22 December 2022
EMA/956806/2022
European Medicines Agency

Clinical Trials Information System - Risk Mitigation Plan

Version number	Approver	Purpose	Date	Notes
1.0	Peter Arlett	Version 1.0	22/12/2022	Version 1.0 of this document has been produced in December 2022. While operational from 22 December, the document will be subject to consultation within the European Regulatory Network over the subsequent weeks. On this basis further updates are anticipated in the light of feedback provided by the relevant parties.

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List of Acronyms

Term/Abbreviation	Definition
ACT EU	Accelerating Clinical Trials in the EU Initiative
CTCG	Clinical Trials Coordination Group
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation (EU) No 536/2014
EEA	European Economic Area
EC	European Commission
EMA	European Medicines Agency
EPOG	Early Phase Oversight Group
EU	European Union
HMA	Heads of Medicines Agencies
MB	EMA Management Board
MP	Mitigation plan
MS	Member States
MSC	Member States Concerned
POEG	Product Owners Expert Group
RACI	Responsible – Accountable – Consulted - Informed matrix
TDA	EMA Data Analytics and Methods Task Force
TDA-CTS	Clinical Trials Workstream within TDA

1. Introduction and context

The Clinical Trials Regulation - CTR (EU) No 536/2014 entered into application on 31 January 2022. From that date sponsors have had a choice to submit clinical trial applications under the CTR (via the Clinical Trials Information System (CTIS)) or under the Clinical Trials Directive. From 31 January 2023 it will be mandatory to submit all new clinical trial applications through CTIS and by 31 January 2025 all ongoing clinical trials will need to have been transitioned to the CTR.

The CTR aims at ensuring that the European Union offers an attractive and favourable environment for carrying out clinical research on a large scale, with high standards of public transparency as well as safety for clinical trial participants.

The Clinical Trials Regulation harmonises the processes for the evaluation, authorisation and supervision of clinical trials that are responsibilities of EU Member States and countries of the European Economic Area (EEA).

Prior to the application of the CTR, clinical trial sponsors had to submit clinical trial applications separately to national competent authorities and ethics committees in each member state to obtain regulatory approval to initiate a clinical trial. The Regulation enables sponsors to submit one application through CTIS, for approval to run a clinical trial in several Member States, facilitating the conduct of multinational trials. CTIS will enables transparency and access to information for any party interested in clinical trials conducted in the EU through its searchable public website.

The Regulation also makes it more efficient for EU Member States the joint evaluation of clinical trial applications, via CTIS.

2. Scope of the plan and key assumptions

2.1. Purpose and scope

The purpose of this CTIS Risk Mitigation Plan is to strengthen planning for the functioning of the CTIS in order to ensure that business-as-usual activities can be performed by users within the system. This is done through a continuous monitoring of operations, in line with the CTIS programme governance.

The continuous monitoring will allow:

- early identification of risks, their classification and assessment;
- a coordinated, rapid and effective response to arising issues.
- CTIS user experience allowing compliance with the CTR

The risk mitigation plan is effective immediately and will cover both the period up to mandatory CTIS use and will continue thereafter to ensure that CTIS functioning enables compliance with the CTR.

This risk mitigation plan is a control tool that the project governance implements for the CTIS programme and it subject to constant review and update to ensure business as usual operations before and after the 31st of January 2023.

2.2. Key assumptions

This Risk Mitigation Plan is subject to the assumptions listed in this section. Specifically:

- Availability of IT infrastructure based on the system disaster recovery plan;
- Availability of EMA/service provider' staff working on CTIS to ensure system functionalities are adequate to perform user activities during trial lifecycle in CTIS;
- Retain knowledge on system functionalities via continuation of contract, into 2024, with the current service provider;
- Adequate allocation of effort and resources on resolution of issues stemming from system functionalities with limited previous usage;
- Delivery of system functionalities identified and prioritised for implementation in the 2023/2024 CTIS delivery plan;
- New sponsors and Member States users trained on the requirements of the Regulation and on CTIS functionalities.
- Capacity of sponsors to submit clinical trial applications and clinical trial data during the trial life cycle;
- Capacity of Member States Concerned (MSC) to perform assessments of clinical trial applications and supervision activities during the trial life cycle;

