AUDIT PROGRAM

Audit Program

- **Background – Definition**
- **Management**
- **Example**
- **Content**
  - System audits vs study audits
- **Risk assessment approach**
  - ICH-GCP E6 new content
  - Management
  - Example

Background - Definition

- There is a requirement to provide assurance that an organisation's clinical trial (CT) activities are conducted in accordance with CT documentation and also to identify any deficiencies in supporting CT processes and systems.
- A mechanism should be in place to provide assurance that the activities are conducted as above; in accordance with the applicable regulations, Standard Operating Procedures (SOPs) and GCP.

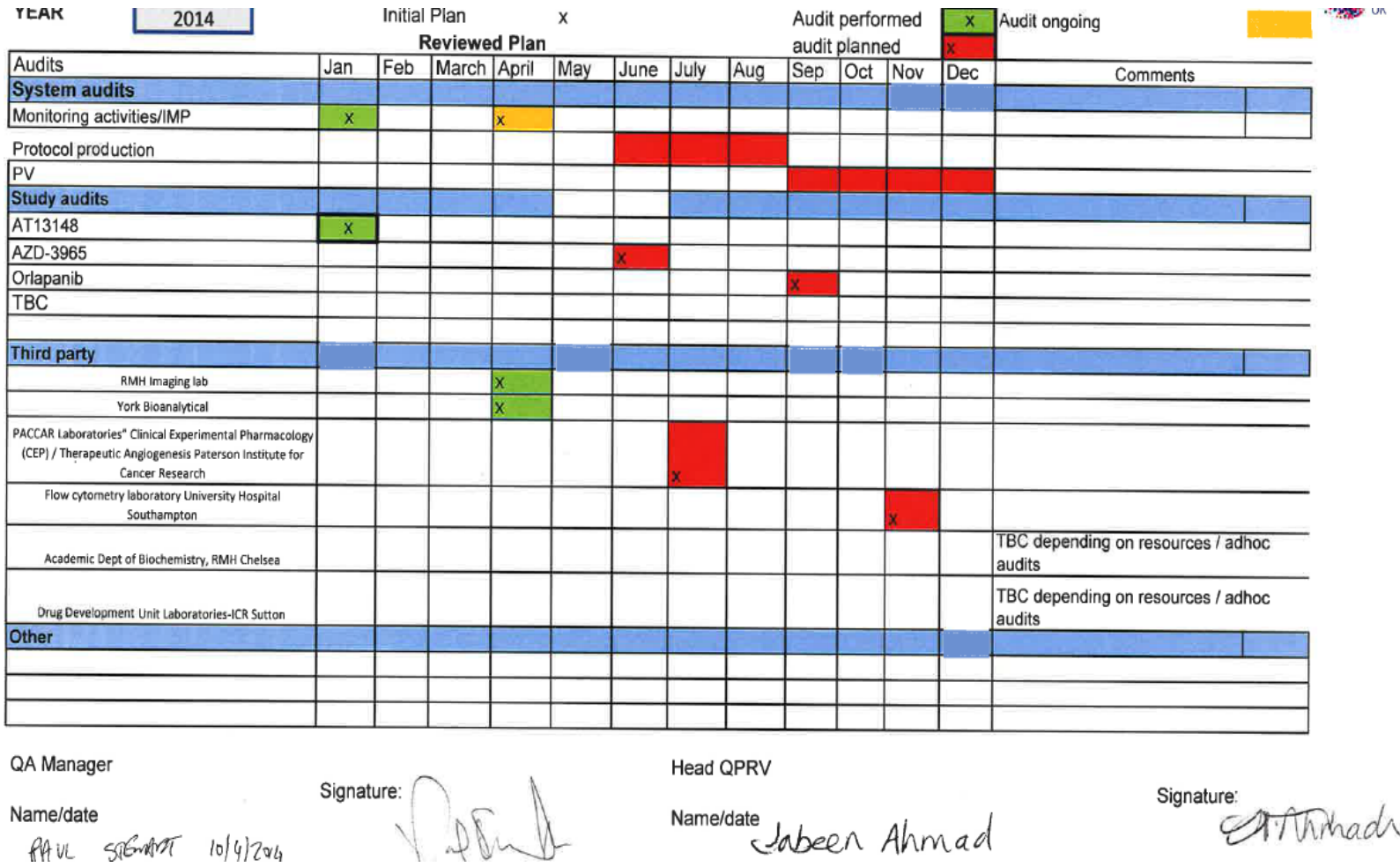
An audit program is a record of the planned QA activities in a defined period of time.

