

How should clinical trials be monitored?

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Why we need reliable evidence from clinical trials

- Essential for appropriate decision making concerning the benefits and risks associated with clinical interventions.
- Decisions made in the absence of reliable evidence (either because relevant trials have never been performed or because those that have been performed were poorly designed or conducted) may harm individual patients and public health.

Objectives of Quality Assurance in Clinical Trials

- Protect the safety, rights and wellbeing of study participants
- Ensuring the reliability of the study results.

Potential sources of error

- Design
 - e.g. non-systematic recording of safety outcomes, inappropriate treatment allocation method, potential for inadvertent unblinding
- Procedure
 - e.g. inclusion of individuals with contra-indications to study intervention, drug regimen (incl. dosing & titration)
- Data recording
 - e.g. laboratory assays, physical measurements
- Analysis
 - e.g. non-intention-to-treat, over-emphasis of subgroups
- Errors may be *deliberate* (fraud) or *unintentional*

Baigent et al. Clinical Trials 2008;5:49-55

Impact of errors on the reliability of results

- *Random Errors:*
 - affect the precision of estimates (adding “noise” and reducing statistical power), but will not introduce bias in either direction
[Note: For equivalence assessments, random errors are counter-conservative]
- *Systematic Errors:*
 - lead towards a particular decision.

Regulations & their interpretation

- Regulations should set out the quality objectives that are common to all trials
- Regulations should NOT specify the methods for meeting these objectives
- The interpretation and implementation of the regulations must be flexible, if their objectives are to be fulfilled

ICH GCP: Regulations

- *The sponsor should ensure that trials are adequately monitored.*
- *The sponsor should determine the appropriate extent and nature of monitoring.*
- *The determination of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial.*

ICH GCP E6

FDA Regulations: 21 CFR 312

SPONSOR RESPONSIBILITIES

- ensuring proper monitoring of the investigation(s)
- ensuring that the investigation(s) is conducted in accordance with the protocol
- selecting a monitor to monitor the progress of the investigation.
- monitoring the progress of all clinical investigations being conducted under its IND.

FDA Guidance for Industry

1988 (minor format & edits 1998)

FLEXIBILITY PERMITTED

- These principles are not legal requirements but represent a standard of practice that is acceptable to FDA.
- A sponsor may rely upon this guideline or may develop different procedures.
- A sponsor who selects different procedures for monitoring a clinical investigation may, but is not required to, submit those procedures to FDA for review and comment to avoid the possibility of employing monitoring procedures that FDA might later determine to be inadequate.

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FDA Guideline for the Monitoring of Clinical Investigations

1988 (minor format & edits 1998)

DETAILS ENCOURAGE A COMMON (& OFTEN OUTDATED) APPROACH

- The monitor should visit the investigator at the site of the investigation frequently enough to assure that:
 - the facilities used by the investigator continue to be acceptable for purposes of the study.
 - study protocol is being followed
 - changes to the protocol have been approved by the IRB
 - accurate, complete, and current records are being maintained
 - accurate, complete, and timely reports are being made to the sponsor & IRB
 - the investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.
- The most effective way to assure the accuracy of the data... is to review individual subject records... and compare those records with the reports prepared by the investigator for submission to the sponsor.

BUT...THERE MAY BE MORE EFFICIENT / EFFECTIVE METHODS

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A sensible approach to monitoring

- Risk assessment
 - What might materially affect:
 - Rights of participants
 - Safety of participants
 - Reliability of study results
- Design & analysis
 - How can the study be designed & analysed to:
 - Minimise risks
 - Maximise chance of producing reliable & useful answer
- Monitoring plan
 - How can important (procedural & data recording) errors be detected
 - Tailor to meet risk assessment & design
- Making improvements
 - How can lessons be learnt
 - For the current & for other (future) trials