2.3. Governance

The correct functioning of CTIS is overseen by ACT EU Steering Group, which acts as the principal governance body. The ACT EU Steering Group was delegated this oversight role by the EMA Management Board which together with the Heads of Agencies (HMA), receives regular reports on CTIS functioning. In certain circumstances the ACT EU Steering Group may choose to escalate decisions to the EMA Management Board.

On behalf of the European Medicines Regulatory Network, an Early Phase Oversight Group (EPOG) has been established to take decisions on critical incidents with CTIS occurring during operations in the early phase of operation following launch (including the hypercare period). The EPOG meets on an *ad hoc* basis, as needed. Such *ad hoc* meetings can be called at any time in the event of critical issues requiring urgent advice.

Sponsor and Member State input and engagement is secured through monthly Member State Product Owner Expert Group (MS POEG) meetings and quarterly CTIS Forums.

Business as usual and daily operations of CTIS are monitored by EMA daily at team level, and weekly at CTIS Programme level.

Weekly consultation sessions with product owners ensure that EMA, sponsors and Member States product owners work together towards the prioritisation of resolution of critical and high production issues, as well as further improvements to CTIS functionalities.

2.4. RACI matrix

The table below illustrates the RACI matrix (Responsible, Accountable, Consulted, Informed - see definitions below the table) last agreed by CTIS governance in May 2022.

The RACI Matrix was first endorsed in September 2018 and updated in April 2020 to reflect the new delivery model. The below matrix has been revised and aligned with the post go-live *modus operandi* and in line with the revised governance of CTIS.

		European Commission EMA MB HMA	ACT EU Steerco	Early Phase Oversight Group EPOG	CTIS Product Owners Expert Group (POEG) and CTIS Forum	Starting in 2023: MS and sponsor subject matter experts (CTIS delivery and operations)	EMA+MS product owner spokesperson	EMA teams	EMA Management
CTIS Governance	Define governance & high-level objectives	I	A	N/A	I	I	I	C	R
	Define and implement organisation	I	C	N/A	I	I	I	R	A
CTIS Delivery	General planning and resourcing	I	C	N/A	I	I	C	R	A
	Agile delivery: Prioritisation and consultation (on new functionalities), increment planning, end user testing (for new functionality), solution demos on major improvements	I	I	N/A	C for POEG and I for Forum	C	R	R	A
	Build the deliverables	I	I	N/A	I	I	C	R	A
	Reporting	I	I	N/A	I	I	C	R	A
CTIS business operations	Communication	I	I	N/A	I	I	I	R	A
	Training programmes	I	I	N/A	I	I/C	C	R	A
	User support (including service desk tickets)	I	I	N/A	I	I	I	R	A
	Serious data breaches	I	I	R (actions)	I	I	I	R	A

Responsible (R) - Those who actually carry out the work to achieve the task objectives.
Accountable (A) - The one individual who is ultimately accountable for the success (or failure) of a task and will approve the work created by those Responsible. There is ONE and ONLY ONE Accountable for a specific task /deliverable.
Consulted (C) - Those who would have opinions that need to be sought / weighted in for the task / deliverable and be kept updated of the progress (two-way communication).
Informed (I) - Those who would need to be updated on the task progress (one-way communication).

2.5. Monitoring and reporting

The delivery of activities of the CTIS programme are subject to a structured monitoring and reporting process. The status of CTIS is regularly monitored, with detected issues escalated through the project governance.

EMA, Member State and Sponsor product owners participate in the regular Agile delivery activities and when required escalate issues to CTIS governance. In addition, the Product Owners receive a weekly status report that is also circulated to the EMA Management Board.

This reporting package includes a report on the progress of resolving critical and high issues (burndown of known issues) from the CTIS production environment, status of analysis and resolution of CTIS performance issues, report on any new critical or high production issues identified and a report on status of different mitigation actions described in this document.

