UKCRC Registered Clinical Trials Units

UKCRC Registered CTU Network - Internal Audit Prioritisation Guidance

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UKCRC Registered CTU Network – Internal Audit Prioritisation Guidance

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ACRONYMS	
APR	Annual Progress Report
CE-mark	Conformité Européenne mark
CI	Chief Investigator
CRF	Case Report Form
cSB	Confirmed Serious Breach
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DM	Data Management
DMP	Data Management Plan
DPB	Data Protection Breach
DSUR	Developmental Safety Update Report
eCOA	Electronic Clinical Outcome Assessment
e-consent	Electronic Consent

ePRO	Electronic Participant Reported Outcomes
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICO	Information Commissioner's Office
IRT	Interactive Response Technology
IS	Information Systems
ISF	Investigator Site File
MHRA	Medicines & Healthcare products Regulatory Agency
Ph	Phase (e.g. Phase I, II, II or IV)
PISC	Participant Information Sheet & Consent Form
pSB	Potential Serious Breach
PSF	Pharmacy Site File
QA	Quality Assurance
QP	Qualified person
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
ST	Statistics
TM	Trial Management
TMF	Trial Master File
TMP	Trial Monitoring Plan
UKCRC	UK Clinical Research Collaboration

I. Introduction

Clinical Trials Unit (CTU) internal auditing functions have limited resources and therefore the studies and systems or processes chosen for internal audit often require prioritisation. However, although there are a number of risk-based approaches for other areas of clinical research, there is very little guidance on how to apply a risk-based approach to audit prioritisation. This document is intended to help bridge that gap and has been developed based on a workshop delivered at the 2019 UKCRC Registered CTU Network QA Away Day. It is intended to provide information and guidance on how a risk-based prioritisation tool and strategy might be designed, and also provides a concrete example in Appendix 2. It should be noted that the example in Appendix 2 has only been provided to help illustrate the points in this guideline and with no claim as to its suitability for general use.

A prioritisation strategy needs to make clear which risk factors are used for prioritisation ('IDENTIFY'), how they will be quantified ('DEFINE & WEIGHT'), and how studies and systems/processes will be ranked ('RANK'). The tool developed as a result will reflect the principles of the strategy and can be used to produce prioritised lists of studies and systems/processes for audit.

II. Identifying risk factors

There are a wide number of items which may be used as risk factors – a list of suggested items is provided in Appendix 1. Whilst the list of possible risk factors is large, it should be noted that the more risk factors are included, the more complicated and unwieldy the prioritisation tool will become.

Therefore, it is recommended that a limited number are chosen and the rationale behind this decision is documented and approved at the CTU senior level.

When choosing risk factors, the structure and portfolio of the CTU should be taken into account. For example, using population type as a risk factor may not be useful for CTUs which only run studies recruiting adults with mental capacity. Similarly, for CTUs researching rare diseases, study centres may include smaller sites and those less experienced in research and therefore the study setting may be a useful risk factor, however for CTUs running large scale cancer studies for example, this may be less useful.

Additionally, whilst the focus of factors selected is necessarily on "risk", this may result in some low-risk studies never being prioritised for audit – therefore it should be considered how this may be avoided. For example, for CTUs with relatively small portfolios, the date of a previous internal audit could be captured and a rule established that a study will not be re-audited until all other studies have been audited at least once. It may also be worthwhile considering ways to ensure audit selection does not permanently exclude studies that may not meet the pre-selected risk factors – for example picking one study per year that does not rank as high in the audit tool.

Consideration should also be given to "likeliness" of risk versus "detection" of risk and how these may be balanced. One way to achieve this would be to categorise risk factors into ones which are static and those which can change during the lifetime of a trial. Static factors may include: intervention type, trial population, trial complexity, use of technologies new to the CTU, etc. Changeable factors may include: reported non-compliances, introduction of new systems or processes to ongoing studies, etc. This categorisation of "static" versus "changeable" factors can then be useful when defining and weighting the risk factors.

