NHS Research and Development Forum

Non-Commercial Sponsors' Symposium

How to be a 'good' & compliant Sponsor

8th November 2018 – London

NHS Research and Development Forum

Network

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Welcome all

#noncomsponsors

www.rdforum.nhs.uk

NHS Research and Development Forum

Symposia shaped by:

Forum Fringe – May 2018

Support for sponsors - Prof development & community

"Good & Compliant" - **R&D function is an enabler**

Proportionate process across all study types

Hot topics: **Sponsors are important**

Professional Learning & Development

NHS Research and Development Forum

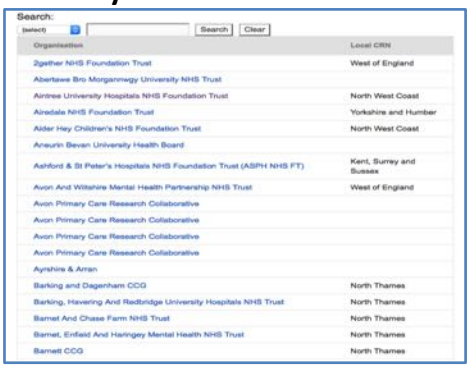
Developing new courses, events & opportunities

www.rdforum.nhs.uk

NHS Research and Development Forum

Building a community of practice

Directory of R&D Offices



Universities welcome

http://www.rdforum.nhs.uk/content/contact-details/

NHS Research and Development Forum

www.rdforum.nhs.uk/content/resource-exchange-home-page/

Resource Exchange Home
Keyword Search
Category List
Submit a Resource
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R&D Functions Wheel

Keyword Search

Embed Research In A Healthcare Setting
Lead & Grow Research
Promote Performance & Impact
Sponsor & Set Up Research
Manage Research Operations &

Search Results

Below are the results of the keyword search. Click here if you would like to see the results that show where the search term appears in the Title of the Resource.

Results for Keyword

Search Term: Sponsor
Resource Type Search:

Chief Investigator Agreement for UCL Sponsored CTIMPS
Type: Example agreement
Author: University College London (UCL)
Keywords: Delegation responsibilities, Chief Investigator, Agreement, CI Agreement
Sponsorship, CTIMPS
Additional Detail: Also contains responsibilities matrix
Link Reference: 1323
Click here to access the resource

Defining research category as Sponsor
Type: Example SOP
Author: University Hospitals Leicester NHS Trust
Keywords: SOP, Sponsor, Joint Research Office
Link Reference: 987
Click here to access the resource

Gaining Sponsorship & supporting Sponsor oversight
Type: Example SOP
Author: University hospitals Bristol NHS Foundation Trust
Keywords: research sponsor sponsorship procedure
Link Reference: 1031
Click here to access the resource

Sponsor & Set Up Research
Sponsor & Set Up Research
Show Categories

Manage Research Operations & Delivery
Manage Research Operations & Delivery
Show Categories

Assure Quality
Assure Quality, Safety & Integrity

NHS Research and Development Forum

Thank you

Sponsors Work stream:

Jess Bisset, Jen Harrison, Heidi Nield, Gemma Jones, Heather Rogers, Sarah Townsend, Birgit Whitman, Sean Scott, Kirsty Rogers, Marie-Claire Good,

Also: Angela Williams & HRA Sponsor reference group, Mind doodle, Speakers & Chairs.

Contact the groups via info@rdforum.org.uk

www.rdforum.nhs.uk

Competing interests

I'm an editorial consultant, an associate editor for The BMJ, and guest professor at the China National Clinical Research Center for Neurological Diseases at Beijing Tiantan Hospital, Capital Medical University

Until retirement in May 2018 I was editor in chief of online-only open access journal BMJ Open, director of academic outreach at BMJ, and editorial lead for BMJ's Research to Publication eLearning programme.

I am receiving a fee from BMJ for delivering this talk.

"The HRA must act now to ensure current regulations are enforced and impose tough sanctions on those who seem to think it is acceptable to disregard valuable research, threaten research integrity and, in some cases, endanger human life.

Many of these trials are funded with public money and the tax payer has a right to expect those who benefit from public funding to follow the rules and publish in full..."

Rt Hon Norman Lamb MP, committee chair, 30 October 2018

Recommendations for the Government

The Government should:

- ask the HRA to publish, by Dec 2019, a detailed strategy for achieving full clinical trials transparency, with a clear deadline and milestones
- consult on whether to provide the HRA with statutory powers to fine sponsors for non-compliance

House of Commons Science and Technology Committee. Research integrity: clinical trials transparency. Oct 2018. https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/1480/148002.htm.

thebmj

Recommendations for the HRA

The HRA should:

- report annually on its performance against the strategy
- set up a national, funded, programme to audit clinical trials transparency, with a single official list of which UK trials have published results and those which are due to but have not
- introduce a system of sanctions to drive improvements in clinical trials transparency, such as withdrawing favourable ethical opinion or preventing further trials from taking place

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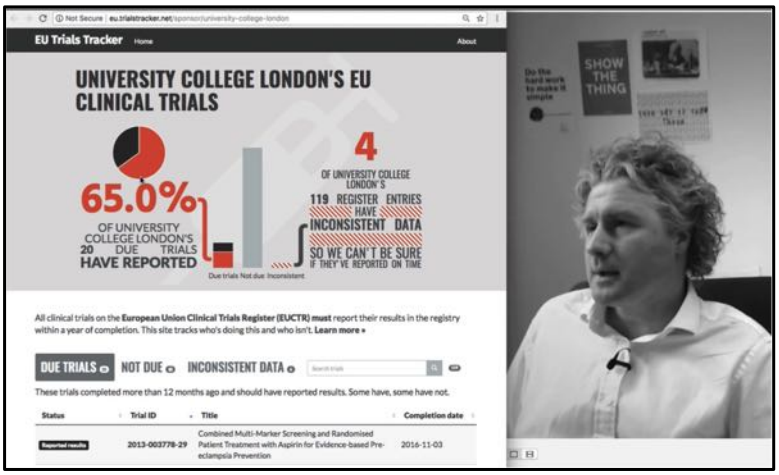
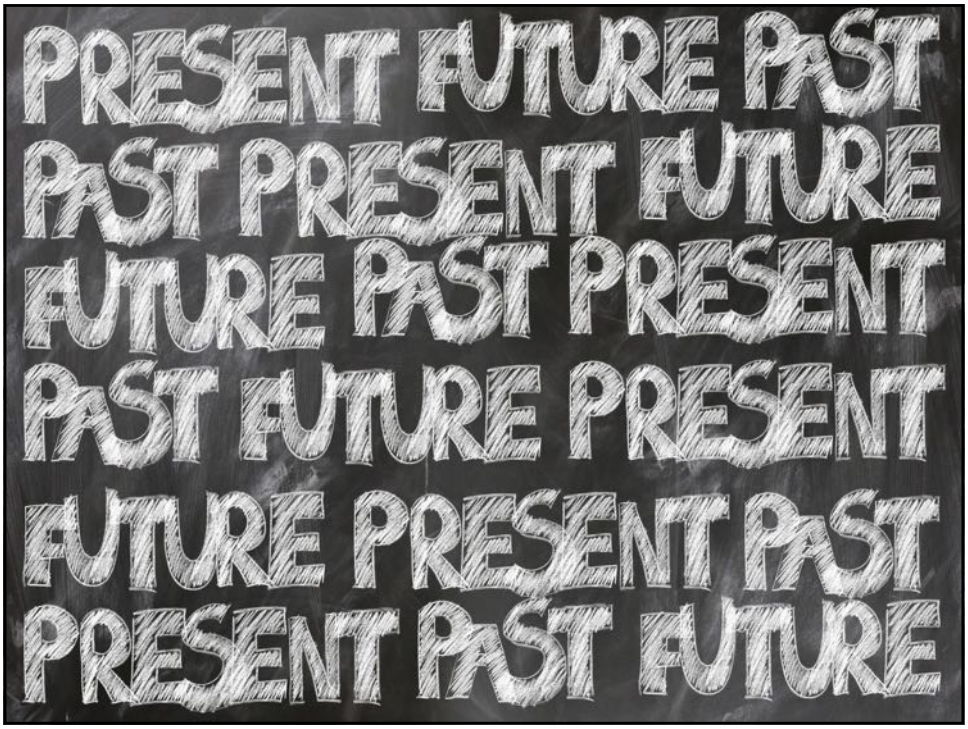


Goldacre B, DeVito NJ, Heneghan C, Irving F, Bacon S, Fleminger J et al. Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource. BMJ 2018; 362 :k3218



Research waste: a long history

In 2015 readers in 55 countries nominated this as the article The BMJ should be most proud of in past 20 years: Altman DG. The scandal of poor medical research. BMJ 1994; 308 :283

It began: “What should we think about a doctor who uses the wrong treatment, either wilfully or through ignorance, or who uses the right treatment wrongly (such as by giving the wrong dose of a drug)? Most people would agree that such behaviour was unprofessional, arguably unethical, and certainly unacceptable...”

thebmj

”...What, then, should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common. [1-7] This is surely a scandal.”

Altman D G. The scandal of poor medical research. BMJ 1994; 308 :283

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Wasteful research can be dangerous research

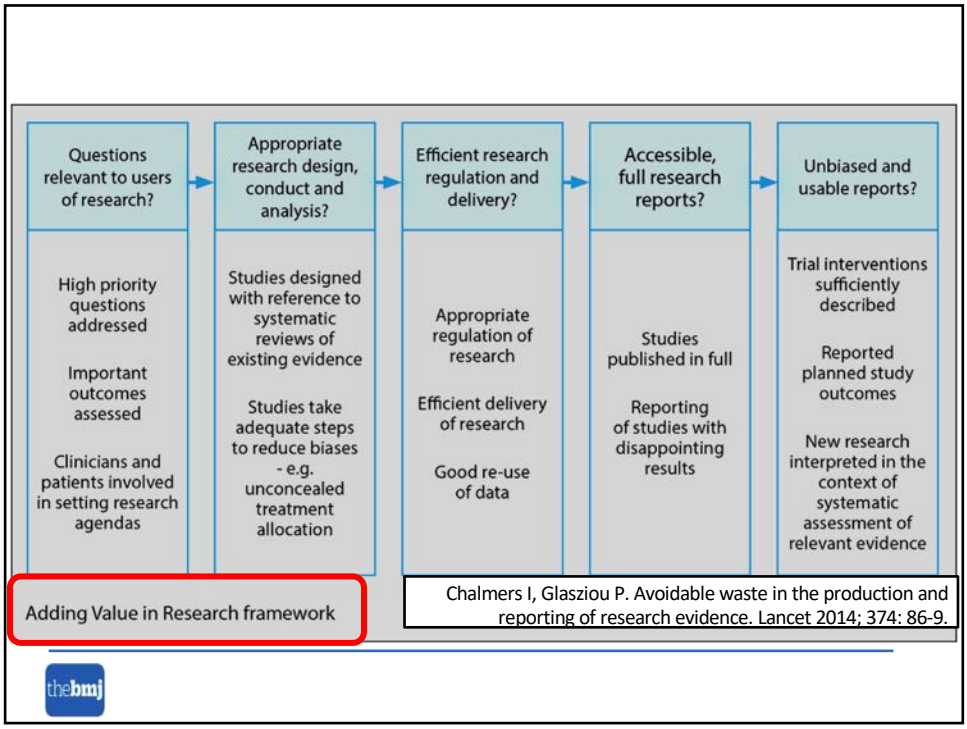
- review identified reporting bias in 40 indications comprising ~50 pharmacological, surgical, diagnostic, and preventive interventions
- study data often withheld by manufacturers and regulatory agencies or publication was actively suppressed
- reporting bias can overestimate or underestimate efficacy and underestimate safety risks of interventions