After 31st of January 2023 the reporting frequency to the EMA Management Board will be reviewed to reflect the level of maturity reached by the system.

3. Risk assessment

This Risk Mitigation Plan is based on possible scenarios related with the use of CTIS.

The baseline scenario **(scenario 1 in the table below)** refers to a use of the system as-per-plan. No blocking issues are detected in the core processes during the use of CTIS. The submission and the evaluation of clinical trial applications is without major disruption and in compliance with the requirements of the CTR. In this first scenario EMA continues to prioritise development of system functionalities in collaboration with CTIS product owners, continues the optimisation of users' support and to resolve non-blocking issue. Of the 11 most burdensome issues which required workarounds, identified by the Member State CTIS experts, the majority will have been resolved by 31 January 2023.

The other three scenarios numbered 2, 3 and 4 in the table below refer to situations where users experience moderate, severe, and critical system challenges respectively that require additional mitigation measures.

Risks have been assessed for these three scenarios, based on their likelihood (i.e., the probability that the scenario materialises) and business impact in terms of negative consequences for the users of CTIS.

The planning described in chapter 4 of this document, addresses the risk scenarios. The management of events described below is conducted by the project team, which oversees the continuous monitoring of CTIS operations.

Risk mitigation for the following scenarios is included in the plan:

- MS/EMA workload increased moderately due to the need for CTIS workarounds **(scenario 2 in the table below)**;
- MS/EMA workload increased severely due to CTIS workarounds or increased support needed for the CTIS user community: helpdesk, comms, workarounds **(scenario 3 in the table below)**;
- Prolonged CTIS downtime causing inability to submit or process trials **(scenario 4 in the table below)**.

TABLE: Risk scenarios reviewed by EMA Management Board December 2022.

Mitigation measures for each applicable scenario are presented in the table. As individual mitigations make occur in more than one risk scenario, the are presented in the Mitigation Plan of Section 4 of this document grouped by work area. To help navigate between the risk scenarios and the Mitigation Plan, references to the relevant parts of Section 4 are included in the table below.

Each scenario will be handled by applying a combination of applicable mitigation measures.

Scenario	Likelihood	Severity	Mitigation
1. As per plan. No blocking bugs in core CTIS functionalities. Workarounds: 7 of 11 Member State concerns already resolved. Submission and processing of trial in compliance with CTR.	High	Low	• Continue as per agreed plan • Prioritization of problems with product owners • Intensify listening to users feedback • Continued optimization of user support • Resolve non-blocking technical issues
2. MS moderate workload increase due to CTIS workarounds	Low/Medium	Medium	• As above + • Users support via application of *ad hoc* data fixes in CTIS (MP 4.1, task 2) • Dedicated resources for *ad hoc* data fixes exclusively allocated to CTIS (MP 4.1, task 2) • (Re)-prioritize management of incidents reported by users based on their impact (MP 4.1, tasks 1 and 2) • Simplification of processes related to CTIS use based on users feedback (MP 4.4, task 1) • EMA perform specific CTIS tasks on behalf of users (MP 4.1, task 2) • Reallocation of EMA staff from other activities (MP 4.2, task 1)
3. MS/EMA workload increased severely due to CTIS workarounds or increased support the CTIS user community (helpdesk, comms, workarounds)	Low	High	• As above + • User support prioritisation (MP 4.1, tasks 1 and 2) • Allocation of slots for clinical trial submissions (MP 4.3, task 2) • Preparation of simplified content for assessment reports (MP 4.4, task 1) • Expand service provider support on CTIS use (MP 4.1, task 1) • Temporarily close Public Portal to focus on core CTIS *(Improved users support via MP 4.1 by limiting the number of reported issues on CTIS functionalities in secure domains)*
4. Prolonged CTIS downtime: Inability to submit or process trials	Very Low	Very High	• As above + • Technical disaster recovery scenarios in place (highest priority) (MP 4.5, task 3) • Disaster recovery rehearsals (MP 4.5, task 3) • Establish a crisis response team (EMA/MS/EC) (MP 4.5, task 3) • Continue extensive stress testing prior to 31st Jan 2023 (MP 4.5 activity 4)