Management

- It is recommended that the audit program is reviewed and approved by a member of staff with the appropriate authority.
- It is recommended that the management of the audit program is described in an SOP.
- It is important that it is reviewed and changes documented:
  - Study timelines may change;
  - Risk and priorities may change;
  - Unscheduled audits required that will impact the plan.

Important to ensure that changes are managed in a controlled manner.

Example



YEAR 2014 | Initial Plan x | Reviewed Plan | Audit performed x | audit planned x | Audit ongoing

Audits	Jan	Feb	March	April	May	June	July	Aug	Sep	Oct	Nov	Dec	Comments
System audits													
Monitoring activities/IMP	x			x									
Protocol production													
PV													
Study audits													
AT13148	x												
AZD-3965						x							
Orlapanib									x				
TBC													
Third party													
RMH Imaging lab				x									
York Bioanalytical				x									
PACCAR Laboratories" Clinical Experimental Pharmacology (CEP) / Therapeutic Angiogenesis Paterson Institute for Cancer Research							x						
Flow cytometry laboratory University Hospital Southampton											x		
Academic Dept of Biochemistry, RMH Chelsea													TBC depending on resources / adhoc audits
Drug Development Unit Laboratories-ICR Sutton													TBC depending on resources / adhoc audits
Other													

QA Manager

Name/date RAVL SUBRAMONY 10/4/2014

Signature:

Head QPRV

Name/date Jabeen Ahmad

Signature:

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Audit Program Content

Depends on the type of audits performed by the organisation:

- Trial specific
- Trial site
- Process
- Systems
- Facility or vendor
- Documentation

System Audits

- Looking at the functionality of a complete system
  - (QMS, PV, DM, etc.)
- Aim to evaluate the adequacy of the selected system in order to identify possible deficiencies, or areas for improvement.
- An improvement in the systems will increase the quality of the organisation.
- Regulatory agencies are performing system audits.

Specific Study Audits

- Purpose is to ensure compliance of a specific study management.
- Difficult to cover all processes under a study scope.
- Possible corrective and preventive actions can be managed at a study level and not implemented in the improvement of the activity.
- If system audits are not considered, is important to ensure that the study CAPA implemented are not just at a study level.

