

Notes on Good Practice for Research Organisations in the Management of a Portfolio of Trials 2: Assessment of risk.

1. ASSESSMENT OF RISK

All trials need to undergo risk assessment and each organisation needs to consider its level of responsibility for ensuring that there is a system in place to conduct an assessment of individual trials.

This will need agreement between organisations and transparency with regard to both the methodology and results of the assessment.

Prospectively, risk assessment needs to be undertaken as early as possible so that measures can be built into the protocol and reflected in the grant application, which would assist in the minimisation of risk and the maximisation of resources available to manage the risk.

Retrospectively, the organisation will need to prioritise the trial risk assessment process, starting with those which fall into the banding of potentially high risk.

There is a spectrum of risk in undertaking trials, generally decreasing from trials of new products, to comparisons of previously licensed products (i.e. Phase I or II to Phase III or IV).

For each trial, or groups of trial, by type, potential hazards should be identified and then the risk of harm assessed.

Where risk of harm is identified, systems should be put in place to manage and/or minimise the risk.

Guidance on individual trial management and monitoring good practice can be found in the output from Workstream 4.

In summary it is recommended that for every clinical trial a **Trial Management Systems Document** is prepared.

This will contain a description of the systems in place for each of the major aspects of trial management, including monitoring procedures.

The level of detail required will depend on three factors: the clinical trial risk assessment, the organisational structure within which the trial is being conducted and the design and methods of the clinical trial.

Once an organisation has a view of the potential risks of its particular trial portfolio, an action plan needs to be developed which will address both generic system weaknesses and individual trial management arrangements.

An organisation may also take the view that quality is preferable to quantity – that use of resources in terms of trial management should be directly at trials which are more likely to produce results of benefit to science and/or directly to clinical practice and patients.

Equally, a poorly managed trial may produce no usable results, even though it consumed the same resources and presented the same risks and inconveniences to participants as the

potentially more productive trials it squeezed out.

With regard to the assessment and management of risk associated with trials, a Checklist in *Appendix 1* provides some initial guidance and, in *Appendix 2*, the key aspects are translated into a Risk Assessment Matrix in the style of the NHS standard risk assessment system –two examples of working models are provided.

2. SOURCE DOCUMENTS

[**Trial Management and Monitoring Guidance – MRC/DH Joint Project on Clinical Trials**](#)

[**The Medicines for Human Use \(Clinical Trials\)**](#)

[**Description of the Medicines for Human Use \(Clinical Trials\) Regulations 2004**](#)

[**EU Clinical Trials Directive: Sponsorship responsibilities in publicly funded trials**](#)

[**Responsibilities, liabilities and risk management in clinical trials of medicines – DH/Universities UK Joint Statement**](#)

[**Research for Patient Benefit Working Party: Final Report**](#)

[**MRC-EU Clinical Trials Directive Policy Statement**](#)

[**MRC Guidelines for Good Clinical Practice in Clinical Trials**](#) *[to be amended in 2004 so that it refers to the EUCTD and UK Regulations]*

Department of Health. The Research Governance Framework for Health and Social Care. Draft 2nd Edition, HM Stationery Office, London, 2003. *[2nd Edition to be revised so that it and the EUCTD are consistent]*

Research Governance in Health and Social Care – NHS Permission for R&D Involving Patients

NHS Research Governance Controls Assurance Indicators

[**NHS R&D Forum Guidance via Working Groups, Website and Workshops**](#)

APPENDIX 1
Checklist for Risk Assessment and Management

	Assessing Risk to the Organisation	Organisational Risk Management
Reputation	<ul style="list-style-type: none"> • is the funder/source of funds reputable? • is there any reason to protect against fraud / misconduct? • are the trial results likely to attract undesirable publicity? • are partner organisations competent? Controls assurance/equivalent standards in place? 	<ul style="list-style-type: none"> • institutional policy on acceptance of funding from reputable funding bodies • ensure that staff are aware of institutional policies on management of fraud and misconduct • consider any controversial aspects of the trial and anticipate likely findings : is negative publicity likely to arise? • develop management systems to control risk across organisational boundaries and assess competence of other organisations
Ethics	<ul style="list-style-type: none"> • is the protocol ethical, e.g. are consent and confidentiality procedures appropriate? • is the disease group being studied particularly sensitive e.g. children or adults without the capacity to give consent? 	<ul style="list-style-type: none"> • ethical review by Research Ethics Committee • check local consent process is appropriate • ensure systems are in place to record and report adverse events
Feasibility	<ul style="list-style-type: none"> • can the participants be recruited considering inclusion / exclusion criteria? • are the researchers qualified / trained appropriately eg. GCP, Health & Safety ? • are the researchers experienced in trial management? • is the time scale of the study appropriate to allow completion? • is sufficient researcher time included? • are the arrangements for trial management appropriate? 	<ul style="list-style-type: none"> • early discussion with service providers to ensure availability of participants, taking on board inclusion / exclusion criteria • research management and support systems in place to facilitate research eg. A Trial Management Systems Document has been agreed and a project team meets regularly to review trial progress, recording actions which are followed up
Financial Risk	<ul style="list-style-type: none"> • are both the research and treatment costs identified correctly and is funding available? • what are the long term financial implications of continuing a treatment found to be effective beyond the trial itself? 	<ul style="list-style-type: none"> • early discussion with University Research Grants Office / NHS R&D Office about costings • early discussion with Pharmacy Department about long-term implications of continuing an effective medication • there are clear procedures in place for the management of the trial budget