Once risk factors have been chosen, a decision will be needed on how to format and 'weight' them.

A variety of formats may be used. Some factors will have simple formats (e.g. yes/no for risk factor about international setting); some may be more suited to categorisation (e.g. categories A, B, C for intervention risk mapping to MHRA CTIMP Types); and for others, a simple numeric count format will be applicable (e.g. count format for risk factors of number of breaches).

III. Weighting risk factors

Not all risk factors will have the same importance for prioritisation purposes and therefore consideration should be given to how these can be weighted to avoid unhelpful skewing of results. A variety of methods may be employed, for example, numerical, or other simple logic formulae (e.g. "red-flags" as used on the example provided in Appendix 2).

Determining weighting will be very dependent upon the CTU's experience and portfolio. For example, a CTU which manages a mixture of CTIMPs and non-CTIMPs will need to carefully consider their weighting decisions in order to avoid only CTIMPs being selected for audit as they are always "top of the list". Another example is a CTU which manages mainly adult trials and has little experience in paediatric trials – they will need to ensure that if a paediatric trial is taken on, their prioritisation tool is sensitive enough to be able to react to this new area of research which may present a higher than normal risk for the CTU.

Weighting can be enhanced via simple methods such as grouping. For example, if previous audit/inspection findings are chosen as a risk factor, studies which have a relatively high number of audit/inspection findings will likely rank higher for audit prioritisation than other studies, however these studies may actually be of lower inherent risk. Similarly, if a large number of static risk factors are used, then a study with a high intervention risk (e.g. unlicensed product) may rank below a low-risk intervention study that does not involve vulnerable populations, or inexperienced centres. In such cases, it may be that a mixture of numerical and "red-flags" quantification factors can help balance this out, e.g.:

- Intervention risk (MHRA Type C study) = "red-flag";
- Other inherent "static" risk (inexperienced centres OR vulnerable population) = "red-flag";
- Non-compliance "changeable" risk (>1 Reported Serious Breach OR ≥1 critical audit finding) = "red-flag".

IV. Ranking

Whilst some level of ranking considerations will necessarily feed into the above decisions on how to weight/quantify risk factors, it is recommended that overarching ranking is also considered when designing the audit prioritisation strategy.

CTUs will usually manage a number of studies which are at different "stages", from set-up through recruitment and follow-up to close-out and archiving. Therefore, it may be risk-proportionate to design a tool which ranks studies based on their stage and prioritise those still recruiting or treating participants over those in final analysis. Whilst this may mean that studies which have completed data collection would not be prioritised for full study audits, the activities performed at the end of studies (e.g. database lock, statistical analysis, etc.) may be covered by systems or process audits (see below), as opposed to study audits. Therefore, it is important to ensure that where study stage is used as a way to prioritise studies, system/process audits are also conducted and that these cover processes across the whole study lifespan.

Additionally, the prioritisation tool should take into account dates of the last internal audit, otherwise studies that had a large number of findings, but which have since improved, may continually be prioritised for audit year after year.

All CTUs have systems and processes which require auditing in addition to studies, and many CTUs will run a mixture of regulated studies (e.g. CTIMPs, device trials) and non-regulated studies. A decision will therefore need to be taken on how many systems/processes to audit versus studies, and how many regulated versus non-regulated studies to audit. One way to achieve this is to create three separate lists (regulated studies; non-regulated studies; systems/processes), apply the tool to each list, and then decide the ratio at which to audit from each list (e.g. 2:1:1). For example, if monthly audits are performed, each yearly quarter might involve two regulated study audits, one non-regulated study audit and one system/process audit. The ratios will depend on the amount and type of systems/processes running in the CTU and its portfolio in addition to the CTU resources available for conducting audits.

V. Documentation and Review

The examples above illustrate the importance of applying care in the choice not only of the risk factors themselves, but also format choices and methods of quantification, weighting, and ranking. It is crucial that decisions are tailored to the CTU and its current portfolio and experience. One tool may work well for one CTU, but not for another.