Risk Assessment

MRC/DH/MHRA Joint Project
Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

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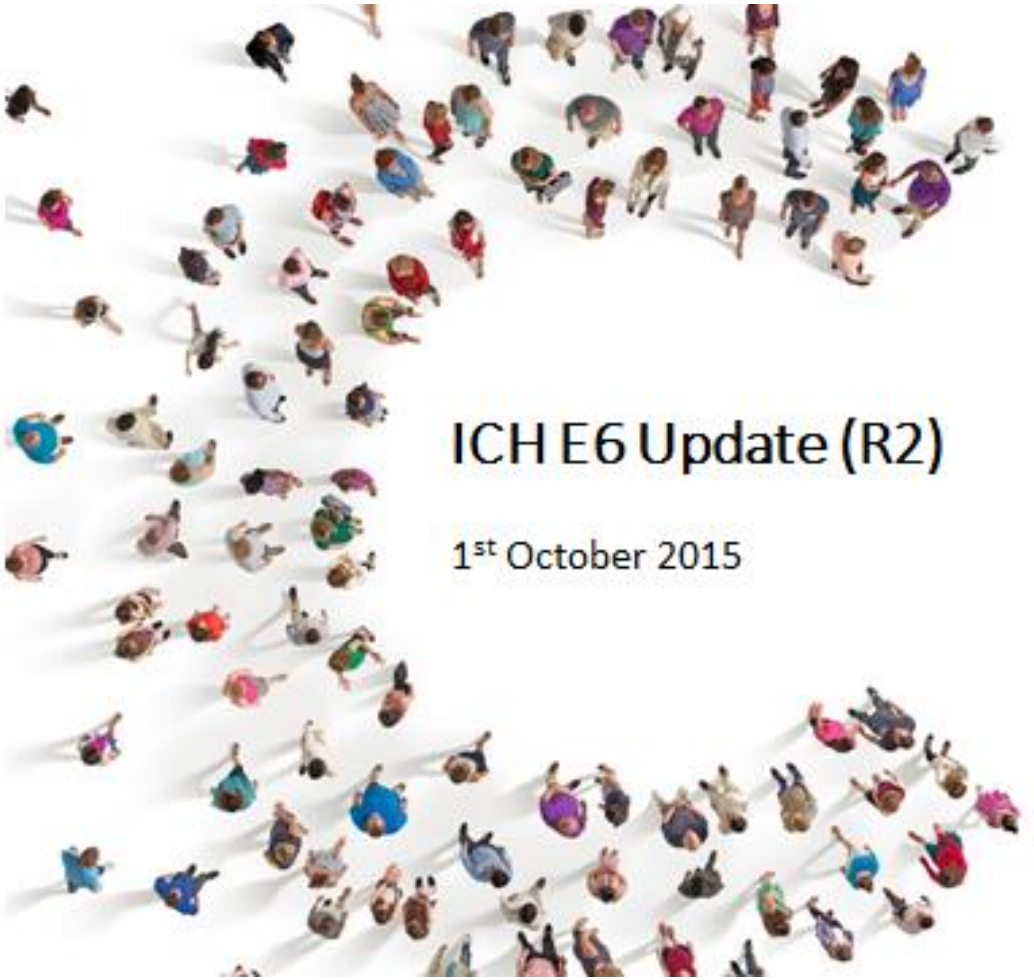
MHRA Categorisation Based upon Potential IMP Risks

- Type A: no higher than the standard medical care (SMC).
- Type B: somewhat higher than the SMC – authorised IMP new indications, combinations, different conditions.
- Type C: markedly higher than the SMC – non authorised IMP.

Risk Assessment

MHRA Risk Adapted Approach Guidance

- For every trial, however, there is also a core set of risks inherent to the protocol that relate to the safety of the participants and the integrity/reliability of the results.
- All organisations involved need to understand these risks so that the control measures, resources, procedures and processes implemented during the trial ensure the safety of the trial participants, and lead to high-quality results.



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ICH-GCP Update

QUALITY MANAGEMENT SYSTEM:

- Throughout the lifecycle of a trial from protocol development to reporting and in a cross-functional manner.
- Prospectively identify critical data and processes to identify events that would impede successful completion of the study or adversely affect participants.
  - System level (e.g. facilities, SOPs, computerised systems, personnel, vendors)
  - Clinical trial level (e.g. investigational product, trial design, data collection and recording)

Risk Assessment

- Risk Identification
- Risk Control
- Risk Analysis & Evaluation
- Risk Communication
- Risk Review
- Risk Reporting

Risk Identification: risks to successful trial conduct, acquisition of critical data and completion of critical study processes should be identified.

Risk Control: the sponsor should determine those risks that may have impact on human subject protection or data integrity which can be accepted, and those risks that should be reduced through risk mitigation.

Risk Mitigation Activities: may be incorporated into protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to SOPs and training in new processes or procedures.

Risk Analysis and Evaluation: the identified risks should be evaluated by considering the likelihood of errors occurring, the impact of such errors on human subject protection and data integrity, and the extent to which such errors would be detectable.

Risk Communication: the risk management activities should be documented and communicated to key stakeholders to facilitate risk review and continual improvement during clinical trial execution.

