Australian Clinical Trials Alliance

Risk Management: Guidance for CTNs

Version 1.0

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PURPOSE OF THIS DOCUMENT

This document is intended to assist Clinical Trial Networks (CTNs) in establishing risk management guidelines and or policies.

THE ROLE OF ACTA IN DEVELOPING RISK MANAGEMENT GUIDELINES

The Australian Clinical Trials Alliance (ACTA) is providing advice to assist CTNs in developing risk management guidelines. The generic advice provided by ACTA should be considered and applied by each CTN, taking into consideration the specific requirements of the CTN as well as state or territory laws and regulations.

ACKNOWLEDGEMENTS

We acknowledge the contributions of ACTA CTN members and members of ACTA's Efficient and Effective CTNs Reference Group in the preparation, development, and review of this document. We would like to thank Australian and New Zealand College of Anaesthetists Clinical Trials Network (ANZCA CTN) and Murdoch Children's Research Institute (MCRI) for sharing their policies that have been considered to develop this document.

USE OF THIS DOCUMENT

ACTA encourages the use of all materials listed on its website (www.clinicaltrialsalliance.org.au) in the pursuit of improving the clinical trials enterprise. ACTA requests that the following acknowledgement is included in any CTN authorship and publication guidelines that are developed and documented using knowledge gained from this document:

> "[Name of CTN] acknowledges the contribution of the Australian Clinical Trials Alliance to the development of trial endorsement processes within our network (reference: *Risk Management: Guidance for CTNs*)."

DISCLAIMER

The information in this document is for general guidance only. ACTA does not make any representations or warranties (expressed or implied) as to the accuracy, currency or authenticity of the information provided.

ABBREVIATIONS

ACTA	Australian Clinical Trials Alliance
AS/NZS: ISO	Australian Standards/New Zealand Standards: International Organization for Standardization
ANZCA	Australian and New Zealand College of Anaesthetists
CTN	Clinical Trials Network
EMA	European Medicines Authority
FDA	Food and Drug Administration
GCP	Good Clinical Practice
MCRI	Murdoch Children's Research Institute
NHMRC	National Health and Medical Research Council
NSQHS	National Safety and Quality Health Service
NSW	New South Wales
RACT	Risk Assessment and Categorisation Tool
TGA	Therapeutic Goods Administration
VCCC	Victorian Comprehensive Cancer Center
VMIA	Victorian Managed Health Insurance Authority

OVERVIEW

RISKS IN CLINICAL TRIALS

There are several definitions of risk depending on the context, industry, and other circumstances. AS/NZS ISO 31000:2018 defines risk as "the effect of uncertainty on objectives".[1] The effect can be either positive or negative. The Therapeutic and Goods Administration (TGA) defines risk as "a measure of the combination of the likelihood and the consequence of an undesirable event".

There are several contributory factors, but clinical trial risks can be categorised into two groups:

1. System level risks (e.g. facilities, staff, information technology, standard operating procedures, and contractors).
2. Trial level risks (e.g. investigational medical products, experimental procedures, data collection, data storage and security).

CTN risks can also be further categorised into organisational level, CTN level, study level, site level and operational level risks. These risks may vary according to site experience and location. CTNs need to manage risks in compliance with statutory, regulatory, ethical, organisational and governance requirements.

RISK CULTURE

Risk culture can be defined as the influence of organisational culture on risk management.[2] Organisational culture is defined as "the values, beliefs, knowledge and understanding, shared by a group of people with a common purpose".[3] It is possible for an organisation to have multiple organisational cultures.

Organisational risk culture has been defined as "the norms and traditions of behaviour for individuals and of groups within an organisation that determine the way in which they identify, understand, discuss and act on the risks the organisation confronts and the risks it takes".[4]

A diagnostic assessment of the CTN risk culture can be conducted internally or externally using the 'Risk culture diagnostic spectrum' questionnaire (Table 1). It can be used as a gap analysis tool for improving risk culture.