APPENDIX 2

Risk Assessment Tool

Table 1

HAZARDS TO PATIENTS		
GENERIC HAZARDS	EXAMPLES	MANAGEMENT STRATEGIES
Novel or unproven interventions	Novel drugs, devices, surgical procedures, potential for unexpected adverse events Unproven effectiveness Use for new indication Increased susceptibility of patient population Novel handling requirements e.g. drugs, tissue Equipment safety	Regulatory (MHRA) and ethical (REC) approvals Data Monitoring and Ethics Committee Adverse event reporting systems QC checks on equipment
Inexperienced clinical team	New clinicians Unfamiliar with underlying condition Unfamiliar with expected adverse events	Project team with experienced support Training
Additional invasive tests or exposure	Additional invasive tests Increased radiological exposure	Data Monitoring and Ethics Committee IRMER / ARSAC Adverse event reporting systems
Consent – uninformed, absent, pressured	Time to consider Information provided – clarity, appropriate Experience and knowledge of person taking consent Timing relative to diagnosis Capacity to give consent Participation in multiple trials Failure to act on withdrawal of consent Consent not recorded and /or filed Incorrect use or storage of tissue samples	REC approved literature and process. Training and awareness Panel of people equipped to act as legal representative Communication systems e.g. alerts stickers in patient notes, contact details on consent form Centralised tissue bank management Audit of consent procedures including verification of signed consent forms
Patient confidentiality, non-clinical test results	Breach of confidentiality Genetic susceptibility or incurable diseases – breach of anonymisation	Normal hospital systems Minimise staff who have access to confidential information Follow REC approved processes Training and awareness

HAZARDS TO STUDY		
GENERIC HAZARDS	EXAMPLES	MANAGEMENT STRATEGIES
Organisational complexity	Multi-centre studies Multi-disciplinary studies Complex series of events / stringent timings required Non-standardised methods Complex data collection requirements Poor data quality and integrity	Trial Management Protocol Trial Steering Committee Trial Co-ordinator posts Multidisciplinary project teams Standardised data collection forms, Electronic processing, back ups Regular data quality checks Audit – source data verification
Study power, recruitment and consent	Plausibility of treatment effect and patient numbers Insufficient patient pool Poor fit with clinical pathway Restricted access to patients Large referral base Competing trials Restrictive inclusion/exclusion criteria Patient health/ compliance/ability to travel Patient travel costs Patient preferences Length and frequency of follow up Ineffective communication with patient (before and after trial) Failure to record consent	Statistical input to design and power Support from R&D, RDSG Multidisciplinary project teams Input from service Realistic recruitment schedules Pilot studies Adequate resources External communication and trial promotion Training in consent process
Study results	Violation of Inclusion / exclusion criteria Financial / non-financial incentives Randomisation procedure Blinding / anonymisation arrangements Source data availability for verification Results not disseminated / implemented	Trial Management Protocol Independent randomisation via R&D Statistical input to data monitoring and audit Interim reports Literature updates from Library R&D Annual Report
Staff competence and experience	Standardisation of methods Data collection quality Communication with patient Co-ordination with other functions Administrative support Adequacy of financing	Training Appropriate level of resources Project team meetings Research Manager support

HAZARDS TO ORGANISATION		
GENERIC HAZARDS	EXAMPLES	MANAGEMENT STRATEGIES
Consent – uninformed, absent, pressured	See hazard to patients for examples	
Patient confidentiality	See hazard to patients for examples	
Non-clinical test results	See hazard to patients for examples	
Liability	Clarity of liability arrangements with collaborators Legal obligations under UK Regulations for medicinal trials Clarity of liability information in patient information sheet e.g. arrangements for non-negligent harm	Clear identification of sponsor Partnership agreements Monitoring of collaborating sites Systems to ensure reporting obligations for medicinal trials (SUSARs, amendments, termination)
Service impact	Direct impact via e.g. tests required Indirect impact via e.g. staff time	Contact with service early in planning and throughout the trial Multidisciplinary project teams
Intellectual Property	Opportunities overlooked Lost opportunity due to disclosure	Internal awareness R&D Annual Report

Table 2		SEVERITY OF IMPACT			
IMPACT ON:	INSIGNIFICANT	MINOR	MODERATE	MAJOR	CATASTROPHIC
PATIENT	None	Unexpected complications Extended stay < 3 d Full recovery	Some permanent loss of function or loss of earnings	Major disability or death	Multiple disability or death
	◀..... Novel or unproven interventions▶				
	▶..... Inexperienced Clinical Mgt Team▶				
	▶..... Consent – uninformed, absent, pressurised▶				
	▶..... Additional invasive tests or exposure▶				
	▶..... Patient confidentiality / non clinical test results▶				
Likelihood	INSIGNIFICANT	MINOR	MODERATE	MAJOR	CATASTROPHIC
RARE	Low risk				
UNLIKELY		Medium risk			
POSSIBLE				High risk	
LIKELY					
ALMOST CERTAIN				No go?	