It is recommended that decisions, their rationale and applicability to the CTU in question are clearly laid out in a formal document (e.g. Internal Audit Policy, or similar) to ensure clarity and consistency for CTU staff involved in audit scheduling, but also to record the rationale behind the decisions made, and how these are tailored to the CTU's experience and portfolio.

It is recommended that this document be reviewed at regular intervals, but also if/when the CTU undergoes significant changes, whether that be the adoption of studies in new areas (disease, population, methodology, etc.), the acquisition of new technologies or systems, or organisational change (e.g. mergers).

To conclude, it is important to remember that, although a Prioritisation Strategy and Tool will provide consistency in how studies and CTU systems/processes are chosen for audit year to year, audit scheduling should not be constrained by this tool or considered fully "automated". Once the tool is applied and prioritised lists have been produced, these should still be reviewed by appropriate CTU senior staff and carefully considered. The process for prioritisation should allow for changes to be made, which should be fully documented (along with justification) in the audit schedule. Finally, the audit process should also be able to add "for cause" audits if required – consideration should be given to ensuring capacity within the audit team to accommodate such audits.

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Appendix 1: Examples of Risk Factors

Risk Factors – Studies

- study intervention type
- phase of trial
- level of CTU involvement
- unusual recruitment rates
- blinded vs unblinded trials
- endpoints – labs, etc.
- adaptive trial design
- Serious Breaches (potential / confirmed)
- Data Protection Breaches (caused by CTU / caused by externals)
- previous audit/inspection findings
- date of last audit
- use of new tools or technologies (e.g. image analysis, IRT, ePRO, eCOA, e-consent, etc.)
- high-risk decision making – e.g. dose escalation
- size of trial / potential trial impact (i.e. is it going to change prescribing practice)

Risk Factors – Systems/Processes

- SOP dates (review)
- staff training
- validation findings
- patient impact
- data impact
- interconnectivity of systems
- newness of system / lifecycle
- Serious Breaches (potential / confirmed)
- outcome of previous audit/inspection (i.e. findings)
- date of last audit

Appendix 2: Example of Audit Prioritisation

1. Process of Prioritisation

Step 1: split audit areas into three separate lists: regulated studies, non-regulated studies, processes/systems.

> *Regulated studies are those which fall under either the Medicines for Human Use (Clinical Trials) Regulations, or the Medical Devices Regulations (e.g. CTIMPs and medical device investigations). Non-regulated studies are all others (e.g. non-CTIMPs).*

Step 2: filter out studies based on their "stage".

> *Only studies which have yet to be archived should remain visible. This Step 2 only applies to the regulated studies and non-regulated studies lists.*

Step 3: populate the Prioritisation tool with details of Risk Factors for each list.

> *The tool uses two over-arching categories of Risk Factors: "static" and "changeable". Each category is further split into multiple sub-categories within which the individual risk factors sit. For each individual risk factor, data must be added (further guidance on this is provided in section 2 below).*

Step 4: apply "red-flagging".

> *Within each sub-category, red-flags should be applied where appropriate. See section 2 for further detail on how to assign red-flags. N.B. in the example given, "red-flags" are only applied at the sub-category level – the level at which weighting such as "red-flags" are applied should be carefully considered to avoid "masking" of multiple risks within a single category.*

Step 5: prioritise lists.

> *The total number of red-flags are added up for each over-arching category ("static" / "changeable"). Each study list is then prioritised firstly by total number of "changeable" red-flags, then by total number of "static" red-flags. The system/process list is categorised first by "changeable" red-flags, then by total number of "static" (significant) red-flags and finally by total number of "static" (some risk) red-flags.*

Step 6: create an annual schedule.