Scenario	Likelihood	Severity	Mitigation
			• If prolonged, consider measures to enable Member State supervision for new trials and ongoing trials under the Regulation (MP 4.5, task 1)

4. Mitigation Plan

This section describes the risk mitigation planning developed to address the three scenarios (i.e., scenarios 2, 3 and 4) presented in the table above.

The plan is based on areas of work which identify different tasks. A combination of the most relevant tasks will be used, based on the applicable scenarios presented in the table above in section 3, to address the risks identified.

4.1. User support prioritisation

User support prioritisation		
Action owner	EMA TDA-CTS	
Action description	Provide adequate support to CTIS users to perform activities in CTIS during the trial life cycle.	
Approach	Incidents resolution arising from CTIS use are prioritised based on each incident score in the criticality assessment. Incidents that will receive the highest priority are those that put at risk the submission or evaluation of clinical trial applications. The lower the criticality score, the lower the priority given to the incident.	
Preparedness activities	**Activity 1**: Increase user support service capacity, provided by EMA experts, on CTIS functionalities and establish dedicated priority teams, working on specific system areas to manage incidents.	Status: planned
	Activity 2: Draft a (communication/training) plan for the EMA staff that provides users support to CTIS users, in order to swiftly and efficiently address issues raised from CTIS in production environment.	Status: planned
	Activity 3: Develop a report and continuously monitor workload for reported issues, including submitted clinical trial applications.	Status: planned

User support prioritisation		
Tasks description	**Task 1:** Finalise an EMA internal (communication/training) plan to ensure an optimal cascade of information to support efficiently CTIS users on prioritised issues for resolution.	Applicable to scenarios 2 and 3
	Task 2: Following prioritisation of reported incidents, the dedicated resources proceed with prompt resolution of issue via *ad hoc* system fixes. *Ad hoc* fixes may include performing activities in the system on behalf of the users.	Applicable to scenarios 2 and 3
	Task 3: Monitor the resolution of prioritised reported issues and the enhanced support to system users.	Applicable to scenarios 2 and 3
	Task 4: Monitor CTIS functionalities regularly and re-apply the ad hoc data fix, if needed.	Applicable to scenarios 2 and 3
	Task 5: Communicate to CTIS users.	Applicable to scenarios 2 and 3

4.2. Reallocation of EMA staff from other activities

Reallocation of EMA staff from other activities		
Action owner	EMA Executive Board	
Action description	To provide better support to CTIS users, it can be decided to temporarily reallocate EMA staff from other activities in order to strengthen the CTIS team dealing with resolving system issues, and quickly re-establish a business-as-usual scenario for CTIS users. Selection of staff to be reallocated should be done based on relevant competences, availability, and with due considerations to the impact that this reallocation may have on other activities for which the Agency is subject to legal and public health obligations.	
Approach	List of criteria to identify resource. Principles on duration and scope of the reallocation, in line with decision of relevant EMA mangers.	
Preparedness activities	**Activity 1:** identify and keep an updated list of relevant personnel on permanence.	Status: ongoing

Reallocation of EMA staff from other activities		
	Activity 2: mobilisation of staff from the list of personnel on permanence and cascade actions list to the relevant personnel.	Status: ongoing
	Activity 3: monitor expected improvements on resolution of issues in CTIS, as consequence of the enlarged team.	Status: ongoing
Tasks description	**Task 1:** Increase EMA resources to support CTIS users by identifying and training EMA staff, allocated to CTIS, based on the following profile/skills: • EMA staff member with relevant experience in project management or • EMA staff with relevant experience in clinical trials or • EMA staff with relevant experience in use of database or • EMA staff with relevant experience in liaising with system users / stakeholders	Applicable to scenarios 2 and 3
	Task 2: Senior staff members to ensure efficient knowledge transfer and training of new colleagues within the CTIS team.	Applicable to scenarios 2 and 3
	Task 3: Communicate to CTIS users.	Applicable to scenarios 2 and 3