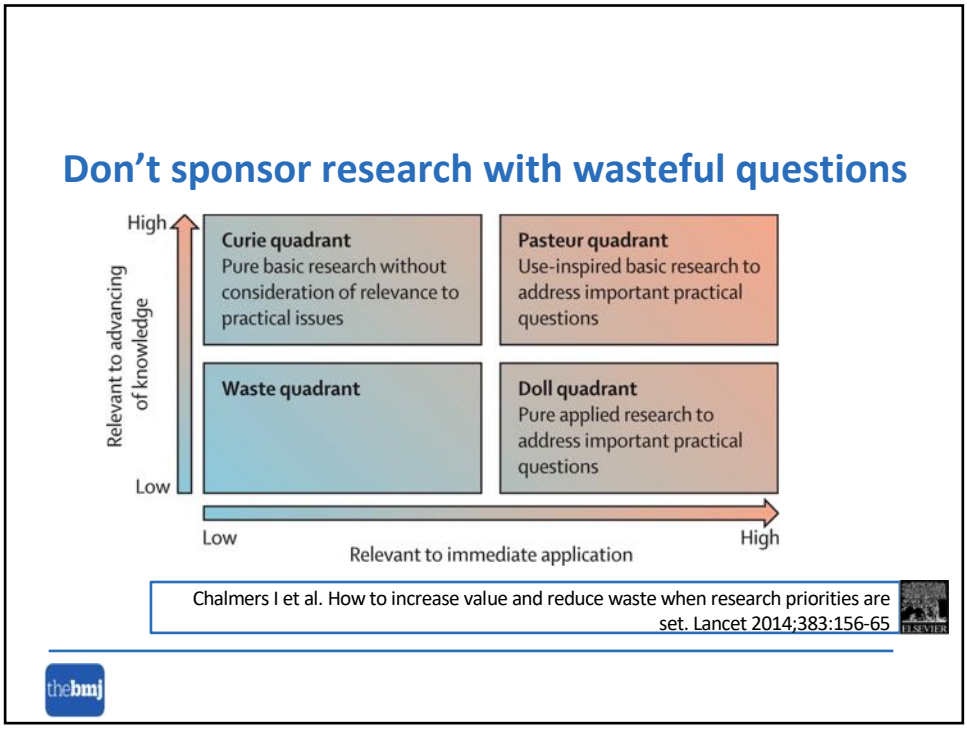
McGauran, N, Wieseler, B, Kreis, J, Schüler, YB, Kölsch, H, and Kaiser, T. Reporting bias in medical research—a narrative review. Trials. 2010; **11**: 37

thebmj

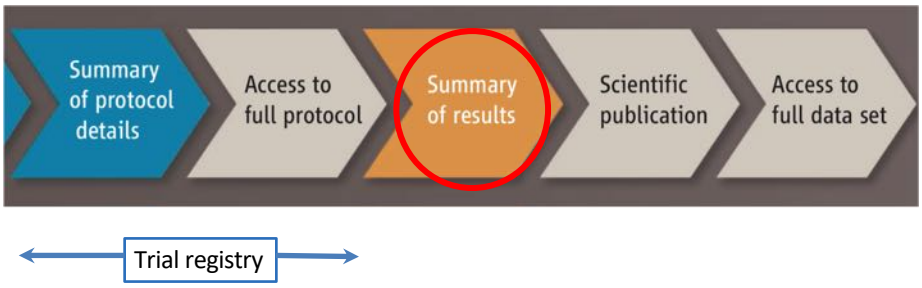
In a 1980 clinical trial 9/49 patients with suspected acute myocardial infarction on lorcainide died, versus 1 on placebo. Paper not published till 1993.
During 1980s drugs in same class widely used, despite reports of lack of effectiveness and more reports of increased mortality. Overall death toll [approx 5 million] from these drugs was 'larger than U.S. combat losses in wars such as Korea and Vietnam'

McGauran, N, Wieseler, B, Kreis, J, Schüler, YB, Kölsch, H, and Kaiser, T. Reporting bias in medical research—a narrative review. *Trials*. 2010; **11**: 37


Questions relevant to users of research?
Appropriate research design, conduct and analysis?
Efficient research regulation and delivery?
Accessible, full research reports?
Unbiased and usable reports?
High priority questions addressed
Important outcomes assessed
Clinicians and patients involved in setting research agendas
Studies designed with reference to systematic reviews of existing evidence
Studies take adequate steps to reduce biases - e.g. unconcealed treatment allocation
Appropriate regulation of research
Efficient delivery of research
Good re-use of data
Studies published in full
Reporting of studies with disappointing results
Trial interventions sufficiently described
Reported planned study outcomes
New research interpreted in the context of systematic assessment of relevant evidence
Adding Value in Research framework
Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet 2014; 374: 86-9.


Don't sponsor research with wasteful questions
High
Low
Relevant to advancing of knowledge
Curie quadrant
Pure basic research without consideration of relevance to practical issues
Pasteur quadrant
Use-inspired basic research to address important practical questions
Waste quadrant
Doll quadrant
Pure applied research to address important practical questions
Low
High
Relevant to immediate application
Chalmers I et al. How to increase value and reduce waste when research priorities are set. Lancet 2014;383:156-65

Require clinical trial transparency at all stages



Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. Science 2008 Mar 7;319(5868):1340-2.

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Aim for replication where possible

- scientific evidence is strengthened when important findings are replicated by multiple investigators using independent data, analytical methods, laboratories, and instruments
- replication is standard in basic sciences
- it is critically important in epidemiological studies, particularly when they affect policy or regulatory decisions
- but time and expense required for epidemiological studies means many are often not fully replicable, so policy decisions must be made with available evidence - and studies should be **reproducible**

Peng RD, Dominici F, Zeger SL. Reproducible Epidemiologic Research. Am J Epidemiol 2006;163: 783-9 doi:10.1093/aje/kwj093

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Require reproducibility

Methods reproducibility

Results reproducibility, via **sharing data**, metadata, code

Robustness, generalisability, and inferential reproducibility, without

- selective reporting, data mining/dredging/torturing
- p-hacking, HARKing (hypothesising after results known)

Goodman SN, Fanelli D, Ioannidis JPA. What does research reproducibility mean? Sci Trans Med 2016: 341PS12 http://stm.sciencemag.org/content/8/341/341ps12.full

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How journals can help

Since 1 July 2018, manuscripts submitted to any ICMJE journal* that report the results of clinical trials must contain a data sharing statement.

Clinical trials that begin enrolling participants on or after **1 January 2019** must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration this should be reflected in the manuscript's statement and updated in the registry record.

www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

*International Committee of Medical Journal Editors (ICMJE) current journals: *Annals of Internal Medicine*, *The BMJ*, *Deutsches Ärzteblatt*, *Ethiopian Journal of Health Sciences*, *JAMA*, *Journal of Korean Medical Science*, *New England Journal of Medicine*, *New Zealand Medical Journal*, *PLOS Medicine*, *Lancet*, *Revista Médica de Chile*, *Ugeskrift for Laeger* (members in 2016-17)

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Vivli's mission:
To promote, coordinate, and facilitate scientific sharing and reuse of clinical research data through the creation and implementation of a sustainable global data-sharing enterprise"
vivli.org launched July 2018

thebmj

NHS Research and Development Forum

Discussion: What does a 'good' & compliant non-commercial sponsor look like?

Chair: Rachel Smith

NHS Research and Development Forum

Dr. Janet Messer

Director of Approvals Service, HRA

www.rdforum.nhs.uk

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

What does a compliant Non-commercial sponsor look like?

Kath Meely
Senior GCP Inspector, MHRA
R&D Forum 8 November 2018

News

- The GCP Guide will have a new look front cover but the content has not changed
- MHRA Innovation Office – single point of access to expert regulatory information for all types of organisations in order develop innovative medicines, devices, or manufacturing processes

https://www.gov.uk/government/groups/mhra-innovation-office

Sponsor Oversight

A person who is the Sponsor of a Clinical Trial may delegate any of all of his functions, but any such arrangement shall not affect the responsibility of the Sponsor (**2004/1031 Regulation 3**)

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Sponsor Oversight

The Sponsor maintains overall responsibility for the conduct and reporting of the trial and so there should be mechanisms in place to demonstrate oversight of activities contacted/delegated to ensure patient safety and data integrity

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What does compliant look like?

Quality Management System

- Procedures that describe Clinical Trials activities
- Procedures meet regulatory requirements
- Key procedures in place to ensure oversight of trials if activities delegated to a CTU

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What does compliant look like?

Contracts and agreements

- Identify all providers of services e.g. CTU, statistician in university department, specialist laboratory etc.
- Detailed information on what has been delegated to vendor/Chief Investigator/contractor etc.
- Include in agreement that compliance with protocol and regulations supersede any internal processes and procedures
- Sub-contracting – agreement of sponsor required
- Delegation of duties – no gaps or ambiguity so that non adherence happens with regulatory requirements e.g. responsibility for reporting USMs and serious breaches

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Vendor Oversight

- A move towards an outsourced model – particularly for specialised electronic systems such as electronic CRFs, electronic Patient Reported Outcomes, Interactive Response technologies
- Increased use of Clinical Trials Units to manage clinical trial activities
- Levels of oversight can be risk assessed – feed into risk assessment and mitigation

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What does compliant look like?

Vendor Oversight (1)

- Risk based – assess what activities will be undertaken and potential impact on patient safety and data integrity
- Vendor Assessment – e.g. review of QMS, audits
- Review of vendor performance
- Document meetings/key decisions
- Document review and approval – Initial and updates e.g. Data Management Plans, SAP
- Co-monitoring visits
-

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What does compliant look like?

Vendor Oversight (2)

- Review of Reference Safety Information (RSI) on a regular basis to ensure that updated information in RSI versions on the conduct of the CT and safety of trial subjects
- Issue Escalation – procedures in place to ensure that sponsor is promptly notified of issues so appropriate action is taken e.g. Serious breach notification within 7 days of identification

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What does compliant look like?

Investigator Oversight

- How is IMP managed at sites e.g. pharmacy control, on ward or travels with patient?
- Monitoring – central/on-site/targeted
- Aware of changes in staff – training, experience, impact on the trial
- Completion of CRFs in a timely manner – trigger if not adhering to agreed completion times
- Effective communication with sites
- Identification of source data at each site e.g. electronic health records, paper medical records, worksheets

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What does compliant look like?

Audits

- Types of audits performed e.g. systems, investigator sites, vendors
- Experience of auditors to meet increasing complexity of trials and the systems used to manage them

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What does compliant look like?

Trial Master File (TMF)

- The TMF shall at all times contain the essential documents relating to that clinical trial
- If the trial is being managed by a CTU define which bits of the TMF are held with which party
- Sponsor needs to demonstrate oversight of trial activities e.g. oversight file which remains with the sponsor
- Oversight file remains part of TMF but with the ability to be able to re-construct what oversight the sponsor had of the trial whilst it was ongoing

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Common issues seen with vendors

eVendors

- The final approved protocol is commonly not provided to them to build the system in the first place e.g. IRT for randomisation, dose administration
- No oversight of amendments – implementation of amendments in systems without regulatory approval
- Impact of this is that ineligible can be enrolled; the dosing is incorrect
- Issues generally impact on commercial sponsors but increasing use of eVendors with non-commercial sponsors

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Summary

- Sponsor oversight is evident at site by the processes that are in place
- PI/CI oversight can be demonstrated
- Detailed contracts in place for all vendors and collaborators
- You cannot ignore CT requirements

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MHRA Sources of Information

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What does a 'good' & compliant non-commercial sponsor look like?