> *The studies/processes which come out at top of each list will be used to create an annual audit schedule. Schedules will be based on a ratio of regulated study / non-regulated study / process audits of 2:1:1.*

2. Risk Factors – Quantification and Weighting

2.1 Studies – Risk Factors

STUDIES – Risk Factors					
Category	**Sub-category**	**Individual Risk Factor**	**Format**	**Notes**	**"Red-flag" criteria (by Sub-category)**
Static	**Intervention**	**Intervention Type**	(CTIMPs): Type A, B, C (Regulated Devices): Yes / NO (Non-regulated): Category 1, 2, 3	*Regulated trials* – CTIMPs will use MHRA classifications. Device trials will be categorised based on whether device has CE-mark or not. *Non-regulated* – Category 1 = clinical treatment (e.g. surgery, radiotherapy, drug, device, etc.) Category 2 = other invasive intervention (e.g. human tissue sampling, imaging, etc.) Category 3 = other non-invasive intervention (e.g. questionnaires, interviews, etc.) or collection of identifiable data	*Red-flags: CTIMPs* = Type A + PhI or PhII Type B + PhI or PhII or PhIII Type C *Red-flags: Regulated devices* = CE-marked + Ph I or Ph II No CE-mark *Red-flags: Non-regulated* = Category 1 Category 2 + PhI or PhII or PhIII Category 3 + PhI or PhII
Static	**Intervention**	**Trial Phase**	PhI, PhII, PhIII, PhIV, Feasibility	ICH E8 Phase definitions will be used. Feasibility study = Small study to inform larger study (if successful)	
Static	**Design / Setting**	**Blinding**	Yes / No	Blinded trials include any blinding at the CTU, site or other collaborators (does not include single blind for patients)	Red-flag = ≥2 "YES" responses
Static	**Design / Setting**	**International**	Yes / No	International trials include those with non-UK sites (does not include trials with international collaborators)	

STUDIES – Risk Factors					
Category	**Sub-category**	**Individual Risk Factor**	**Format**	**Notes**	**"Red-flag" criteria (by Sub-category)**
Static	**Design / Setting**	**Vulnerable population**	Yes / No	Vulnerable population trials include those recruiting children, adults lacking capacity, pregnant women, the elderly, and persons with disabilities, and also include deferred consent studies	
Static	**CTU**	**Hybrid CTU support**	Yes / No	Hybrid trials include those where one work-stream (TM, DM, IS, ST) is not delegated to CTU, or where substantial trial conduct activities are performed by non-CTU staff (e.g. use of coordinating centres in international studies, use of specialist vendors for endpoint analysis (labs, imaging, etc.)	Red-flag = ≥2 "YES" responses
Static	**CTU**	**Staff risk**	Yes / No	Trials with staff risk include: • CTU TM staff employed <1 year • trial has had TM handover within previous year (e.g. sick leave / mat leave / staff departure) • CTU TC has >1 trial in set-up / recruiting • CI (new / historical concerns)	
Static	**CTU**	**Novelty**	Yes / No	Novel trials include: • processes/systems which are new to CTU (e.g. new IS systems, new collaborators, new data obtention pathways, etc.) • conditions / disease areas new to CTU	
Changeable	**Audit / Inspection**	**Internal Critical Findings**	Number	Once a trial is re-audited, this will be wiped to zero.	Red-flag = ≥1

STUDIES – Risk Factors					
Category	**Sub-category**	**Individual Risk Factor**	**Format**	**Notes**	**"Red-flag" criteria (by Sub-category)**
Changeable	**Audit / Inspection**	**External Critical Findings**	Number	Once a trial is internally audited, this will be wiped to zero.	
Changeable	**Severity**	**Severity of SBs**	0, 1, 2	Since previous CTU audit: • 0 = no potential SBs (pSBs); • 1 = one or more pSBs; • 2 = one or more confirmed SBs (cSBs)	Red-flag = ≥2
Changeable	**Severity**	**Severity of DPBs**	0, 1, 2	Since previous CTU audit: • 0 = no DPBs • 1 = one or more DPBs (non-reportable to ICO); • 2 = one or more DPB reported to ICO	
Changeable	**SB Quantity**	**Total SB Quantity**	Number	Total number of pSBs overall, or since last CTU audit	Red-flag = ≥3
Changeable	**SB Quantity**	**Increasing SB**	Number	Total number of potential SBs (pSBs) since last CTU audit schedule review	
Changeable	**DPB Quantity**	**Total DPB Quantity**	Number	Total number of DPBs overall, or since last CTU audit (excludes external DPBs)	Red-flag = ≥3
Changeable	**DPB Quantity**	**Increasing DPB**	Number	Total number of DPBs since last CTU audit schedule review	