Table 2 cont'd		SEVERITY OF IMPACT				
IMPACT ON:	INSIGNIFICANT	MINOR	MODERATE	MAJOR	CATASTROPHIC	
STUDY	Objectives fully met	Primary objective met Not meet some secondary objectives	Not meet primary and secondary objectives Impact on Trust research reputation	No valid data or learning Fraudulent data	Misrepresented findings impact standard clinical practice	
	←———— Organisational complexity —————→					
	←———— Study power, recruitment & consent —————→					
	←———— Study Results —————→					
	←———— Staff Competence and experience —————→					
Likelihood	INSIGNIFICANT	MINOR	MODERATE	MAJOR	CATASTROPHIC	
RARE	Low risk					
UNLIKELY		Medium risk				
POSSIBLE				High risk		
LIKELY						
ALMOST CERTAIN				No go?		

Table 2 cont'd		SEVERITY OF IMPACT			
IMPACT ON:	INSIGNIFICANT	MINOR	MODERATE	MAJOR	CATASTROPHIC
ORGANISATION	None	~ 1 day local press Financial loss < £5K	National Press Prosecution Financial loss < £100K	DoH action Financial loss < £5m	Major Inquiry Financial loss > £5m
	←————— Liability —————→				
	←———— Patient confidentiality / non clinical test results —————→				
	←———— Consent – uninformed, absent, pressurised —————→				
	←———— Service Impact —————→				
	←———— Intellectual Property —————→				
Likelihood	INSIGNIFICANT	MINOR	MODERATE	MAJOR	CATASTROPHIC
RARE	Low risk				
UNLIKELY		Medium risk			
POSSIBLE				High risk	
LIKELY					
ALMOST CERTAIN				No go?	

**IoP / SLaM Clinical Trials Co-ordinating Committee
Risk Assessment Tool**

Principal Investigator: Trial title: Funding Body: Trial of medicines	Yes/No
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Rate the following risks according to two scales of impact if things go wrong and likelihood of a hazard occurring.

Hazard	Impact if it happens 1-Low 2-Moderate 3-Significant 4-Severe 5-Catastrophic	Likelihood of it occurring 1-Remote 2-Unlikely 3-Possible 4-Likely 5-Certain	Risk (Impact X Likelihood)
Undesirable publicity - controversial aspects?			
Recruitment unrealistic			
Researchers not trained / qualified appropriately			
Adverse drug reactions (in particular consider where subjects are children and / or where drug is not licensed for indication)			
Adverse events arising from other procedures			
Poor academic value - publication rights, IP			
Not fully costed			
Post-trial treatment costs			
Partnership organisations - inadequate controls			
Poor management / monitoring			

Comments

This trial is: accepted as being within an acceptable level of risk
 not accepted

IoP / SLaM R&D Office signature Name:
 Date:

RISK ASSESSMENT MATRIX

		Likelihood				
		1 Remote	2 Unlikely	3 Possible	4 Likely	5 Certain
Impact	1 Low	1	2	3	4	5
	2 Moderate	2	4	6	8	10
	3 Significant	3	6	9	12	15
	4 Severe	4	8	12	16	20
	5 Catastrophic	5	10	15	20	25

To rate a risk or near miss:

1. Grade the impact of the worse case scenario [overleaf]
2. Multiply this impact [1-5] by the likelihood [1-5], to get your rating.

RISK MANAGEMENT

KEY	Risk Level	Action and Time scales
A	CATASTROPHIC	Immediate action must be taken to manage the risk. Control measures should be put into place which will have the effect of reducing the impact of an event or the likelihood of an event occurring. A number of control measures may be required.
B	SEVERE	Significant resources may have to be allocated to reduce the risk. Where the risk involves work in progress urgent action should be taken.
C	SIGNIFICANT	Efforts should be made to reduce the risk, but the costs of prevention should be carefully measured and weighed against the impact of an event. Establish more precisely the likelihood of harm as a basis for determining the need for improved control measures.
D	MODERATE	On or below this level a risk is acceptable. Existing controls should be monitored and adjusted. No further action or additional controls are required. Consideration may be given to a more cost-effective solution or improvement that imposes no additional cost burden.
E	LOW	Acceptable risk. No further action or additional controls are required. Risks at this level should be monitored, and reassessed at appropriate intervals.