Table 1: Risk culture diagnostic spectrum

		Strong		Fair		Weak	
Test category		**5**	**4**	**3**	**2**	**1**	**0**
A	Leadership tone on risk						
B	Governance processes related to risk						
C	Transparency on risk strategy, appetite, and exposure						
D	Resources related to risk management						
E	Technical risk skills						
F	Decision-making processes, timeliness, and success						
G	CTN/Risk management relationship						
H	Communications frequency and clarity						
I	Incentive mechanisms related to risk-taking						
J	Risk-related surprises						

Total score

Strong risk culture: 40–50, proactive, in command of risks, avoids problems

Fair risk culture: 20–39, reactive, generally avoids problems

Weak risk culture: 0–19, unaware, susceptible to problems

IMPORTANT NATIONAL AND STATE OR TERRITORY LEGAL AND REGULATORY POLICIES, GUIDELINES AND FRAMEWORK LINKED TO RISK MANAGEMENT

Table 2: Guidelines and framework linked to risk management

Type of document	Organisation	Title	Reference
Regulatory	Therapeutic Goods Administration (TGA)	Risk management plans for medicines and biologicals: Australian requirements and recommendations The Therapeutic Goods Administration's risk management approach to the regulation of therapeutic goods	1 2
	European Medicine Agency (EMA)	ICH guideline Q9 on quality risk management	3
	Food and Drug Administration (FDA)	Oversight of clinical investigations – a risk-based approach to monitoring	4
State	NSW Health NSW Office of Communities	Clinical trials – insurance and indemnity Risk management for not-for-profit organisations	5 6
	South Australia	Risk management framework	7
	Victoria Managed Health Insurance Authority (VMIA) Victoria Comprehensive Cancer Center (VCCC)	Clinical trials: risk and insurance guide Risk management: investigator-initiated clinical trial	8 9
	Department of Health: Western Australia	Clinical risk management guidelines for the Western Australian health system risk management policy	10
	Queensland	Health, safety, and wellbeing risk management standard	11
Standards	AS/NZS ISO 31000:2018 National Safety and Quality Health Service (NSQHS)	Risk management — principles and guidelines The national clinical trials governance framework and user guide for health service organisations conducting clinical trials	12 13
Funding bodies	National Health and Medical Research Council (NHMRC)	Risk-based management and monitoring of clinical trials involving therapeutic goods	14