STUDIES – Risk Factors					
Category	**Sub-category**	**Individual Risk Factor**	**Format**	**Notes**	**"Red-flag" criteria (by Sub-category)**
Changeable	**Non-serious Quantity**	**Total non-serious Quantity**	Number	Total number of non-serious issues overall, or since last CTU audit (excludes external DPBs)	Red-flag = ≥7
Changeable	**Non-serious Quantity**	**Increasing non-serious**	Number	Total number of non-serious issues since last CTU audit schedule review	

2.2 Systems/Processes Risk Factors

SYSTEMS / PROCESSES – Risk Factors					
Category	**Sub-category**	**Individual Risk Factor**	**Format**	**Notes**	**"Red-flag" criteria (by Sub-category)**
Static	**n/a**	**Patient Safety**	Significant / Some risk	Assess the impact of each system/process failing in relation to Patient Safety.	Red-flag for "significant" column – total number of "significant" risks identified for the system/process. Red-flag for "some risk" column – total number of "some risk" risks identified for the system/process.
Static	**n/a**	**Patient mental integrity / rights**	Significant / Some risk	Assess the impact of each system/process failing in relation to Patient mental integrity / rights.	
Static	**n/a**	**Data credibility**	Significant / Some risk	Assess the impact of each system/process failing in relation to Data credibility.	
Static	**n/a**	**Regulatory requirements**	Significant / Some risk	Assess the impact of each system/process failing in relation to regulatory requirements.	
Changeable	**Audit / Inspection**	**Internal Critical Findings**	Number	Once a system/process is re-audited, this will be wiped to zero.	Red-flag = ≥1

SYSTEMS / PROCESSES – Risk Factors					
Category	**Sub-category**	**Individual Risk Factor**	**Format**	**Notes**	**"Red-flag" criteria (by Sub-category)**
Changeable	**Audit / Inspection**	**External Critical Findings**	Number	Once a system/process is internally audited, this will be wiped to zero.	
Changeable	**Severity**	**Severity of SBs**	0, 1, 2	Since previous CTU audit: • 0 = no potential SBs (pSBs); • 1 = one or more pSBs; • 2 = one or more confirmed SBs (cSBs)	Red-flag = ≥2
Changeable	**SB Quantity**	**Total SB Quantity**	Number	Total number of pSBs overall, or since last CTU audit	Red-flag = ≥3
Changeable	**SB Quantity**	**Increasing SB**	Number	Total number of potential SBs (pSBs) since CTU audit schedule review	
Changeable	**Non-serious Quantity**	**Total non-serious Quantity**	Number	Total number of non-serious issues overall, or since last CTU audit	Red-flag = ≥7
Changeable	**Non-serious Quantity**	**Increasing non-serious**	Number	Total number of non-serious issues since last CTU audit schedule review	

3. Completed Audit Prioritisation Tool

3.1 Completed Tool for Regulated Studies

Study Details	Static Study-specific Factors												
	Intervention	Intervention	Intervention	Intervention	Design / Setting	Design / Setting	Design / Setting	Design / Setting	CTU	CTU	CTU	CTU	
Study acronym	CTIMPs (Type A, B, C)	Device CE-mark (y/n)	Trial Phase (I, II, III, IV, Feas)	Intervention RED-FLAG	Blinding (y/n)	International (y/n)	Vulnerable population (y/n)	Design / Setting RED-FLAG	Hybrid CTU support (y/n)	Staff risk (y/n)	Novelty (y/n)	CTU RED-FLAG	TOTAL RED-FLAGS (static factors)
AVID	C	N/A	II	y	n	n	n	n	y	y	y	y	2
BLOSOM	B	N/A	IV	n	n	y	y	y	n	n	n	n	1
BLUEMOON	B	N/A	III	y	y	n	y	y	y	y	n	y	3
CARE-3	B	N/A	II	y	y	n	y	y	n	y	y	y	3
CUBE	B	N/A	III	y	n	n	n	n	n	n	n	n	1
REALIGN	n/a	yes	III	n	n	n	n	n	n	n	n	n	0
SAPHIRE	A	N/A	II	y	y	n	n	n	n	y	y	y	2
SPINDLE	n/a	no	III	y	y	y	y	y	n	n	y	n	2
STREAM	n/a	no	I	y	y	n	n	n	n	y	n	y	2