4.3. Clinical trial application - allocation of slots

Clinical trial application allocation of slots		
Action owner	EMA TDA-CTS and CTCG	
Action description	In view of the mandatory use of CTIS for new applications as of 31st January 2023, a considerable increase in the number of applications submitted to CTIS can be expected. For a better and more predictable user experience, it can be considered to control submissions of applications, minimising peaks and troughs, based on predefined criteria.	
Approach	Manage the submission of applications to CTIS via slots, making use of predefined criteria.	

Clinical trial application allocation of slots		
Preparedness activities	**Activity 1:** Agree on a process to define the criteria for the prioritisation of submission of applications in slots.	
	Activity 2: Define criteria to prioritise[1] the type of applications to be submitted to CTIS.	
Tasks description	**Task 1:** Monitor that the process to agree on the prioritisation criteria is established, within agreed timelines.	Applicable to scenario 3
	Task 2: In order to achieved better experience for CTIS users via the controlled process on application submissions, monitor that the submission and evaluation of the clinical trial applications for the prioritised trials can be performed smoothly and successfully in CTIS.	Applicable to scenario 3
	Task 3: Ensure that a clear communication to CTIS users, particularly sponsors, is in place on the submission of applications per slots.	Applicable to scenario 3

4.4. Simplify preparation of assessment reports

Simplify preparation of assessment reports		
Action owner	CTCG	
Action description	To reduce the workload on users, simplified process for the preparation of the final assessment reports, for the evaluation of part I and part II of a clinical trial application dossier.	
Approach	Member States to consider reducing time effort allocated in the preparation of the assessment reports (part I and part II, as applicable) in CTIS.	Notes
Preparedness activities	**Activity 1**: Simplify content of assessment reports part I and part II.	Status: planned
	Task 1: To reduce burden on protection of personal data and commercially confidential information in assessment reports, produce a	Applicable to scenario 2 and 3

[1] *Propose to prioritise: trials in public health emergency settings, trials for the treatment of unmet medical needs, trials with therapeutic intent, deprioritise trials already authorised under the clinical trials directive 2001/20/EC*

Simplify preparation of assessment reports		
	shorter and concise document with focus on conclusions aspects.	
	Task 2: Ensure that clear communication to CTIS users, particularly for member states, is in place on simplified process for preparing assessment reports.	Applicable to scenario 2 and 3

4.5. Enable Member States assessment and supervision under the Regulation, but outside CTIS, for new and ongoing trials

Enable member state assessment and supervision for new trials and ongoing trials under the regulation		
Action owner	CTCG	Contact details
Action description	In case of system failure and persistent system downtime, consider allowing submissions of clinical trials data, assessment and supervision of authorised trials outside CTIS. The exchange outside CTIS should be enabledin those cases when safety and wellbeing of clinical trials participants' is at risk, for example, in case of safety issues to be notified to the Regulatory Authorities. In the event of prolonged down time, such activity should also be enabled for critical new clinical trial applications.	
Methodology	A stepwise approach should be followed: 1- In a first instance, the exchange of clinical trial data outside the CTIS should be limited to safety issues and until the system recovery is in place 2- If the system downtime is prolonged the exchange of clinical trial data outside CTIS should be used also for new clinical trial applications.	Notes
Preparedness activities	**Activity 1:** Inform European Commission, Sponsors and Member States, define and agree the process to be followed and the tools to be used, such as Eudralink, as an alternative solution to the use of CTIS.	Status: planned
	Activity 2: Define the responsibilities within the parties, including the establishment of a crisis management team.	Status: planned