A CTU Perspective

Professor Gareth Griffiths
Director of Southampton Clinical Trials Unit

First my history and experience

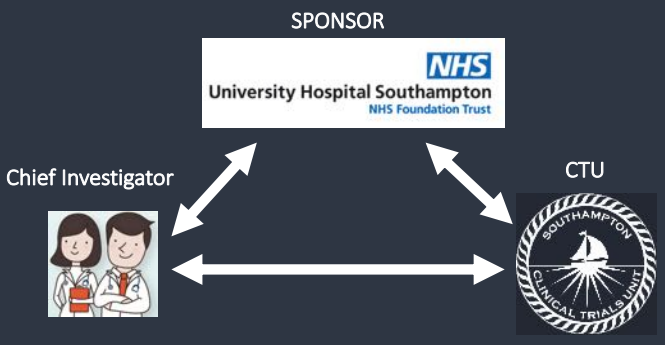
MRC Clinical Trials Unit

1996-2005

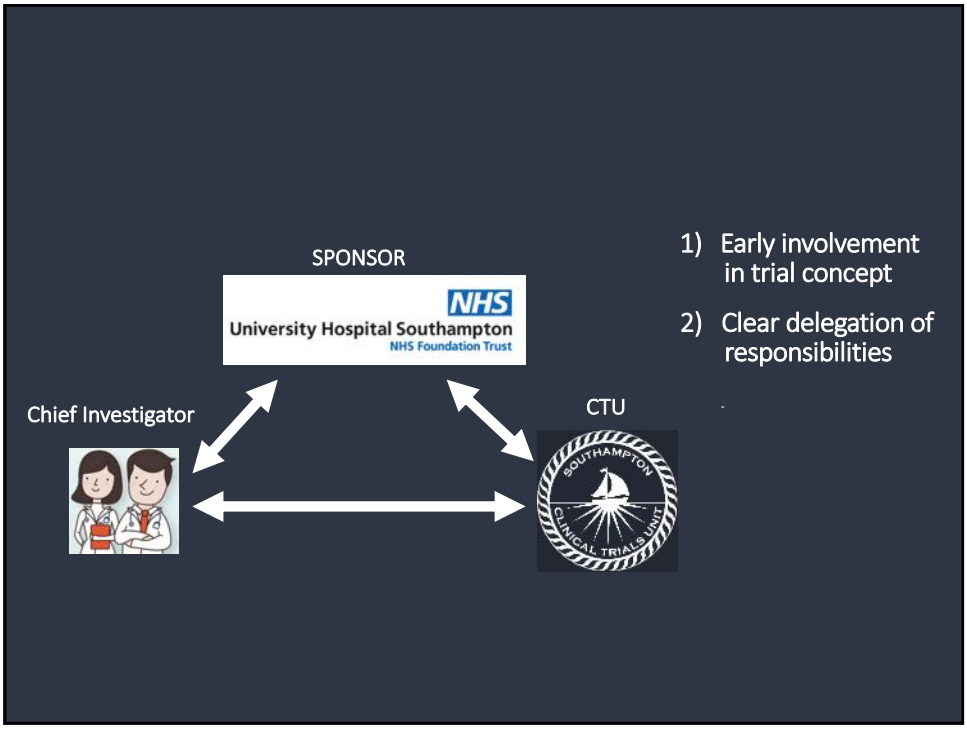
2005-2014

2014-present

Top 8 things that make a 'good' and compliant sponsor



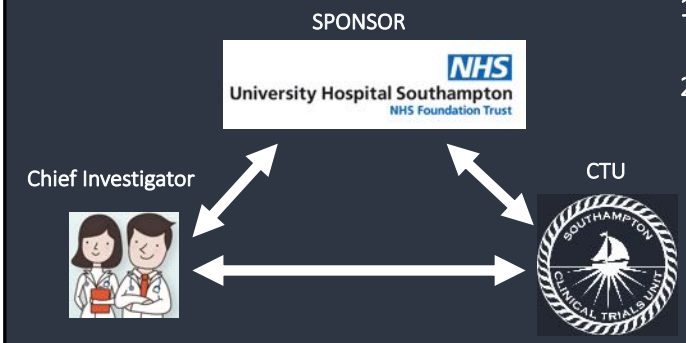
1) Early involvement in trial concept



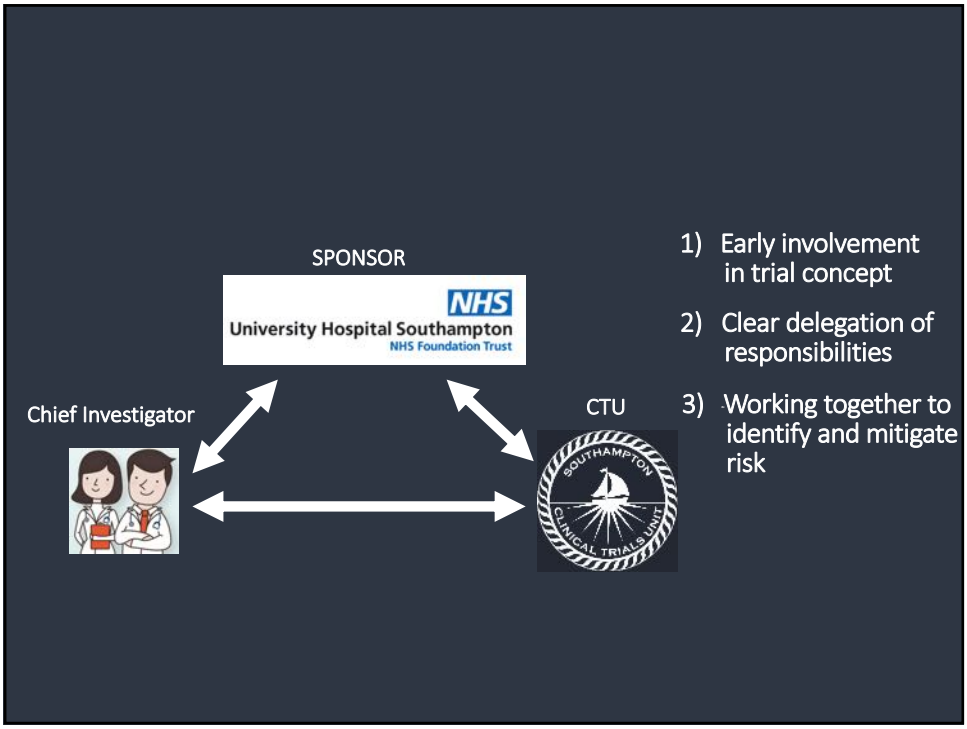
	Activity	Sponsor	SCTU	CI	Other parties
RISK ASSESSMENTS					
1	Conduct Trial Risk Assessment				
STUDY PLANNING AND MANAGEMENT					
1	Create Project Plan (Gantt) for study set –up, live and reporting phase				
2	Review and approve Project Plan				
PROTOCOL & AMENDMENTS					
1	Protocol preparation and trial design				
2	Protocol review				
3	Protocol finalisation (SCTU)				
4	Protocol sign-off				
5	Protocol distribution to sites				
6	Protocol amendment preparation				
7	Protocol amendment review				
8	Protocol amendment finalisation (SCTU)				
9	Protocol amendment sign-off				
10	Protocol amendment distribution to sites				
PATIENT INFORMATION SHEET, CONSENT FORM, GP LETTERS etc.					
1	Document(s) Preparation				

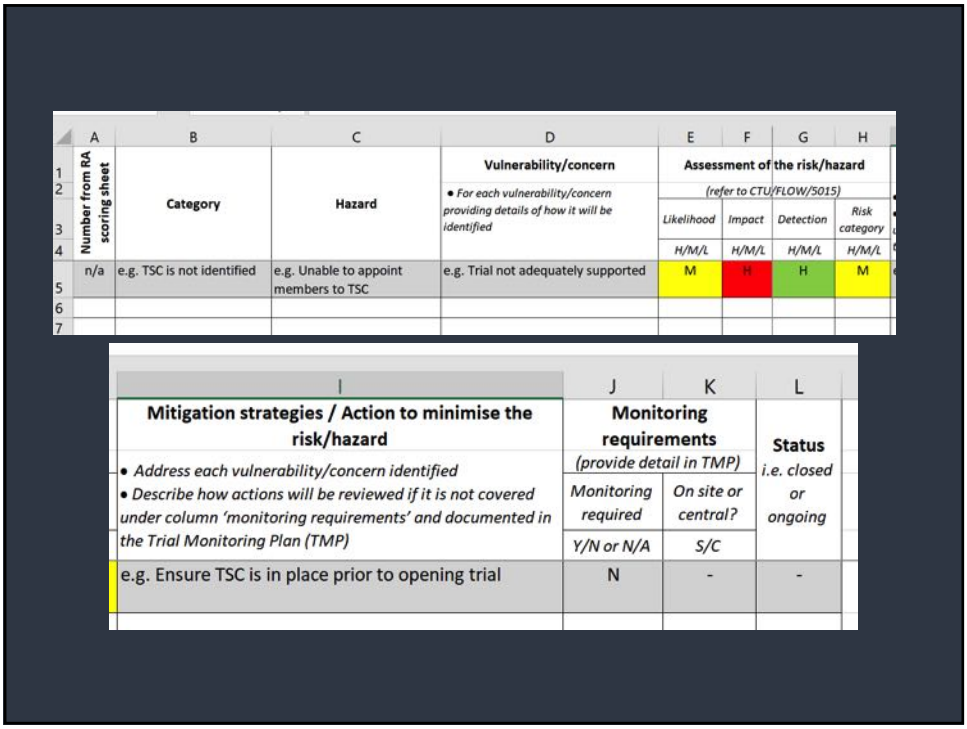
3	Publication sign-off				
4	Publication submission				
TRIAL OVERSIGHT COMMITTEES					
1	Coordination of and reporting to Trial Management Group				
2	Coordination of and reporting to Trial Steering Committee				
3	Coordination of and reporting to Data Monitoring and Ethics Committee				
THIRD PARTIES e.g. other labs, industry (devices, equipment etc)					
1	Agreement/Contract with third party(ies)				
2	Arranging and co-ordinating supply(ies) to Sites				
3	Main contact				

Sponsor: UHS	**Chief Investigator of XXX trial**	**SCTU: Director**
Name:	**Name**:	**Name**: Gareth Griffiths
Signed:	**Signed**:	**Signed**:
Date:	**Date**:	**Date**:



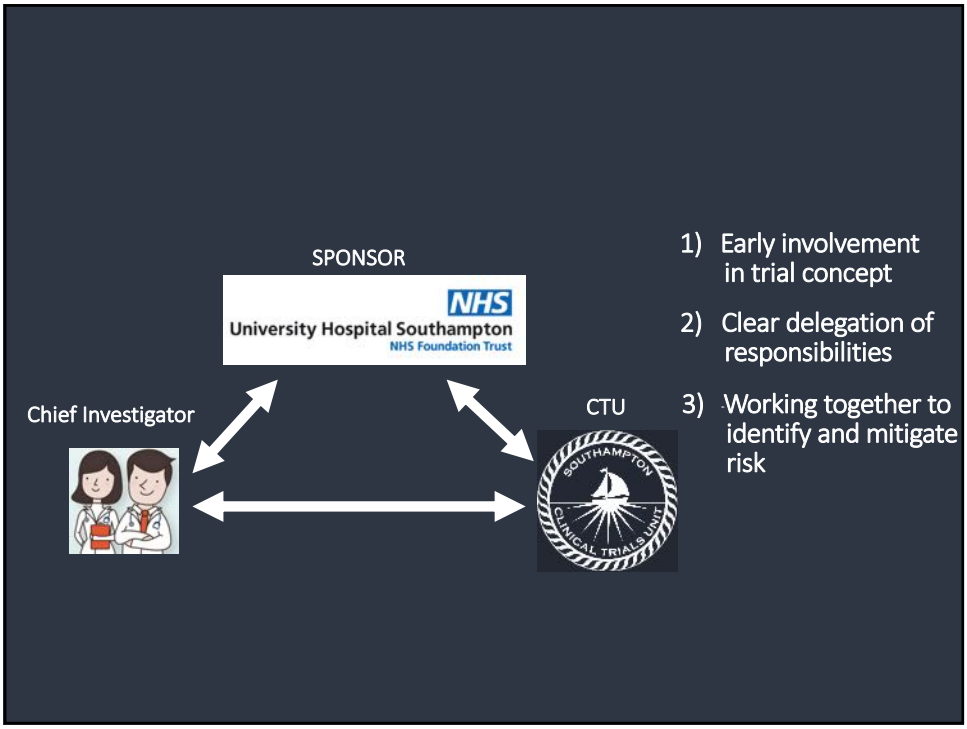
1) Early involvement in trial concept
2) Clear delegation of responsibilities