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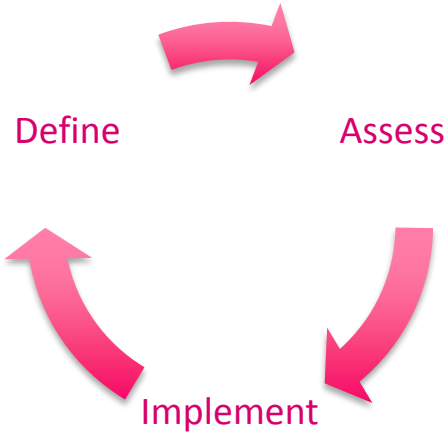
Risk Review: the sponsor should periodically review risk control measures to ascertain whether the implemented quality risk management activities remain effective and relevant, taking into account emerging knowledge and experience.



Risk Reporting: the sponsor should describe the quality management approach implemented in the trial (ICH E3, section 9.6 Data Quality Assurance) and summarise important deviations from the predefined quality limits in the clinical study report.

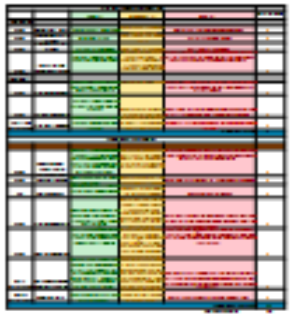
Risk Assessment

- Predefined quality limits should be established to identify systematic issues that can impact subject safety or data integrity.

- Detection of deviations from the predefined quality limits should signal a need for further action.

Risk assessment tool Example

Risk Assessment Tool



- Tool contains both **Project Level** and **Site Level**

- **PROJECT LEVEL**
  - Novelty of IMP
  - Known clinical safety issues
  - Preclinical safety issues
  - IMP storage/handling
  - Protocol complexity
  - Patient Population
  - Project Relevance

SITE LEVEL:

- Key Personnel experience/changes
- Protocol Deviations
- Recruitment Rate
- Data queries
- Data quality
- SDV up-to-date
- AE/SAE reporting
- Pharmacy deviations / accountability

Risk assessment tool Example

Risk Assessment Tool – Evolutionary Risk Metrics

15	Evolutionary Risk Metrics					CRUK SM001	CRUK mAb001
16							
17	CSM	Relevance of substantial amendments	General Amendments	Impact on Data Integrity/ Scientific value	Impact on Safety/ Welfare	1	1
18	CSM	Key Personnel	No Key Personnel changes	Changes to Lead Research Nurse/CRA	Change to CI/PI High CRA turnover	1	1
19	PV	Total SUSARs	No SUSAR or less than expected according to IMP development status	SUSAR as expected according to IMP development	High number of SUSAR	1	1
20	CSM	Protocol Deviations	Non compliances only	High frequency of non-compliances or low level of deviations	High incidence of deviations or serious breach	1	1
21	CSM	Recruitment vs plan	Low	As expected	High	1	1
22	Data Management	Data Management queries/ Subject	Within normal parameters	Poor Quality OR Late data	Poor Quality AND Late data	1	1
23	Quality Assurance	Audit History	Audited within 3 years/ no Critical/Major findings	Audited > 3 years/ Major findings at previous audit	Never audited/Critical finding at previous audit	3	1
24							
25					Total Risk Score:	27	18

Used by QA to determine audit plan

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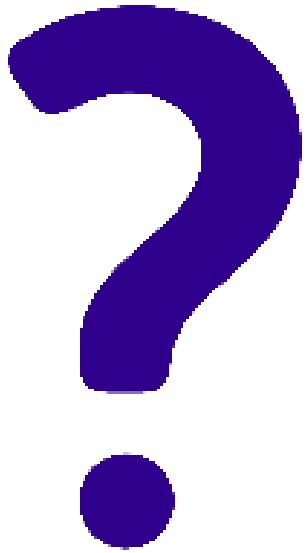
Risk assessment tool (Third parties)

SCORE	HIGH	MEDIUM	LOW
Endpoint Selection	Primary :6	Secondary :4	Tertiary:1
Audit History	Never Audited or significant change :6	Over 3 years: 4	less than 3 yrs:1
Compliance	CAPA not properly followed: 4	CAPA actions delayed: 2	CAPA closed in agreed timescale: 1
Methodology risk score Validation of method/ established methodology	Validation is incomplete and methodology is under development :6	Validation is incomplete or methodology is under development: 4	Validation is complete and methodology is well established: 1

Thank You

Any Questions?



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