Enable member state assessment and supervision for new trials and ongoing trials under the regulation		
	Activity 3: Activate disaster recovery rehearsal procedure.	Status: planned
	Activity 4: Strengthen stress testing activities.	Status: planned
Tasks description	**Task 1:** Apply the agreed process to allow the exchange of clinical trial data outside of CTIS in case of safety issues for example for substantial modifications of authorised trials, reporting of serious breaches, etc.	Applicable to scenario 4
	Task 2: Ensure that clear communication to CTIS users, particularly sponsors, is in place on the submission of clinical trials data outside CTIS.	Applicable to scenario 4
	Task 3: Establish a crisis management team that monitors resolution of CTIS downtime via the application of the disaster recovery procedure.	Applicable to scenario 4
	Task 4: EMA to upload the essential documents in CTIS when the system is again available.	Applicable to scenario 4
	Task 5: Communicate to CTIS users.	Applicable to scenario 4

Annex I - Risk Mitigation Dashboard

The risk mitigation dashboard is to be used to monitor the execution of the mitigating tasks as described above, in case of issues triggering scenarios 2, 3 and 4.

EXAMPLE

Mitigating Strategy	Preparedness status	Tasks	Status	Notes/Comments
4.1: User support prioritisation	◑	1) Finalise an EMA internal (communication/training) plan to ensure an optimal cascade of information to support efficiently CTIS users on prioritised issues for resolution.	◔ or RAG rating	
		2) Following prioritisation of reported incidents, the dedicated resources proceed with prompt resolution of issue via *ad hoc* system fixes. *Ad hoc* fixes may include performing activities in the system on behalf of the users.	◑ or RAG rating	
		3) Monitor the resolution of prioritised reported issues and the enhanced support to system users.	◑ or RAG rating	
		4) Monitor CTIS functionalities regularly and re-apply the *ad hoc* data fix, if needed.	◑ or RAG rating	

Mitigating Strategy	Preparedness status	Tasks	Status	Notes/Comments
4.2: **Reallocation of EMA staff from other activities**	◑	1) Increase EMA resources to support CTIS users by identifying and training EMA staff, allocated to CTIS, based on the following profile/skills: • EMA staff member with relevant experience in project management or • EMA staff with relevant experience in clinical trials or • EMA staff with relevant experience in use of database or • EMA staff with relevant experience in liaising with system users / stakeholders	◑ or RAG rating	
		2) Senior staff members to ensure efficient knowledge transfer and training of new colleagues within the CTIS team.	◑ or RAG rating	
4.3: Clinical trial application allocation of slots	○	1) Monitor that the process to agree on the prioritisation criteria is established, within agreed timelines.	○ or RAG status	
		2) In order to achieved better experience for CTIS users via the controlled process on application submissions, monitor that the submission and evaluation of the clinical trial applications for the prioritised trials can be performed smoothly and successfully in CTIS.	○ or RAG status	
		3) Ensure that a clear communication to CTIS users, particularly sponsors, is in place on the submission of applications per slots.	○ or RAG status	
4.4: Simplify preparation of	○	1) To reduce burden on protection of personal data and commercially confidential information in assessment reports, produce a shorter and concise document with focus on conclusions aspects.	○ or RAG status	

Mitigating Strategy	Preparedness status	Tasks	Status	Notes/Comments
assessment reports		2) Ensure that clear communication to CTIS users, particularly for member states, is in place on simplified process for preparing assessment reports.	○ or RAG status	
4.5: Activities outside CTIS, for new and ongoing trials	○	1) Apply the agreed process to allow the exchange of clinical trial data outside of CTIS in case of safety issues for example for substantial modifications of authorised trials, reporting of serious breaches, etc.	○ or RAG status	
		2) Ensure that clear communication to CTIS users, particularly sponsors, is in place on the submission of clinical trials data outside CTIS.	○ or RAG status	
		3) Establish a crisis management team that monitors resolution of CTIS downtime via the application of the disaster recovery procedure.	○ or RAG status	
		4) EMA to upload the essential documents in CTIS when the system is again available.	○ or RAG status	

● implementation completed
◕ Implementation almost completed
◑ partial implementation
◔ implementation started
○ implementation not started