RISK MANAGEMENT PROCESS IN CLINICAL TRIALS

RISKS MANAGEMENT PROCESS

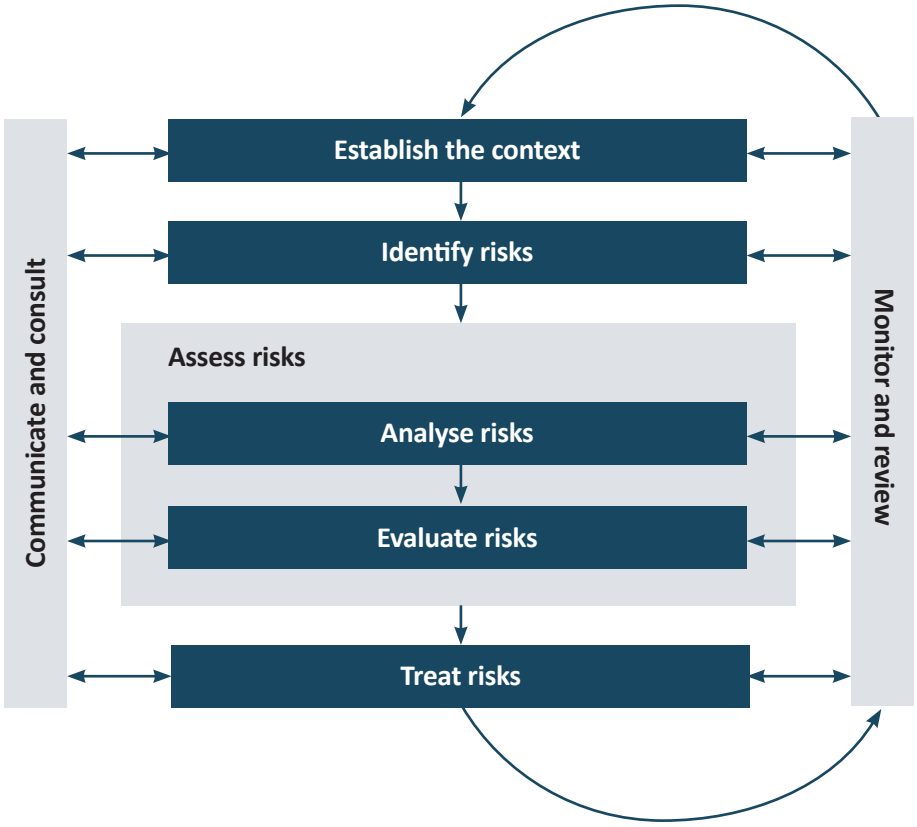

Figure 1: Risk management process

Establishing the context for risk management in a CTN

This is the process of data collection for risk identification and may involve brainstorming sessions, gathering expert opinions, or conducting surveys from study sites. External and internal factors that impact the operational environment of the CTN as well as individual clinical trials are identified.

The **external** factors may be cultural, political, legal, regulatory and financial in nature. Those factors may operate in a local, regional, national or international environment. Identification of perceptions and values of external stakeholders like the funding, regulatory, ethical, and independent data and safety monitoring bodies or committees is also very important. **Internal** factors that should be contextualised include CTN objectives/goals, research priorities, organisational assets, competence of study teams, maturity of study sites and internal stakeholder perceptions and values.

Risk management planning

Risk management planning is part of the governance functions of a CTN.[13] Risk management planning should be aligned to all other organisational processes. The Risk Management Plan defines the following:

- Scope and objectives of the risk management process
- The roles and responsibilities
- Integration of risk and other clinical trial functions
- Risk Assessment and Categorisation Tool (RACT)
- Data sources for identifying risks
- Risk tolerance levels
- Risk escalation procedures
- Process for monitoring and evaluation of risks
- Process for communicating risks.

Many organisations confuse a risk management plan and a risk register. A risk register is a tool for documenting and managing risks. Appendix 1 is a template for the Risk Management Plan. Appendix 2 is a sample Risk Register.

Identifying risks

Risk identification can be defined as the process of determining everything that could go wrong at the CTN, study sites and at the level of individual clinical trials. It is a continuous process aimed at identifying every possible situation that may impact on the organisational or study objectives. Risk identification is done through brainstorming and should involve as many stakeholders as possible.

The first step of risk identifications is the identification of risk areas, or clinical trial related units, process, and tasks. Figure 2 shows a classification of risk areas.