Study Details	Changeable Study-specific Factors															
	Audit / inspection	Audit / inspection	Audit / inspection	Severity	Severity	Severity RED-FLAG	Serious Breaches	Serious Breaches	Serious Breaches	Data Protection Breaches	Data Protection Breaches	Data Protection Breaches	Non-serious	Non-serious	Non-serious	
Study acronym	Internal critical findings (number)	External critical findings (number)	Audit / Inspection RED-FLAG	Severity of SB (none=0; unreportable=1; reportable=2)	Severity of DPB (none=0; unreportable=1; reportable=2)	Severity RED-FLAG	Total SB Quantity (number)	Increasing SB (number)	SB Quantity RED-FLAG	Total DPB Quantity (number)	Increasing DPB (number)	DPB Quantity RED-FLAG	Total non-serious issues Quantity (number)	Increasing non-serious issues (number)	Non-serious Quantity RED-FLAG	TOTAL RED-FLAGS (changeable factors)
AVID	n/a	n/a	0	2	0	1	0	0	0	0	0	0	2	2	0	1
BLOSOM	0	0	0	2	0	1	5	0	1	0	0	0	2	1	0	2
BLUEMOON	0	1	0	0	1	0	0	0	0	1	0	0	21	10	2	2
CARE-3	n/a	0	0	2	0	1	2	2	0	0	0	0	1	0	0	1
CUBE	0	n/a	0	2	0	1	0	0	0	0	0	0	0	0	0	1
REALIGN	n/a	n/a	0	2	2	2	6	6	2	7	2	1	1	0	0	5
SAPHIRE	2	0	1	2	0	1	2	0	0	0	0	0	8	2	1	3
SPINDLE	n/a	n/a	0	0	0	0	0	0	0	0	0	0	0	0	0	0
STREAM	n/a	3	1	2	0	1	1	1	0	0	0	0	14	1	1	3

3.2 Completed Tool for Non-Regulated Studies

Study Details	Static Study-specific Factors												
	Intervention	Intervention	Intervention	Intervention	Design / Setting	Design / Setting	Design / Setting	Design / Setting	CTU	CTU	CTU	CTU	
Study acronym	Intervention Category (1, 2, 3)	Device CE-mark (y/n)	Trial Phase (I, II, III, IV, Feas)	Intervention RED-FLAG	Blinding (y/n)	International (y/n)	Vulnerable population (y/n)	Design / Setting RED-FLAG	Hybrid CTU support (y/n)	Staff risk (y/n)	Novelty (y/n)	CTU RED-FLAG	TOTAL RED-FLAGS (static factors)
BIOLIVE	B	N/A	III	Y	Y	N	N	Y	Y	Y	N	Y	3
CIRCE	B	N/A	II	Y	Y	N	N	Y	N	Y	Y	Y	3
CLIPS	C	N/A	II	Y	N	N	Y	N	Y	Y	Y	Y	2
CONE	B	N/A	III	Y	N	N	Y	N	N	N	N	N	1
REVERIE	N/A	N/A	III	N	N	N	Y	N	N	N	N	N	0
TALK-2	B	N/A	IV	N	N	Y	N	Y	N	N	N	N	1