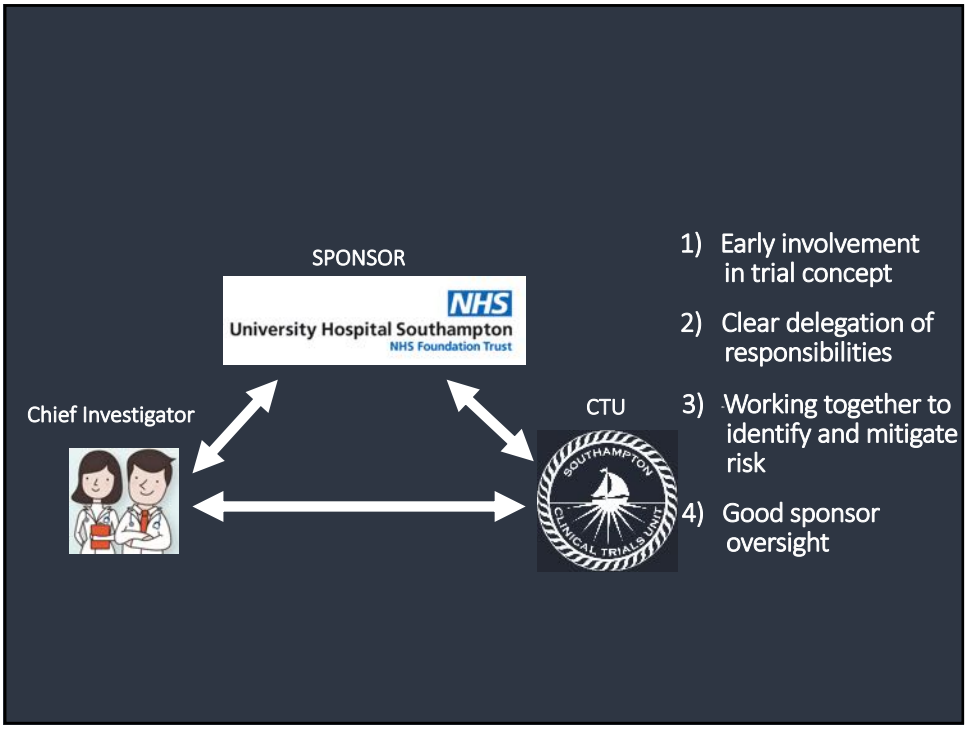




	A	B	C	D	E	F	G	H
1	Number from RA scoring sheet	Category	Hazard	Vulnerability/concern	Assessment of the risk/hazard			
2				• For each vulnerability/concern providing details of how it will be identified	(refer to CTU/FLOW/5015)			
3					Likelihood	Impact	Detection	Risk category
4					H/M/L	H/M/L	H/M/L	H/M/L
5	n/a	e.g. TSC is not identified	e.g. Unable to appoint members to TSC	e.g. Trial not adequately supported	M	H	H	M
6								
7								

I	J	K	L
Mitigation strategies / Action to minimise the risk/hazard	Monitoring requirements (provide detail in TMP)		Status i.e. closed or ongoing
• Address each vulnerability/concern identified • Describe how actions will be reviewed if it is not covered under column 'monitoring requirements' and documented in the Trial Monitoring Plan (TMP)	Monitoring required	On site or central?	
	Y/N or N/A	S/C	
e.g. Ensure TSC is in place prior to opening trial	N	-	-


SPONSOR
NHS
University Hospital Southampton
NHS Foundation Trust
Chief Investigator
CTU
SOUTHAMPTON
CLINICAL TRIALS UNIT
1) Early involvement in trial concept
2) Clear delegation of responsibilities
3) Working together to identify and mitigate risk


SPONSOR
NHS
University Hospital Southampton
NHS Foundation Trust
Chief Investigator
CTU
SOUTHAMPTON
CLINICAL TRIALS UNIT
1) Early involvement in trial concept
2) Clear delegation of responsibilities
3) Working together to identify and mitigate risk
4) Good sponsor oversight

Good sponsor oversight

SPONSOR

University Hospital Southampton NHS Foundation Trust

Regular sponsor oversight meetings with the CTU to ensure patient safety and data integrity

Can include issues such as:
- Trial risk assessment and monitoring plans
- Trial oversight groups
- Protocol development and amendment
- Escalation of serious or unforeseen issues
- CAPAs

Good sponsor oversight

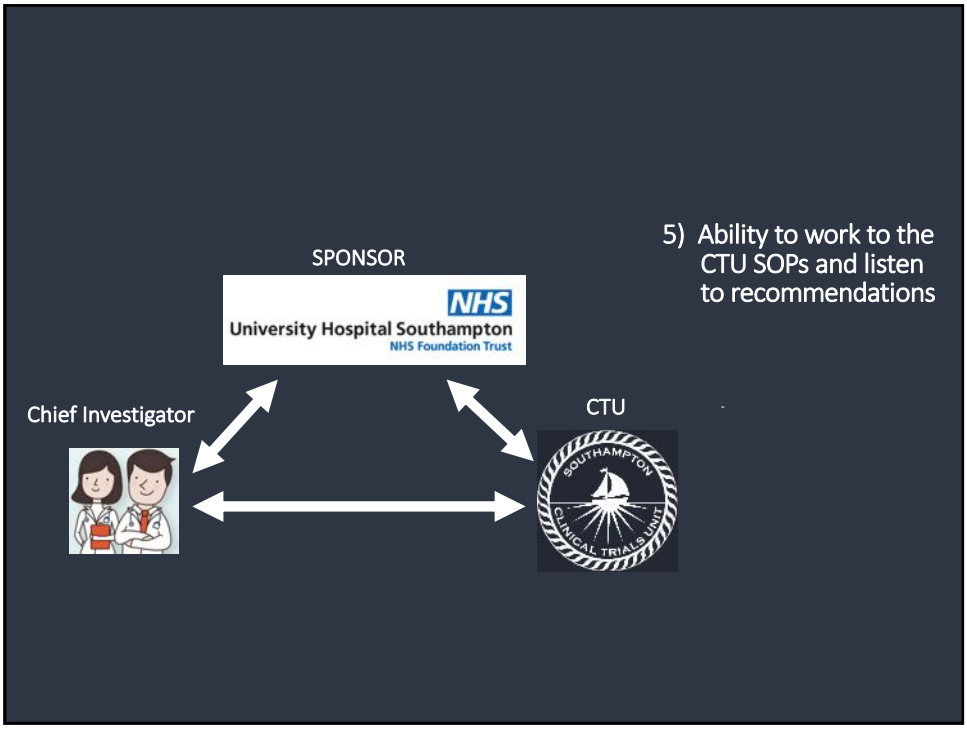
SPONSOR

University Hospital Southampton NHS Foundation Trust

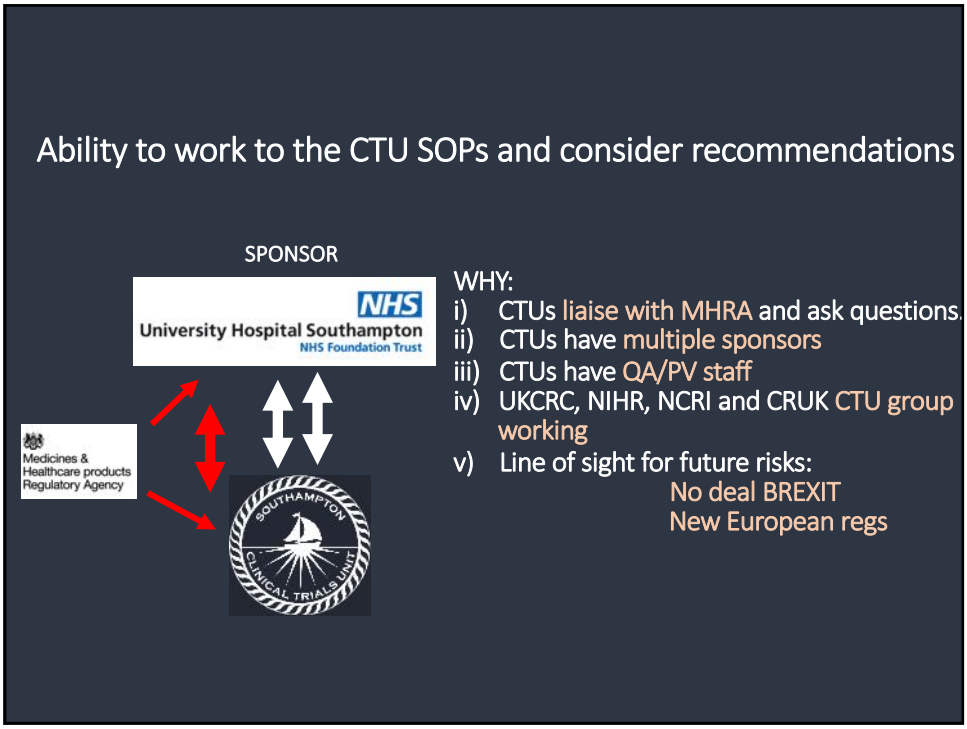
Regular sponsor oversight meetings with the CTU to ensure patient safety and data integrity

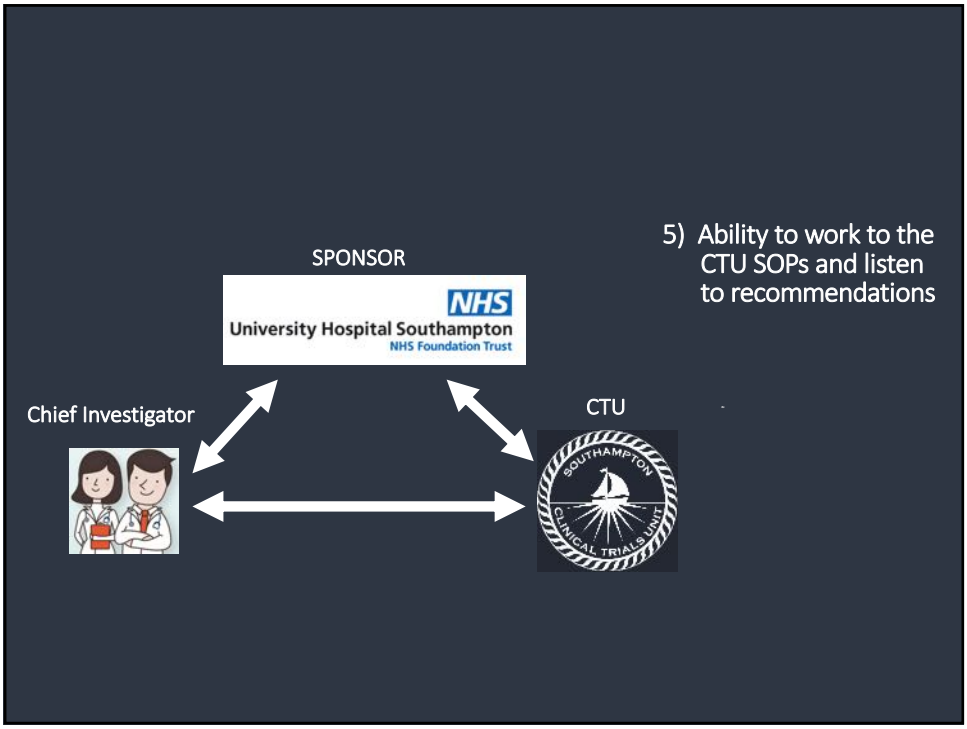
Can include issues such as:
- Trial risk assessment and monitoring plans
- Trial oversight groups
- Protocol development and amendment
- Escalation of serious or unforeseen issues
- CAPAs