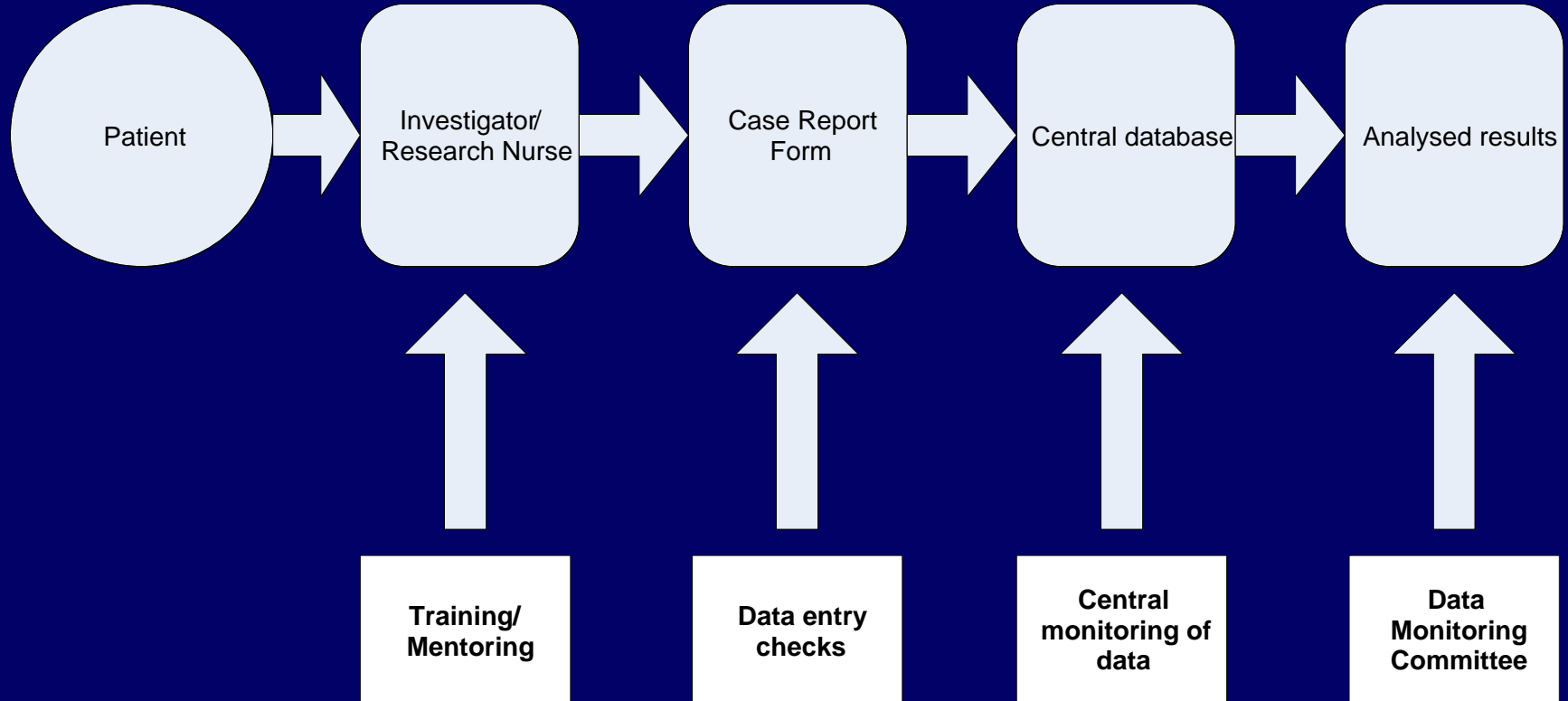
Risk assessment

- Rights of participants
 - informed consent process – *initial & ongoing consent*
 - privacy – *confidentiality, data protection*
- Safety of participants
 - hazards of intervention – *intervention, disease, exclusions, experience*
 - hazards of assessment – *nature & reliability of safety & efficacy assessments*
- Reliability of results (safety & efficacy)
 - power – *plausible effect size, recruitment, compliance, completeness of follow-up*
 - inclusion criteria – *appropriate level of risk*
 - treatment allocation – *randomization process, allocation concealment*
 - outcomes – *completeness of follow-up, method of capture, objective/subjective, potential for misclassification, level of blinding*