Study Details	Changeable Study-specific Factors															
	Audit / inspection	Audit / inspection	Audit / inspection	Severity	Severity	Severity RED-FLAG	Serious Breaches	Serious Breaches	Serious Breaches	Data Protection Breaches	Data Protection Breaches	Data Protection Breaches	Non-serious	Non-serious	Non-serious	
Study acronym	Internal critical findings (number)	External critical findings (number)	Audit / Inspection RED-FLAG	Severity of SB (none=0; unreportable=1; reportable=2)	Severity of DPB (none=0; unreportable=1; reportable=2)	Severity RED-FLAG	Total SB Quantity (number)	Increasing SB (number)	SB Quantity RED-FLAG	Total DPB Quantity (number)	Increasing DPB (number)	DPB Quantity RED-FLAG	Total non-serious issues Quantity (number)	Increasing non-serious issues (number)	Non-serious Quantity RED-FLAG	TOTAL RED-FLAGS (changeable factors)
BIOLIVE	N/A	N/A	0	0	0	0	0	0	0	0	0	0	12	12	2	2
CIRCE	0	N/A	0	0	1	0	0	0	0	2	2	0	15	0	1	1
CLIPS	0	0	0	1	1	0	3	0	1	1	1	0	0	0	0	1
CONE	N/A	N/A	0	0	0	0	0	0	0	0	0	0	0	0	0	0
REVERIE	N/A	N/A	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TALK-2	0	0	0	2	0	1	13	2	1	0	0	0	0	0	0	2

3.3 Completed Tool for Systems/Processes

System/Process Details	Static Factors					
System / Process	Impact on Patient Safety	Impact on Patient Mental Integrity / Rights	Impact on Data Credibility	Impact on Regulatory requirements	Significant Impact - RED-FLAGS	Non-significant impact - RED-FLAGS
Data storage & processing (security and confidentiality)		Significant		Significant	2	0
PISC development & consent/withdrawal monitoring		Significant		Significant	2	0
DMP/TMP/Eligibility	Significant		Significant		2	0
Supplies (procurement, management, QP release)	Significant			Significant	2	0
DSURs & Ethical APRs (& funder APRs)	Significant			Significant	2	0
Pharmacovigilance (reporting and CI review)	Significant		Significant	Significant	3	0
Initial Approvals & Amendments	Some	Some	Some	Significant	1	3
Initiation/Greenlight & Closure	Some	Some	Some	Significant	1	3
CRF development	Significant		Significant	Significant	3	0
TMF/ISF/PSF development & maintenance (completed CRFs)	Some		Some	Significant	1	2
Human samples		Significant		Some	1	1
Randomisation processes			Significant		1	0
Blinding processes	Significant		Some		1	1
Database design, testing, and maintenance	Significant		Significant		2	0
Data: validation, entry, validation/management, import (SAS)	Significant		Significant		2	0
Analysis (SAP & data cleaning)	Significant		Significant		2	0
Non-compliance reporting (SB, DPB, QA incident)	Some	Some	Some	Significant	1	3
End of Trial (notification & reporting) & Archiving				Significant	1	0