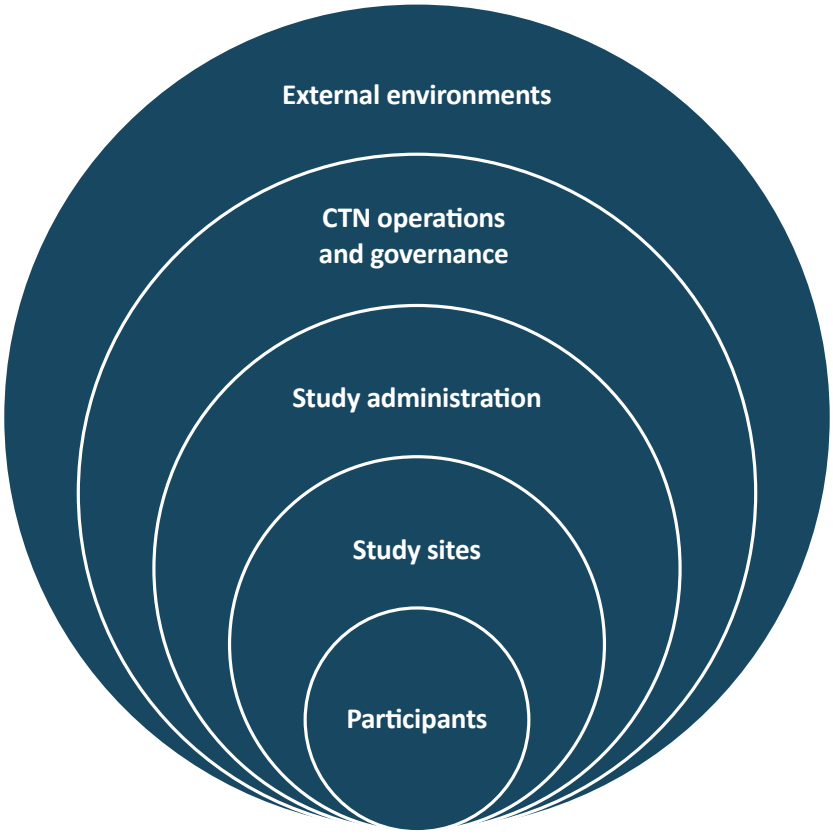

Figure 2: Risk areas

Brainstorming sessions with stakeholders within each of these risk areas will aid in identifying as many risks as possible. Once identified, the risks are entered into the risk register where they are assessed. The next two sections will cover risk assessment, which comprises risk analysis and risk evaluation.

An alternative method of identifying risk is through process mapping.[18] The clinical trial process map is downloadable from http://www.ct-toolkit.ac.uk/routemap/dissemination-of-results/downloads/ct-toolkit-v1.1.pdf

The clinical trial roadmap is a very complicated process with multiple steps. In addition, there are managerial and support functions like information technology (IT), document management, procurement management and regulatory affairs, which impact on trial conduct.

Analysing risks

Risk analysis is a process of understanding the causation, likelihood and consequences of risk whilst taking into consideration the presence and effectiveness of control measures. This is done through a root cause analysis using a cause and effect diagram (Ishikawa/fishbone). An affinity diagram is then used to group the causes into categories (e.g. human resource, equipment, hazards, regulatory and external environmental). An example of causal analysis is shown in Table 3.

Table 3: An example of causal risk analysis

Sources Causes	**Risk area** Risk
Inadequate site assessment and preparation Insufficient suitable patients enrolled from a site	**Study** Study will take longer to reach recruitment target
No GCP training requirement for investigators High numbers of ineligible patients enrolled Consent and follow-up procedures are not followed	**Study administration** High rates of protocol deviations
Weak CTN governance processes CTN Leader does not declare conflict of interest during trial endorsement	**CTN operations and governance** CTN disharmony, complaints and CTN reputation at stake

The next stage of risk analysis is determining the consequences of the identified risks. The consequences could be immediate or delayed, short-term or long-term. Risk analysis is a process of determining the likelihood and severity of a risk. An example is shown in Figure 3.

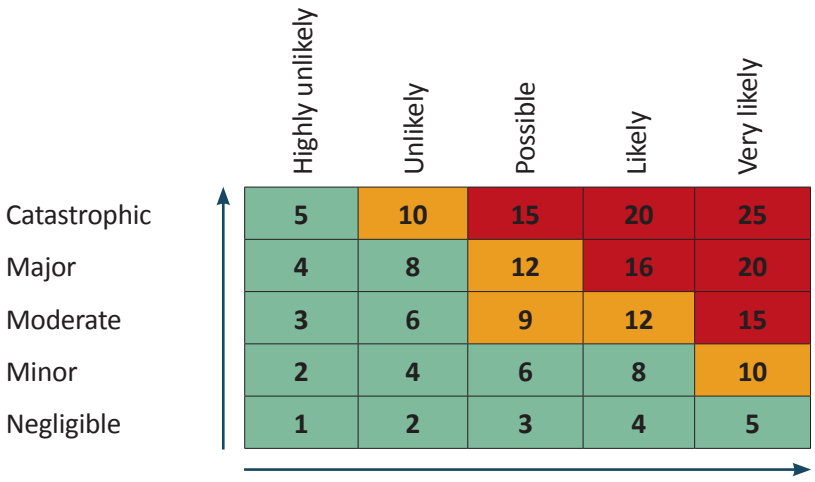

Figure 3: Risk analysis example

Evaluating risks

Risk evaluation compares the level of risk established during the risk analysis phase to the risk criteria set as part of risk management planning (Figure 4). The main purpose of risk analysis is to decide which risks need treatment, and prioritise the implementation of risk treatment.