Quality can be designed



Quality can be monitored



Potentially inefficient / ineffective monitoring: Some examples

- Qualification
 - Curriculum vitae
 - GCP training
- Consent
 - review of forms without review of provision of information
- Source data verification
 - non-critical blood results & physical measurements
 - concomittant medication
 - unimportant adverse events
- Regulatory documentation
 - approval letters, etc in established centres
 - individual SAR (15-day) reports
- Drug accountability
 - pill counts

More efficient / effective monitoring

- Site visits
 - Targeted
 - Mentoring: Training, support, observation, motivation
- Remote assessment
 - Incident alerts
 - Tracking systems
 - Statistical analyses
 - Verification with external sources
 - Professional qualifications, existence of participants
 - Occurrence & nature of events
- Trial oversight
 - Steering Committee
 - Data monitoring committee

Monitoring staff performance

Report: Weight performance by staff (61 - 80 of 83)



user	total	direct	manual	p(manual)	scales	p(scales)	skipped	p(skipped)
MI	401	390	0	1.0	11	0.08	0	1.0
MI	434	429	0	1.0	2	1.0	3	0.07
NA	1	1	0	1.0	0	1.0	0	1.0
OL	95	95	0	1.0	0	1.0	0	1.0
PA	47	46	0	1.0	1	0.5	0	1.0
PA	1093	1078	0	1.0	12	1.0	3	0.4
PE	245	242	0	1.0	3	0.8	0	1.0
RA	15	14	0	1.0	1	0.2	0	1.0
RE	1	1	0	1.0	0	1.0	0	1.0
RI	1023	1001	0	1.0	19	0.4	3	0.4
SA	442	425	0	1.0	17	0.0020	0	1.0
SA	275	271	0	1.0	4	0.7	0	1.0
SA	2	2	0	1.0	0	1.0	0	1.0
SA	5	5	0	1.0	0	1.0	0	1.0
SC	682	670	0	1.0	11	0.6	1	0.8
ST	157	155	0	1.0	1	0.9	0	1.0
SU	6	5	0	1.0	1	0.1	0	1.0
SU	26	25	0	1.0	0	1.0	1	0.06
TC	269	265	0	1.0	4	0.7	0	1.0
TR	19	19	0	1.0	0	1.0	0	1.0