May require urgent action at short notice



5) Ability to work to the CTU SOPs and listen to recommendations

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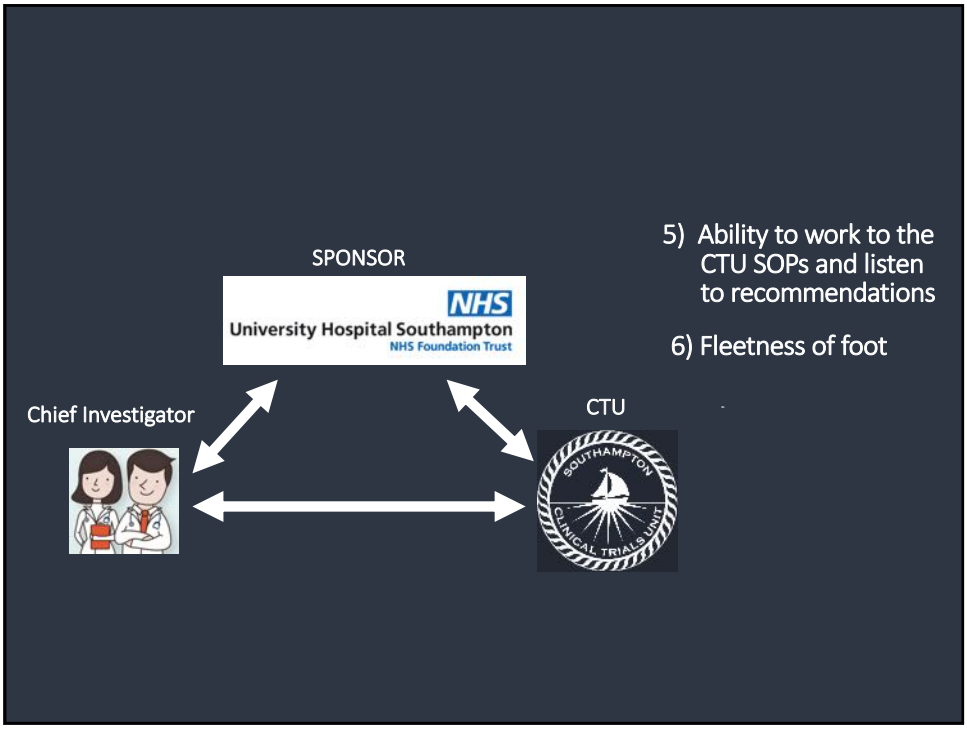
SPONSOR
NHS
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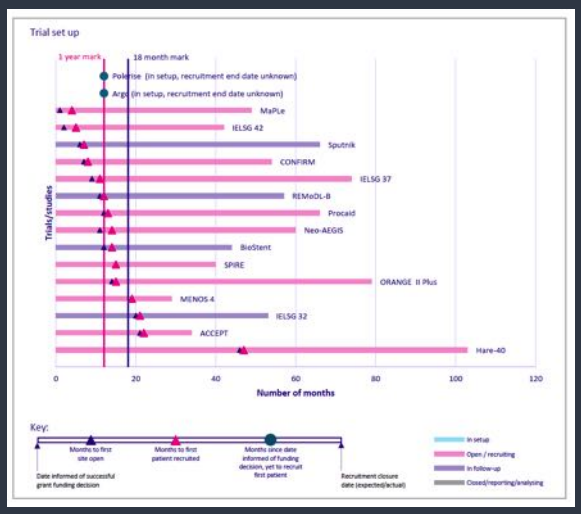
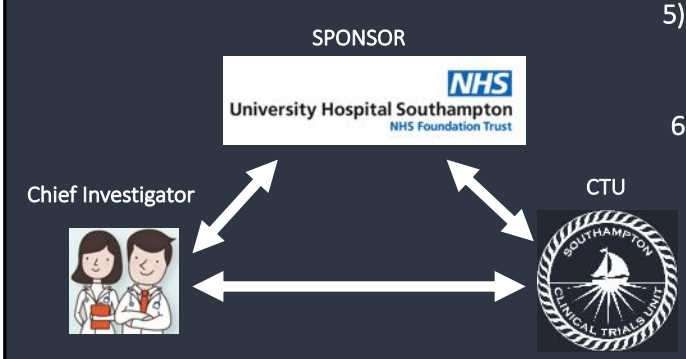
NHS Foundation Trust
Chief Investigator
CTU
SOUTHAMPTON
CLINICAL TRIALS UNIT
5) Ability to work to the CTU SOPs and listen to recommendations
6) Fleetness of foot





5) Ability to work to the CTU SOPs and listen to recommendations

6) Fleetness of foot

SPONSOR

University Hospital Southampton NHS Foundation Trust

Chief Investigator

CTU

5) Ability to work to the CTU SOPs and listen to recommendations

6) Fleetness of foot

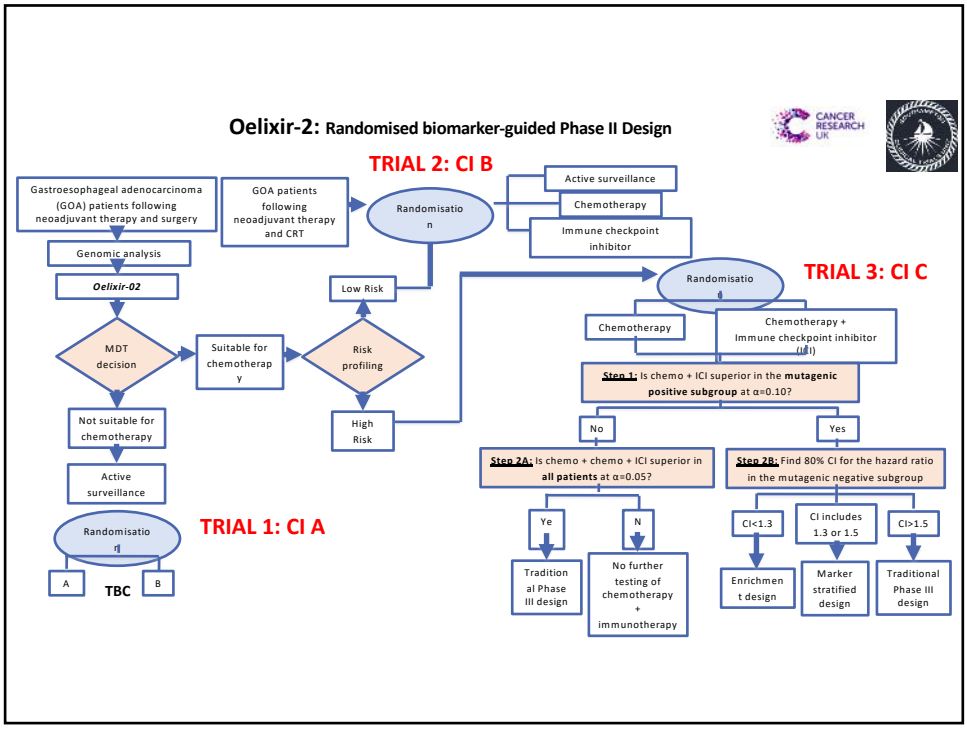
7) Ability to take on new challenges

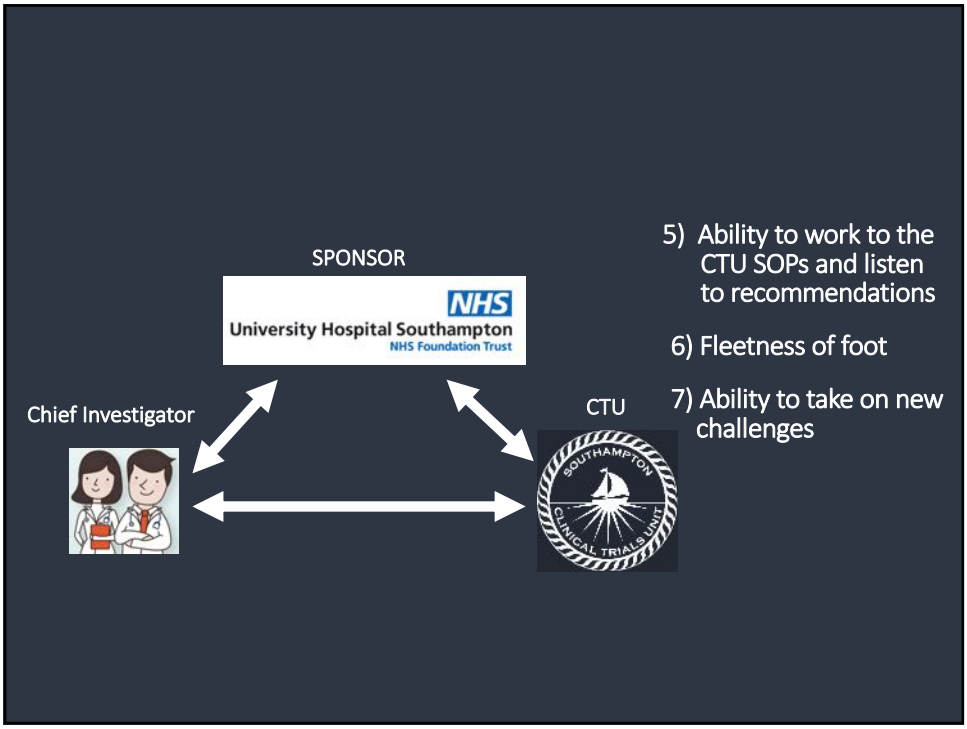
Ability to take on new challenges

IRCI

International Rare Cancers Initiative

- Multiple-CIs in Multi-Arm Multi-Stage (MAMs) trials
- International trials
- Co-Sponsorship


Oelixir-2: Randomised biomarker-guided Phase II Design
TRIAL 2: CI B
TRIAL 3: CI C
TRIAL 1: CI A
Gastroesophageal adenocarcinoma (GOA) patients following neoadjuvant therapy and surgery
Genomic analysis
Oelixir-02
MDT decision
Not suitable for chemotherapy
Active surveillance
Randomisation
A
TBC
B
Suitable for chemotherapy
GOA patients following neoadjuvant therapy and CRT
Risk profiling
Low Risk
High Risk
Randomisation
Active surveillance
Chemotherapy
Immune checkpoint inhibitor
Randomisation
Chemotherapy
Chemotherapy + Immune checkpoint inhibitor (I/II)
Step 1: Is chemo + ICI superior in the mutagenic positive subgroup at α=0.10?
No
Yes
Step 2A: Is chemo + chemo + ICI superior in all patients at α=0.05?
Step 2B: Find 80% CI for the hazard ratio in the mutagenic negative subgroup
Ye
N
CI<1.3
CI includes 1.3 or 1.5
CI>1.5
Traditional Phase III design
No further testing of chemotherapy + immunotherapy
Enrichment design
Marker stratified design
Traditional Phase III design


SPONSOR
NHS
University Hospital Southampton
NHS Foundation Trust
Chief Investigator
CTU
SOUTHAMPTON CLINICAL TRIALS UNIT
5) Ability to work to the CTU SOPs and listen to recommendations
6) Fleetness of foot
7) Ability to take on new challenges

SPONSOR

NHS University Hospital Southampton NHS Foundation Trust

Chief Investigator

CTU

5) Ability to work to the CTU SOPs and listen to recommendations

6) Fleetness of foot

7) Ability to take on new challenges

8) A common aim

A common aim - examples

STRATEGIC PLAN OF SPONSOR

NHS University Hospital Southampton NHS Foundation Trust

- Increase the number of Principal and Chief Investigators by 50% and 20% respectively by 2022
- By 2022 achieve a 50% increase in early-phase experimental medicine research activity
- Report the impact of 5 practice changing research studies in the next 5 years