	Severity				
Likelihood	**Negligible**	**Minor**	**Moderate**	**Major**	**Catastrophic**
Very likely	**Acceptable** Add controls				
Likely			**Acceptable** Add controls	**Unacceptable** Avoid or eliminate	
Possible					
Unlikely	**Acceptable** Routine practice			**Acceptable** Add controls	
Very unlikely					

Figure 4: Risk evaluation example

Treating risks

Risk treatment is a process of reducing risks to acceptable levels. It may involve the following options:

- **Risk avoidance:** A project task or activity that gives rise to a risk is either not implemented or discontinued.
- **Risk acceptance:** A project task or activity is continued after considering that the risk is not different from routine clinical practice.
- **Risk elimination:** The source of the risk is removed before implementation of a project task or activity.
- **Risk mitigation:** Taking steps to reduce the likelihood or consequences of a risk.
- **Risk sharing:** Sharing the risk with other parties (shared funding, subcontracting or insuring).

Monitoring and reviewing risks

This is a process of periodic and ad hoc surveillance of risks management processes to:

- Ensure that risks are effectively and efficiently treated
- Update risk identification and assessment throughout the life cycle of individual clinical trial projects
- Update risk treatments.

The National Health and Medical Research Council[19] provides guidance on frequency of risk monitoring for different categories of Investigational Medical Products (IMP) related clinical trials.

Communicating and consulting on risks

Risk communication and consultation begins during context analysis and continues throughout the risk management process. Risk communication includes the following elements:

- Roles and responsibilities
- Stakeholder identification (e.g. participants, researcher team, healthcare facility teams, CTN members, CTN leadership, sponsors, regulatory bodies, media)
- Define stakeholder risk communication requirements and priorities
- Frequency of communication
- Communication channels.

The Communication and Management Guidance Document addresses these issues in detail.

RISK MANAGEMENT DURING A PANDEMIC (E.G. COVID-19)

Pandemics like COVID-19 are unforeseen events for which adequate risk planning is not possible. Such events may introduce additional risks that organisations should be able to identify, assess, mitigate, document and manage. Table 4 shows risks that have been linked to COVID-19 as well as possible mitigation strategies.

Table 4: Risks that have been linked to COVID-19 and possible mitigation strategies

Risk	Mitigation strategy
Missed study visits due to inability for patients to travel to study sites or limits to non-essential clinic visits.	Telephone or video conferencing consultations have been recommended. If face-to-face consultations are essential, private car transportation to study sites is recommended.
Delays in study initiation activities due to inability to conduct site selection, training or initiation visits as well as travel restrictions for clinical trial teams and vendors.	For well-established clinical trial sites, virtual site initiation and training visits can be done. For newly established sites, a delay or cancellation of site initiation would be recommended.
Protocol deviations arising from inability to adhere study visits, study procedures and monitoring processes.	Consult Ethics Committees for about any anticipated protocol deviations as early as possible. Document and report all protocol deviations to the Ethics Committees.
Delays in clinical material distribution due to national and international travel restrictions.	Consideration for alternative shipping and distribution arrangements for clinical trial materials should be done in compliance with national and international laws.
Delays in ethics and site-specific approvals.	Consider delaying any new non-COVID-19 related studies.
Cancellation or postponement of major scientific meetings.	Virtual meetings are recommended where possible.