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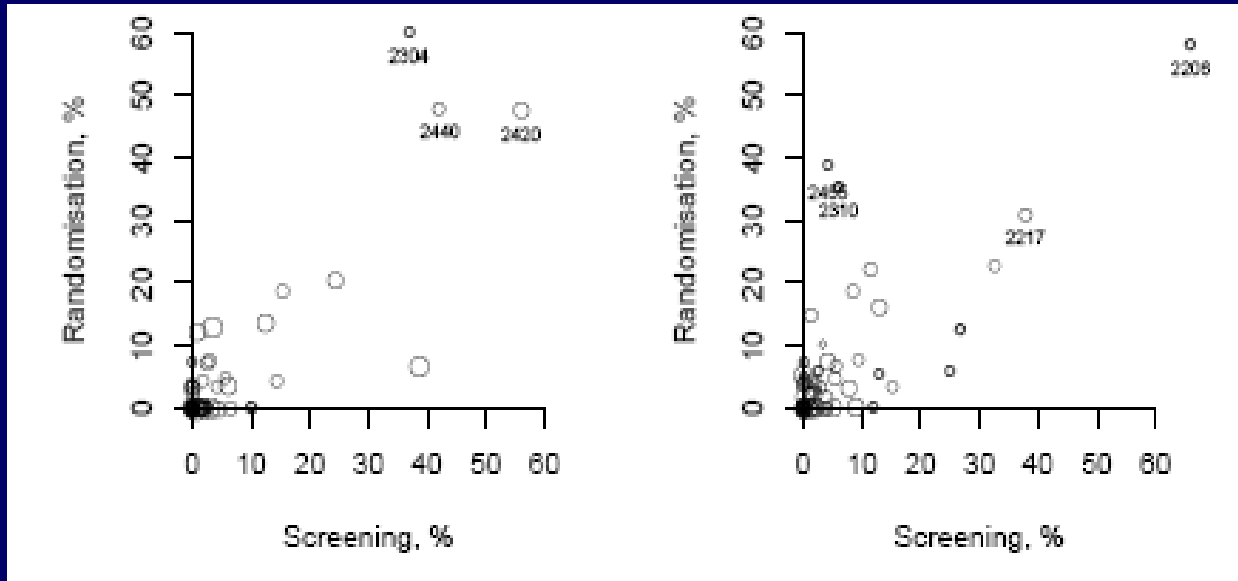
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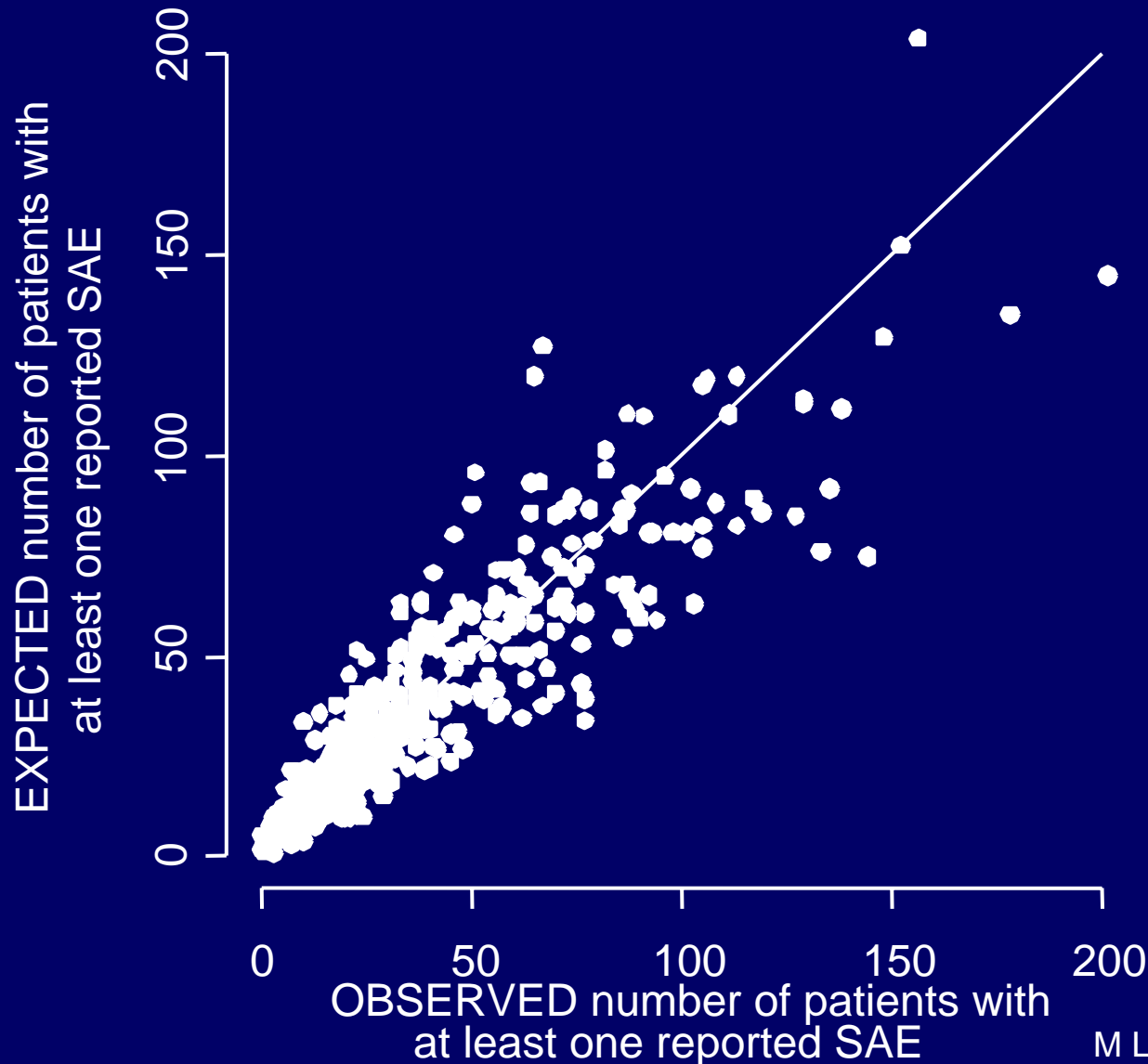