CTU

NHS Research and Development Forum

Penny Vicary

Service user & co-applicant

www.rdforum.nhs.uk

Take Part Be Involved in research

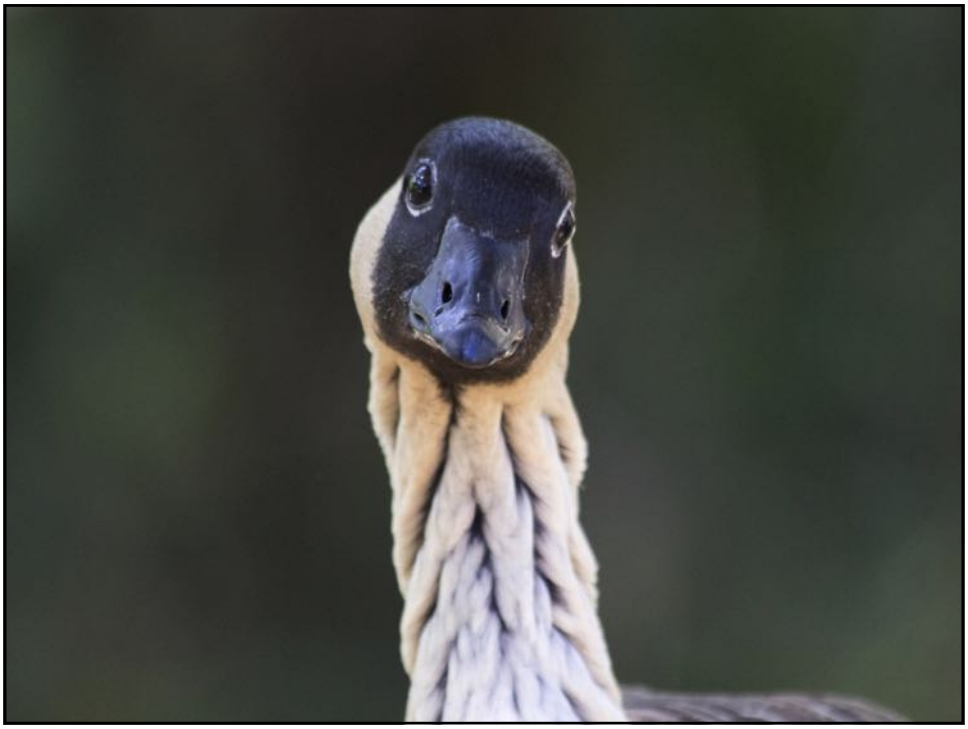
NHS North Bristol NHS Trust

The Perfect Sponsor

Helen Lewis-White

Research Operations Manager

www.nbt.nhs.uk/research



What sites want

Perfect Match

www.nbt.nhs.uk/research

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

A spotlight on: A Regulators View & Risk Assessment

Kath Meely, Senior GCP Inspector, MHRA

R&D Forum 8 November 2018

Overview

- Risk Adaption
- Risk proportionate approach – Regulators view
- Risk Assessments and mitigations
- Risk adaption examples
  - IMP
  - Safety
  - Monitoring
  - eSystems

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Why Risk Adapt?

- Mitigate risks up front
- Reduce duplicate or costly processes
- Focus on results reliability
- Reduce burden, but maintain quality
- MHRA very supportive of this approach

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EU Risk Proportionate approach Recommendations Document

- Developed from the CTR No 536/2014 with specific regard to low intervention clinical trials
- Flexible approach to design and conduct
- Based on risk assessment – including IMP, trial population, protocol complexity, interventions etc.
- All sponsors, not just academic trials
- Identification, evaluation, control, review communication, reporting
- Safety reporting
- IMP management
- Monitoring
- Content of TMF

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Risk Assessment

- The proportionate approach starts with a Risk Assessment
- Ideally this should begin at the protocol concept stage – as consideration of risks could allow mitigations in the protocol/design and also allow for timely funding application for mitigation resources (e.g. monitoring)
- Involve a multi-disciplinary team – allows thorough discussion of any potential risks and how to mitigate them, using expertise from across the research team e.g. statistician, Investigator, data manager etc.

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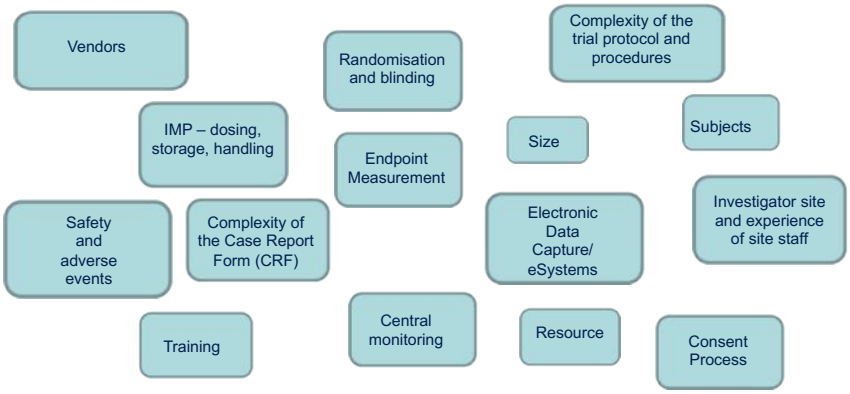
Risk Assessment

Identifies higher risk areas of the trial that can be mitigated	Identifies lower risk areas that can be adapted and simplified and use "less stringent rules"	It is not just about risk based monitoring, but risk based design and management of the trial.

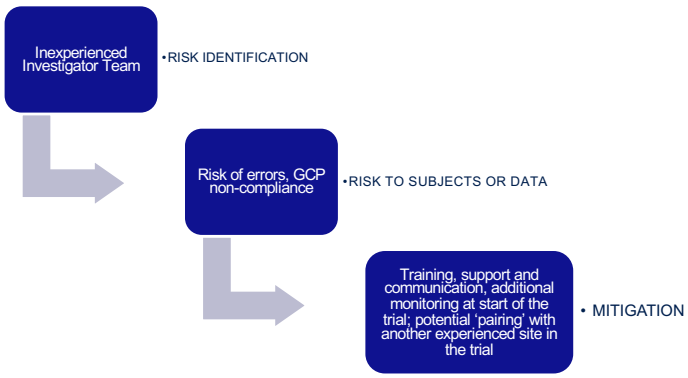
81

What to cover in a Risk Assessment



82

Mitigation and Control



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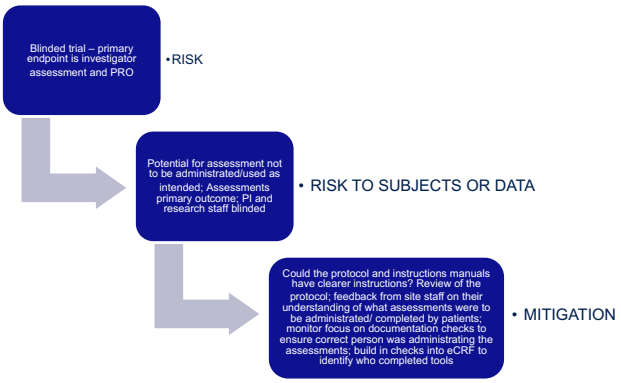
Mitigation



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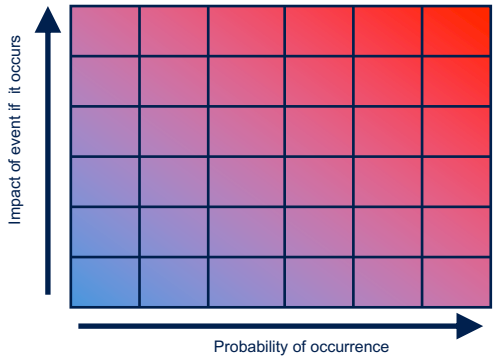
Measuring and Evaluating Risk



85

Risk Review and Communication

- The risk assessment and mitigations should be communicated to ensure that everyone is aware of expectations and actions
- Look for continual improvement
- Communicate new information – safety information, protocol amendments, IB/RSI updates – does this impact on the risk assessment?
- Are the mitigations effective? How do you know?

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Issues seen with Risk Assessments

- Lack of formal procedures
- Conducted too late
- Risk based on IMP alone without a bespoke trial-related assessment, therefore other risks are overlooked
- Numbers used for risk – no description
- Risks assessment based on project risks (timings, cost…)
- Lack of documentation of the risk assessment
- Lack of communication of the risk assessment
- Never reviewed in light of changes such as a protocol or IB amendment

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Risk categories

IMP

Type A = No higher than the risk of standard medical care

Type B = Somewhat higher than the risk of standard medical care

Type C = Markedly higher than the risk of standard medical care

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Risk Adaptions Examples

Electronic HR and IMP

- EHR is used to document IMP administration in hospital
- The trial is a double blind trial with active and placebo
- Can the electronic system support identification of administration of IMP via kit number as patient travels through hospital?
- More than one patient treated in hospital at one time
- Potential to use diary cards/work sheets to track Identification of IMP kit number administered to patient. Mitigate potential risk of the incorrect kit number being administered to patients

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Risk Adaption Examples

Trial Master File

- Combing documents – One document which can serve multiple purposes
  - Screening logs and recruitment logs
  - Signature and delegation logs
  - Site assessment and site initiation
- Absence of documents – as a result of implementing other risk proportionate measures
  - No Investigator Brochure as the SmPC is being used instead
  - CSR may be absent as trial results are in a medical journal publication
  - IMP related documents may not be required

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Risk Adaption Examples

Safety Reporting

- Protocol may define certain events as not needing immediate reporting (despite meeting SAE definition) e.g. trial endpoints or disease defining events. Must be approved!
- Oncology trials – e.g. standard side-effects of chemotherapy, death due to PD
- Anticipated SAEs for that disease under investigation
- Well known and used IMP – low risk of new safety signals

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Risk Adaption

Risks

Electronic systems – risk to randomisation, eligibility data collection – ensure validation (paper back-up?)

eCRF may hold source – 3rd party vendor to hold data?

Central monitoring – consent forms (Sponsor access to personal identifiable information)

Adaptions

Notification Scheme

Normal prescription

No temperature monitoring

SmPC instead of IB

Safety – only collect related AEs and SAEs; expedited reporting to sponsor could exclude anticipated events

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Risk Based Monitoring

- 'Traditional' monitoring resource intensive and SDV-focussed – 100% SDV
- Focus on the reliability of the trial results not the data points; tolerability of error in the dataset?
- SDV concentrates on comparing individual data points, but not on the bigger picture of eligibility, protocol compliance etc.
- Protocol compliance and study conduct are important for reliability of the results
- Recognise the need for a more efficient approach to monitoring and oversight

The sponsor should develop a systematic, prioritised, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring ICH GCP R2

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Monitoring Plan

- Once the oversight and monitoring strategy has been decided, it should be documented (with a rationale) and must be followed
- The strategy should contain risk-based flexibility
- Feedback from the oversight/monitoring activities drives the risk-based approach to monitoring:
  - Triggers for escalation (or de-escalation).
  - Triggers to update risk assessment and oversight and monitoring strategy.

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Risk Based Monitoring

- Centralised monitoring activities should also be documented in sufficient detail in the TMF
- Reports generated/evidence of review
- Meeting minutes
- Thresholds met – and subsequent escalation/follow-up
- Data Validation

Must be able to verify that the monitoring plan has been complied with

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Implementation of Risk Based Monitoring

Not widely implemented - Inspectors have seen a few pilots, but still reluctance to fully utilise:

- Risk averse research community?
- Commercial model fitted to non-commercial trials?
- Regulatory requirements over-interpreted?
- Little published guidance/methodologies ?
- Fear of a negative inspection outcome?

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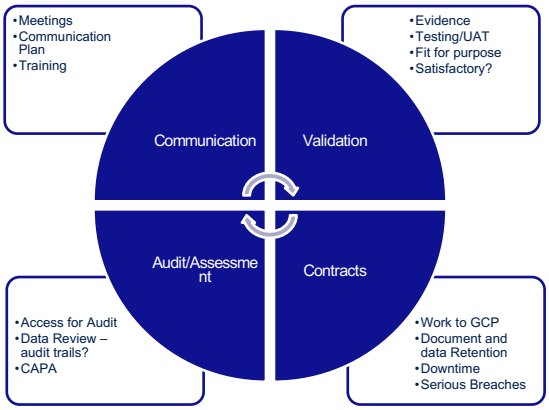
eSystems



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Mitigation

Assessment:
Do all CAPAs need to be closed before work starts?
What is critical?
Don't use – refuse to work to GCP refuse to address CAPA after audit

Validation
Re-testing, if simple system can minor fails be accepted?
Monitor performance of the system

Contracts:
Key – mitigate via more detailed agreements? Processes described in SOPs?

Communication:
Regular Meetings
Issues log
Review of metrics/performance indicators

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Help and Guidance

MRC/DH/MHRA Risk Adapted Approach
http://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

Risk proportionate approaches in clinical trials
Risk https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf

Risk Adaption in Clinical Trials of Investigational Medicinal Products (CTIMPS)
https://mhrainspectorate.blog.gov.uk/2017/11/16/risk-adaption-in-clinical-trials-of-investigational-medicinal-products-ctimps/

MHRA Examples and FAQs
http://forums.mhra.gov.uk/forumdisplay.php?18-Monitoring

MHRA Risk assessment expectations see FAQs
http://forums.mhra.gov.uk/forumdisplay.php?1-Good-Clinical-Practice-(GCP)

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100

NHS Research and Development Forum

Improving the Sponsor Process

Facilitated by Mind Doodle
www.minddoodle.co,

NHS Research and Development Forum

What does good & compliant look like?