System/Process Details	Changeable Factors											
	Audit / inspection	Audit / inspection	Audit / inspection	Severity	Severity	Serious Breaches	Serious Breaches	Serious Breaches	Non-serious	Non-serious	Non-serious	
System / Process	Internal critical findings (number)	External critical findings (number)	Audit / Inspection RED-FLAG	Severity of SB (none=0; unreportable=1; reportable=2)	Severity RED-FLAG	Total SB Quantity (number)	Increasing SB (number)	SB Quantity RED-FLAG	Total non-serious issues Quantity (number)	Increasing non-serious issues (number)	Non-serious Quantity RED-FLAG	TOTAL RED-FLAGS (changeable factors)
Data storage & processing (security and confidentiality)	0	0	0	1	0	3	0	1	0	0	0	1
PISC development & consent/withdrawal monitoring	0	0	0	2	1	13	2	1	0	0	0	2
DMP/TMP/Eligibility	N/A	N/A	0	0	0	0	0	0	12	12	2	2
Supplies (procurement, management, QP release)	0	N/A	0	1	0	0	0	0	15	7	2	2
DSURs & Ethical APRs (& funder APRs)	N/A	N/A	0	0	0	1	0	0	0	0	0	0
Pharmacovigilance (reporting and CI review)	N/A	N/A	0	2	1	0	0	0	0	0	0	1
Initial Approvals & Amendments	N/A	N/A	0	1	0	0	0	0	0	2	0	0
Initiation/Greenlight & Closure	N/A	N/A	0	0	0	5	3	2	7	0	1	3
CRF development	N/A	0	0	0	0	0	0	0	0	1	0	0
TMF/ISF/PSF development & maintenance (completed CRFs)	N/A	N/A	0	1	0	0	0	0	2	0	0	0
Human samples	N/A	N/A	0	0	0	0	0	0	0	0	0	0
Randomisation processes	N/A	N/A	0	0	0	0	0	0	0	4	0	0
Blinding processes	2	N/A	1	0	0	0	1	0	4	0	0	1
Database design, testing, and maintenance	N/A	N/A	0	0	0	2	0	0	0	0	0	0
Data: validation, entry, validation/management, import (SAS)	N/A	N/A	0	1	0	0	0	0	0	0	0	0
Analysis (SAP & data cleaning)	N/A	N/A	0	0	0	0	0	0	0	0	0	0
Non-compliance reporting (SB, DPB, QA incident)	N/A	N/A	0	0	0	0	0	0	0	0	0	0
End of Trial (notification & reporting) & Archiving	N/A	N/A	0	0	0	0	0	0	0	0	0	0

4. Prioritised Lists

Regulated Studies		
Study acronym	TOTAL RED-FLAGS (changebale factors)	TOTAL RED-FLAGS (static factors)
REALIGN	5	0
SAPHIRE	3	2
STREAM	3	2
BLUEMOON	2	3
BLOSOM	2	1
CARE-3	1	3
AVID	1	2
CUBE	1	1
SPINDLE	0	2

Non-Regulated Studies		
Study acronym	TOTAL RED-FLAGS (changeable factors)	TOTAL RED-FLAGS (static factors)
BIOLIVE	2	3
TALK-2	2	1
CIRCE	1	3
CLIPS	1	2
CONE	0	1
REVERIE	0	0

System/Process Details			
System / Process	TOTAL RED-FLAGS (changeable factors)	Significant Impact - RED-FLAGS	Non-significant impact - RED-FLAGS
Initiation/Greenlight & Closure	3	1	3
PISC development & consent/withdrawal monitoring	2	2	0
DMP/TMP/Eligibility	2	2	0
Supplies (procurement, management, QP release)	2	2	0
Pharmacovigilance (reporting and CI review)	1	3	0
Data storage & processing (security and confidentiality)	1	2	0
Blinding processes	1	1	1
CRF development	0	3	0
DSURs & Ethical APRs (& funder APRs)	0	2	0
Database design, testing, and maintenance	0	2	0
Data: validation, entry, validation/management, import (SAS)	0	2	0
Analysis (SAP & data cleaning)	0	2	0
Initial Approvals & Amendments	0	1	3
Non-compliance reporting (SB, DPB, QA incident)	0	1	3
TMF/ISF/PSF development & maintenance (completed CRFs)	0	1	2
Human samples	0	1	1
Randomisation processes	0	1	0
End of Trial (notification & reporting) & Archiving	0	1	0

5. Annual Schedule

Audit Area	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Regulated study	**REALIGN**											
Regulated study		**SAPHIRE**										
Non-regulated study			**BIOLIVE**									
System / process				**Greenlight & Closure**								
Regulated study					**STREAM**							
Regulated study						**BLUEMOON**						
Non-regulated study							**TALK-2**					
System / process								**Consent / Withdrawal**				
Regulated study									**BLOSOM**			
Regulated study										**CARE-3**		
Non-regulated study											**CIRCE**	
System / process												**DMP/TMP / Eligibility**