issues , possibly unrelated to each other.

BA issues will only be solved by BA community engaging with the process

- Technology solutions
- Articulating the consequences of actions and decisions
- Challenging the status quo

THANKS

TO COLLEAGUES AT A4Pbio FOR ADVICE AND COMMENTS
TO EBF ORGANISERS FOR ALLOWING

TO YOU FOR LISTENING

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