Consider Sponsor responsibilities & oversight for all study types

1: Ideas – Approval Phase
2: Set Up – Follow-Up Phase
3: Closure- Dissemination Phase

NHS Health Research Authority

AcoRD

Costing for research in the NHS & the new Schedule of Events Cost Attribution Template (SoECAT): The role of the Sponsor

Alastair Nicholson
Senior Development Manager, HRA

NHS Health Research Authority

1066 and all that….

- 1994: Culyer Report
- 1997: HSG(97)32
- 2005: ARCO
- 2006: Best Research for Best Health
- 2012: AcoRD
- 2014: ACAT
- 2017/2018: NHS England consultation
- 2018: SoECAT
- 2018: ETC Process (in England)

UK Policy Framework

NHS Health Research Authority

"9.10, Sponsors

The sponsor is the individual, organisation or partnership that takes on overall responsibility for: […]

h) putting and keeping in place arrangements for ***adequate finance*** *and management of the research project, including its competent risk management and data management;"*

UK CTR

NHS Health Research Authority

"Sponsor of a clinical trial

3.*—(1) In these Regulations, subject to the following paragraphs, "sponsor" means, in relation to a clinical trial, the person who takes responsibility for the initiation, management and* ***financing (or arranging the financing)*** *of that trial."*

1066 and all that….

NHS Health Research Authority

- 1994: Culyer Report
- 1997: HSG(97)32
- 2005: ARCO
- 2006: Best Research for Best Health
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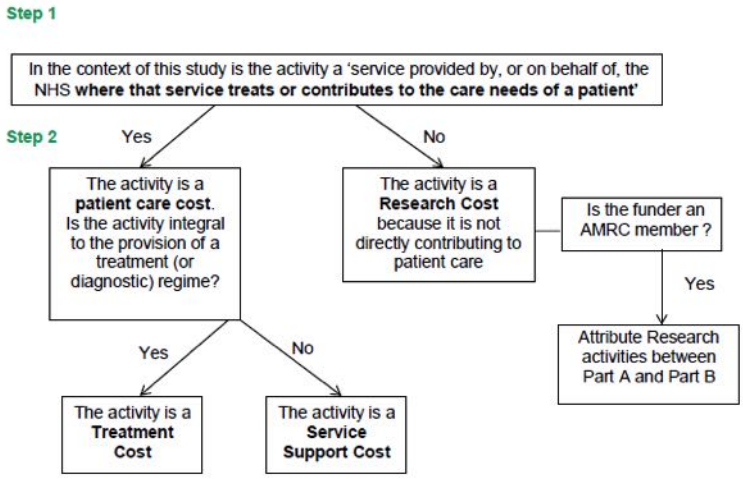
AcoRD

NHS Health Research Authority



AcoRD

NHS Health Research Authority

- Research Costs (Part A and B)
  - Usually met by grant funders (In England Part A met by DHSC, e.g. via CRN)
- NHS Treatment Costs
  - Met by usual commissioning process (In England linked to CRN portfolio – new processes)
- NHS Support Costs
  - Met by R&D budgets of Health Departments (e.g. in England via CRN)

1066 and all that….

NHS Health Research Authority

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- 2006: Best Research for Best Health
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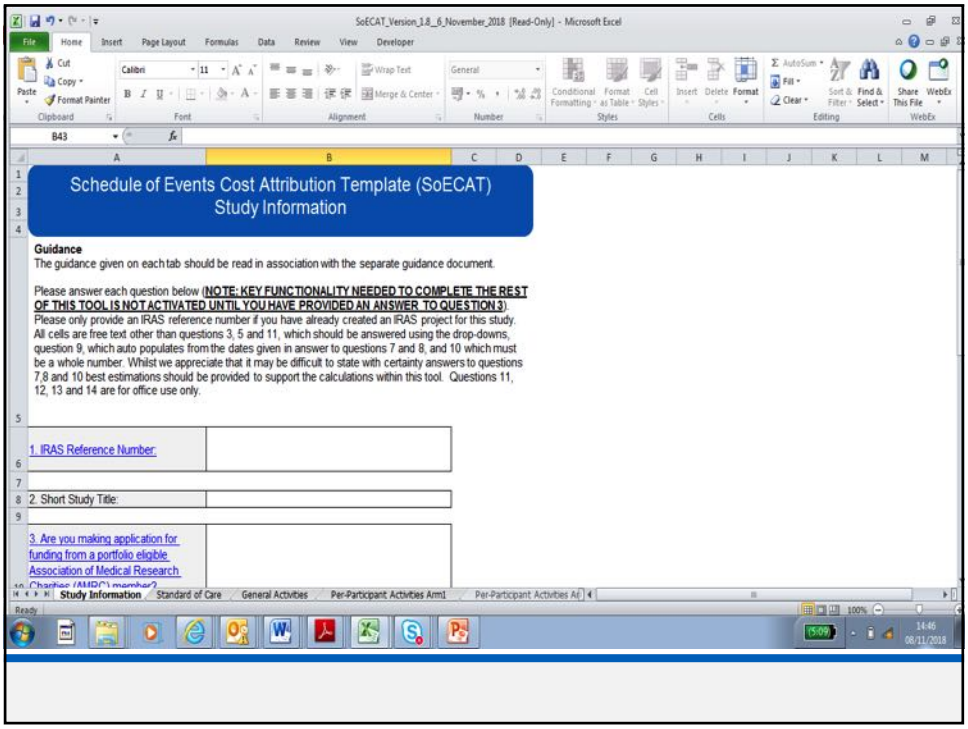
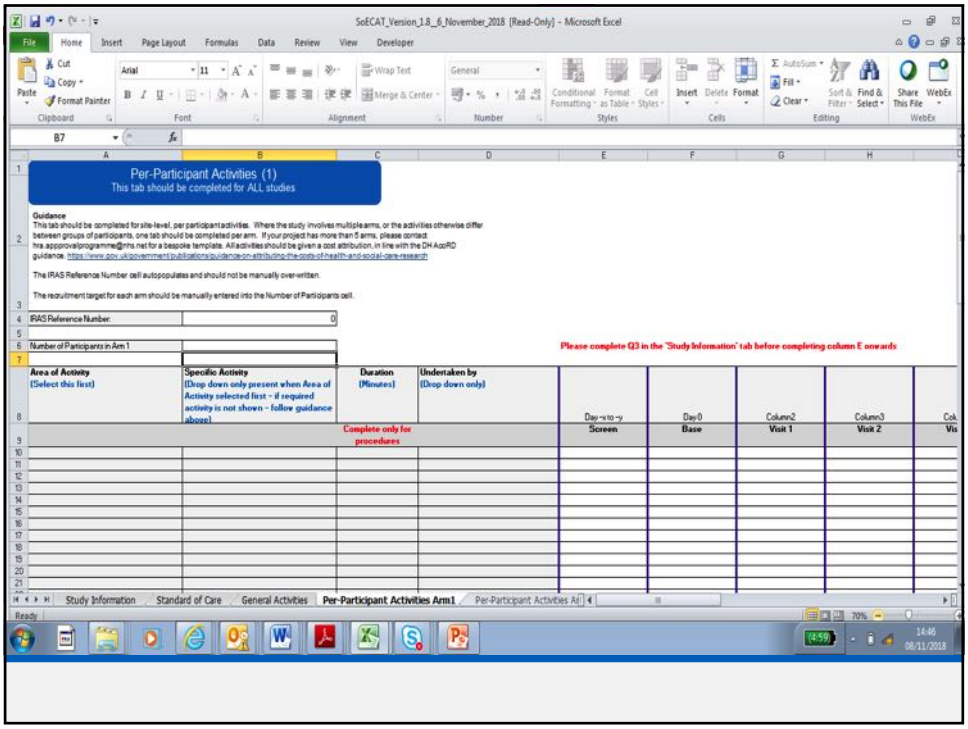

SoECAT_Version_1.8_6_November_2018 [Read-Only] - Microsoft Excel
Schedule of Events Cost Attribution Template (SoECAT)
Study Information
Guidance
The guidance given on each tab should be read in association with the separate guidance document.
Please answer each question below (NOTE: KEY FUNCTIONALITY NEEDED TO COMPLETE THE REST OF THIS TOOL IS NOT ACTIVATED UNTIL YOU HAVE PROVIDED AN ANSWER TO QUESTION 3).
Please only provide an IRAS reference number if you have already created an IRAS project for this study.
All cells are free text other than questions 3, 5 and 11, which should be answered using the drop-downs, question 9, which auto populates from the dates given in answer to questions 7 and 8, and 10 which must be a whole number. Whilst we appreciate that it may be difficult to state with certainty answers to questions 7,8 and 10 best estimations should be provided to support the calculations within this tool. Questions 11, 12, 13 and 14 are for office use only.
1. IRAS Reference Number:
2. Short Study Title:
3. Are you making application for funding from a portfolio eligible Association of Medical Research
Study Information
Standard of Care
General Activities
Per-Participant Activities Arm1


SoECAT_Version_1.8_6_November_2018 [Read-Only] - Microsoft Excel
Per-Participant Activities (1)
This tab should be completed for ALL studies
Guidance
IRAS Reference Number:
Number of Participants in Arm 1
Please complete Q3 in the 'Study Information' tab before completing column E onwards
Area of Activity
(Select this first)
Specific Activity
(Drop down only present when Area of Activity selected first - if required activity is not shown - follow guidance above)
Duration
(Minutes)
Undertaken by
(Drop down only)
Complete only for procedures
Day -x to -y
Screen
Day 0
Base
Column2
Visit 1
Column3
Visit 2
Study Information
Standard of Care
General Activities
Per-Participant Activities Arm1

AcoRD and SoECAT

- Required for submission to NIHR CRN Eligible Partner Funders
- **Support** for completion available from UK AcoRD Specialists
- Signed off by UK AcoRD Specialist
  - UK wide
  - CRN: 3 per LCRN
  - **Roll-out planned**

1066 and all that….

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- 2014: ACAT
- **2017/2018: NHS England consultation**
- 2018: SoECAT
- **2018: ETC Process (in England)**

ACoRD Update

Health Research Authority

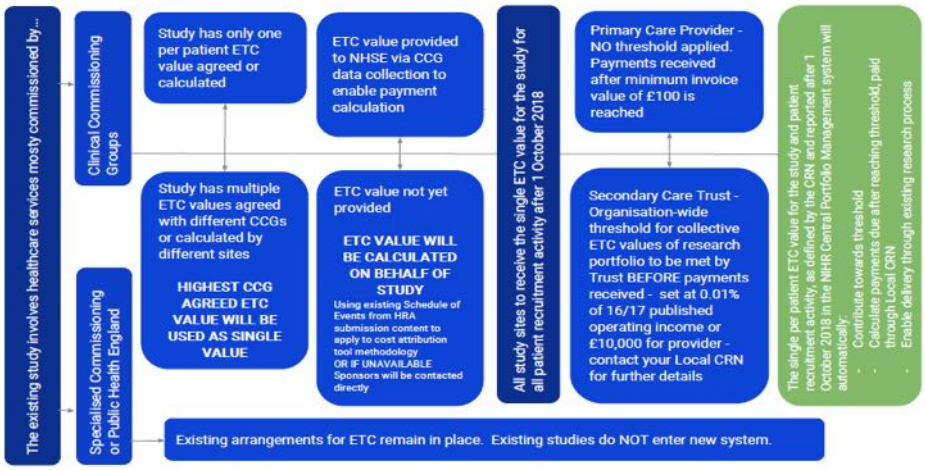
Q2.4 A new cost attribution tool that is similar to the **commercial costing template has been developed to support the cost attribution of non-commercial NIHR CRN Portfolio eligible studies in line with the AcoRD guidance. Do I have to use this tool?**

Health Research Authority

Yes, if you are applying for research funding to a NIHR CRN Portfolio funder. A Schedule of Events Cost Attribution Template (SoECAT) has been developed as a standard mechanism through which individual study activities should be attributed to support the full funding of NIHR CRN Portfolio research studies for sites in England. Completion and provision of this tool in your application for research funding forms a core requirement of the arrangements to access Support and Excess Treatment Cost funding in England from 1 October 2018. NIHR and its research funding partners will require a SoECAT to be completed at application stage for applications to single stage new calls and invitations to final stage applications issued after this date.