Proportion of randomisation and screening visits outside the 5th to 95th (region-specific) percentiles, by centre

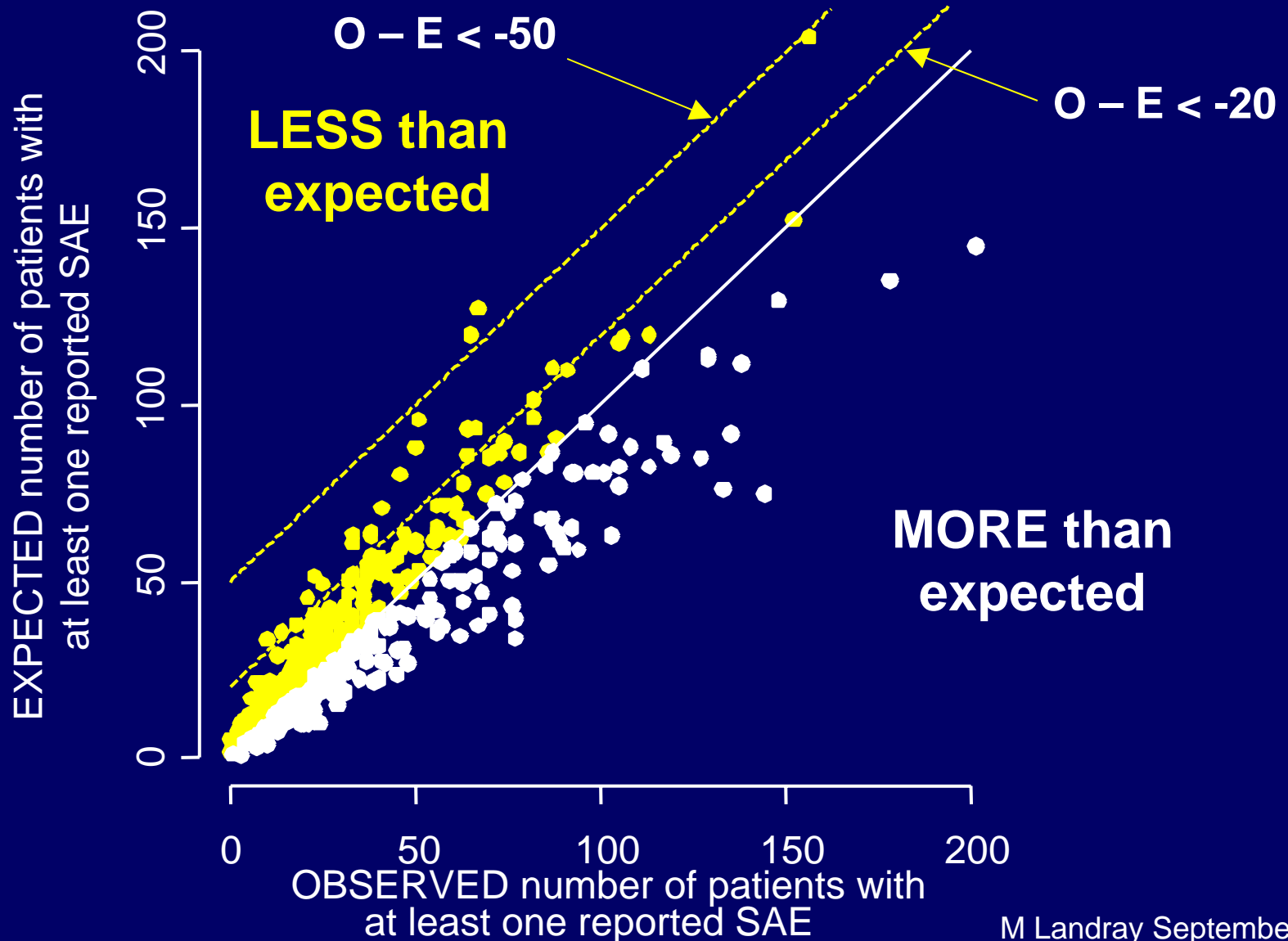


Visit	Q5	Median	Q95
Screening	11	23	46
Randomisation	8	20	41

Example: SAE rates by hospital



Example: SAE rates by hospital



Checking medical registration

http://webcache.gmc-uk.org - GMC LRMP - Microsoft Internet Explorer

Regulating doctors
Ensuring good medical practice

General
Medical
Council

List of Registered Medical Practitioners

Search Again?

Refine Search

Results

Current Details

History

Details

 print view

[Help](#)

Results of search on: 04 Sep 2009 at 16:42:02. The details shown are valid at the date and time of the search only.

<u>GMC Reference Number</u>	3584039
<u>Given Names</u>	Martin Jonathan
<u>Surname</u>	Landray
<u>Gender</u>	Man
<u>Registration Status</u>	Registered

More Details

<u>Primary Medical Qualification</u>	MB ChB 1992 University of Birmingham
<u>Provisional Registration Date</u>	23 Jun 1992
<u>Full Registration Date</u>	01 Aug 1993
<u>Specialist Register entry date</u>	Clinical pharmacology and therapeutics From 23 Jan 2001 General (internal) medicine From 23 Jan 2001
<u>GP Register entry date</u>	This doctor is not in the GP Register
<u>Information for Employers</u>	Details

[Data Protection & Privacy Statement](#)

Making improvements

- Problems identified may be:
 - Design, procedural, data recording, analysis
- Solutions may be particular or general
 - e.g. training, reconfiguration of process
- Lessons may be important for other trials
 - ongoing or planned
 - design or monitoring

Further development of efficient & effective monitoring methods: CTTI Monitoring Project

- Review of current practices
 - There are many, diverse methods currently in use
 - The rationale for using any particular method is unclear
 - All have been accepted by journals and regulatory authorities
- Define key objectives of monitoring
 - Essential step for:
 - evaluation of existing monitoring methods
 - development of new methods
 - deployment of existing methods to new setting
 - [Note: Implementation details to be avoided]
- Assessment of current monitoring techniques :
 - Describe the benefits and limitations of each method
 - Give examples of good practice
 - Identify areas for additional research / evaluation

Summary: Sensible monitoring

- Overall objective: Improve the availability of reliable information from clinical trials on which to base important healthcare decisions
- Monitoring should enhance quality
 - for participants in the trial
 - for future patients whose care relies on the results
- Monitoring should be appropriate *and* proportionate to the risks
- Ineffective or inefficient practice should be abandoned
 - they fail protect participants or study integrity, waste resource, limit recruitment & follow-up, deter participation & enthusiasm
- Monitoring practices with uncertain value should be evaluated