How Excess Treatment Costs will be covered for existing studies in England after 1 October 2018

NHS National Institute for Health Research



*Excludes studies resulting from new single stage or final stage funding calls after 1 October 2018

Version 11 October 2018

NHS Health Research Authority

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Royal National Orthopaedic Hospital NHS
NHS Trust

Devices & Technology

Iva Hauptmannova
Head of Research & Innovation Centre
Royal National Orthopaedic Hospital

R&D Forum Non-Commercial Sponsors' Symposium
8th of November, 2018
London

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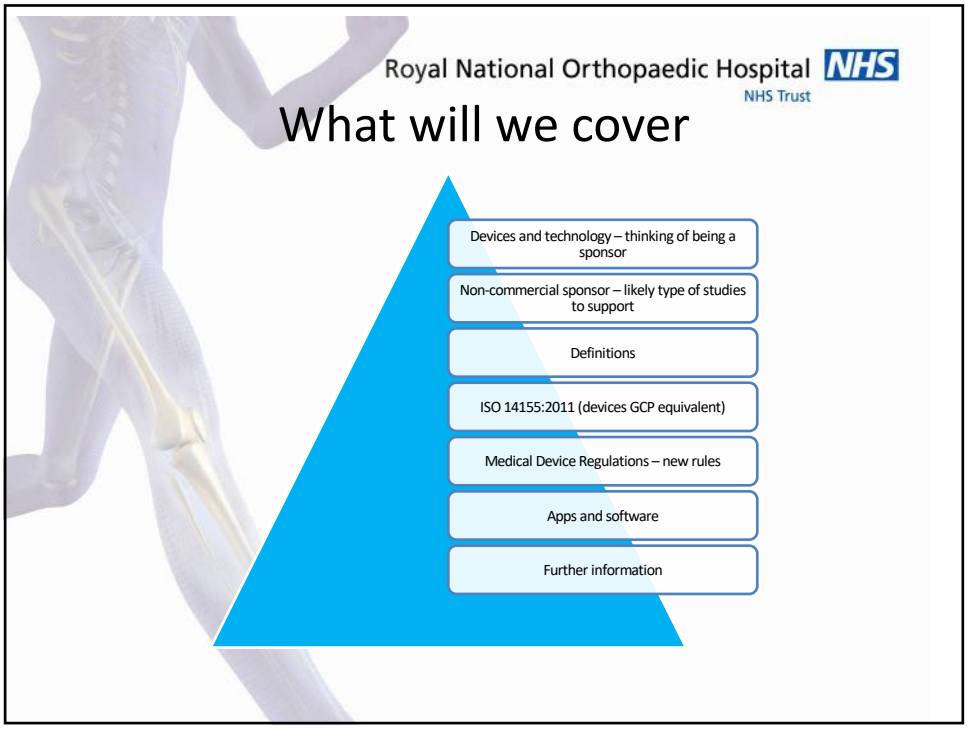
NHS Trust

Devices and Technology – thinking of being a sponsor?


Royal National Orthopaedic Hospital NHS
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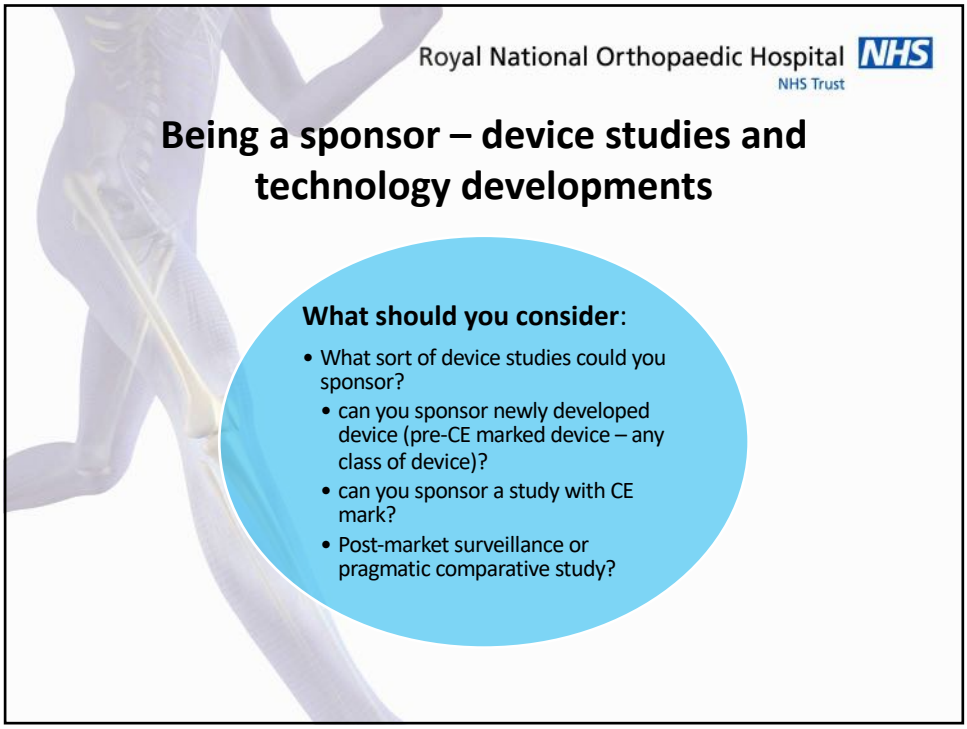
What will we cover
Devices and technology – thinking of being a sponsor
Non-commercial sponsor – likely type of studies to support
Definitions
ISO 14155:2011 (devices GCP equivalent)
Medical Device Regulations – new rules
Apps and software
Further information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Being a sponsor – device studies and technology developments
What should you consider:
• What sort of device studies could you sponsor?
• can you sponsor newly developed device (pre-CE marked device – any class of device)?
• can you sponsor a study with CE mark?
• Post-market surveillance or pragmatic comparative study?

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Non-commercial sponsor

Likely study types for non-commercial sponsors:

- Surveillance
- Pragmatic comparative studies
- New Apps/software
- Prototypes – if you have access to expertise and clean room (for implantable devices)
- Pre-CE mark studies – if you have links to manufacturer

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Definition (using MDR 2017)

Medical Device definition from the Medical Device Regulation MDR 2017/745

"medical device" means any instrument, apparatus, appliance, software, implant, reagent, material or other article **intended** by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilization of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

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Classification

4 main categories in Europe:

- Class I
- Class IIa
- Class IIb
- Class III

Classification is driven by risk associated with the device. Higher the risk higher the classification:

Class I: usually devices, which have measuring function: syringe with volumen measurement, ECG etc.

Class IIa: Adhesives for topical use, stents

Class IIb: Urethral stents, tracheal cannulae

Class III: Brain spatulas, spinal needles

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Classification - additional

- Borderline In-Vitro Diagnostic medical device
- Borderline Active Implantable Medical Device – Medical Device
- Borderline Medical Device – Medicinal Product
- Borderline Medical Device – Biocides
- Borderline Medical Device – Cosmetic Products
- Accessory to a Medical Device or an In-Vitro Diagnostic Medical Device
- Classification (Review class of borderline products)
- Software and mobile applications

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NHS Trust

As no-commercial sponsor do you need to know all that?

- As non-commercial sponsor it is good to have an understanding of device classification
- Non-commercial sponsor is unlikely to sponsor new medical device research – unless you have the right collaborator
- That does not mean you cannot be involved and sponsor studies with devices
- Main focus would be post-market surveillance, pragmatic studies (comparing devices already on the market), and possibly software development
- Whichever the type you should be aware of ISO 14155: 2011

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ISO 14155: CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN SUBJECTS

- Introduced at the same time as ICH GCP, but not considered detailed
- ISO: 14155:2011 version aligned with GCP standards and use as standard for conducting medical device studies
- Specifies definitions and reporting requirements adverse events/reactions for device studies
- Set outs out scope, ethical considerations, validation and assessment required for studies involving medical devices

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Medical Devices – New Rules - MDR

- Tighter regulations under Medical Device Regulations (MDR) from May 2020

Some key changes:

- Change in classification of some devices
- New certification requirements for sterilisation
- Increased requirement for clinical reporting (increase number of post-market surveillance studies)
- Unique Device Identifier (UDI) legal requirement

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NHS Trust

Likely studies for non-commercial sponsors & income opportunities

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Post-market surveillance

Few tips

- Does your Trust already have that device on the shelves?
- If you not how will conducting the study disrupt the Trust supply chain and existing agreements (volume based use)

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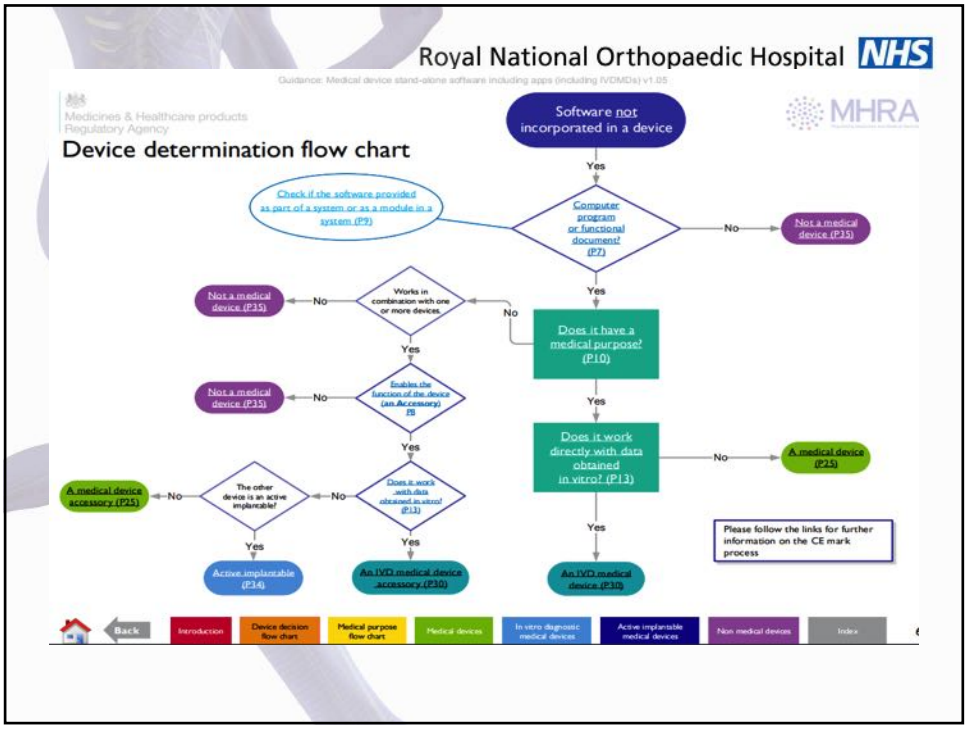
Pragmatic Studies

- Non-commercial studies using already commercially available devices in a comparative study (e.g. TARVA trial)
- Supply of devices is key
- Might consider discussion with manufacturer, but not required



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Data Driven Health Technology

- Exciting opportunities for developing AI
- Can be quite a challenge when it comes to data sharing
- Large amounts of data needed to AI
- Some guidance is provided:
  - Initial Code of Conduct for Data-Driven Health and Care Technology (DHSC, 5th Sep. 2018)
  - The code provides 10 principles and commitments
- Engage with the right partners – involve IG team and IM&T
- Design a review process
- Know when you don't know something

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NHS Trust

Further Information

- **Great free online mini-course**: https://easymedicaldevice.com/2018/03/medical-device-definition/ cover both European and US regulations, and other coutries.
- Medical Device Software Application: https://www.gov.uk/government/publications/medical-devices-software-applications-apps

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Research and Development Forum

Thank You & Close

Please hand in your feedback forms as you leave