REFERENCES

1. Therapeutic Goods Administration (TGA). (2019). *Risk management plans for medicines and biologicals: Australian requirements and recommendations*. Canberra.
2. Therapeutic Goods Administration (TGA). (2011). *The Therapeutic Goods Administration's risk management approach to the regulation of therapeutic goods*. Canberra.
3. European Medicines Agency (EMA). (2015). *ICH guideline Q9 on quality risk management*. EMA, London.
4. Food and Drug Administration (FDA). (2013). *Oversight of clinical investigations — a risk-based approach to monitoring*. US Department of Health and Human Services, Silver Spring, MD.
5. NSW Health. (2011). Clinical trials – insurance and indemnity, in *Policy Directive,* Office for Health and Medical Research, Sydney.
6. NSW Office of Communities. (ND). *Risk management for not-for-profit organisations*. NSW Office of Communities.
7. Government of South Australia. (ND). *Risk management framework*. Department for Communities and Social Inclusion.
8. Victorian Managed Insurance Authority (VMIA). (2015). *Clinical trials: risk and insurance guide*. Victoria State Government, Melbourne.
9. Victorian Comprehensive Cancer Center (VCCC). (2020). *Risk management: investigator initiated clinical trial.* Available from: https://www.viccompcancerctr.org/what-we-do/clinical-trials-expansion/investigator-initiated-trials/risk-management
10. The Office of Safety and Quality in Health Care Clinical Risk Management Guidelines for the Western Australian Health System, in *Information Series No. 8.* Deapartment of Health WA, Perth.
11. Queensland Health. (2018). *Health, safety and wellbeing risk management standard*.
12. International Standards Organization (ISO). (2018). *Risk managment: ISO 31000:2018. International Organization for Standardization*, ISO.
13. Australian Commission on Safety and Quality in Health Care (ACSQHC). (2020). *National clinical trials governance framework – guide for implementation*. Sydney.
14. National Health and Medical Research Council (NHMRC). (2018). *Risk-based management and monitoring of clinical trials involving therapeutic goods*.

APPENDIX 1: TEMPLATE FOR A RISK MANAGEMENT PLAN

<Insert CTN/CC name>

BACKGROUND

Use this section to describe the organisational context as well as explain the importance of the risk management plan. Explain the aims and scope of the risk management plan. Include the risk management roles and responsibilities in this section.

Example:

The (insert CTN name) is committed to effective and efficient identification, treatment and monitoring of risks that may affect the implementation of our strategic and business objectives. Implementation of this plan will be done through the Risk Management Committee (any other relevant committee) of the CTN.

This risk management plan is applicable to all our CTN operations as well as clinical trial sites that are affiliated to our CTN. This risk management plan aims to:

- provide guidance for all risk management activities of the CTN
- describe the risk management processes that are to be followed by all members of the CTN, clinical trial sites, contractors, and visitors
- minimise the CTN's exposure to significant risks through identification, assessment, treatment and monitoring of risk.

TOP 5 RISKS

We have identified the following as our top 5 risks:

1. <Insert risk here and provide a detailed summary of that risk>
2. <Insert risk here and provide a detailed summary of that risk>
3. <Insert risk here and provide a detailed summary of that risk>
4. <Insert risk here and provide a detailed summary of that risk>
5. <Insert risk here and provide a detailed summary of that risk>

RISK MANAGEMENT APPROACH

Describe your approach to identifying and managing risks in this section.

Example:

Our project teams will identify, score, and prioritise the various project risks. We document the risks with the highest impact on the risk register and assign Risk Managers to each of those risks. Risk Managers are responsible for monitoring the risks and implementing the appropriate mitigation strategies. Risk Managers are also expected to provide regular status reports on their assigned risks.

Upon completion of a project, the Project Manager analyses all risks as well as the risk management process. The results of this analysis are documented in our lessons learned document and inform future risk management processes.

RISK IDENTIFICATION

Explain how risks will be identified. Typical methods include an historical review of similar projects, expert interviews and risk assessment meeting with project teams and stakeholders.

RISK QUALIFICATION AND PRIORITISATION

This section will discuss how risk analysis will be done. The process of risk analysis and prioritisation will be discussed. Risk analysis is usually done using a probability-impact matrix tool.

RISK MONITORING

Discuss how project and organisational risks will be actively monitored and documented. This section will also identify any trigger conditions for each of the high priority risks.

RISK MITIGATION AND AVOIDANCE

This section will identify the options for managing each of the project and organisational risks within the context of time, cost, and scope constraints.

APPENDIX 2: RISK REGISTER

The following table is a sample format of a risk register that could be used to document the CTN's risks and controls, along with an example of risk assessment criteria.

Note: this is an indicative risk register template only and should be tailored according to each CTN.

			Current risk rating				Target risk rating		
Risk #	**Risk**	**Current treatments to manage risk**	**Likelihood**	**Severity**	**Rating**	**Action plan (additional controls required)**	**Likelihood**	**Severity**	**Rating**
1	Insufficient study enrolments	• Selection of experienced study sites • Use of Quality Registers to identify suitable participants • Aggressive marketing campaigns • Recruitment of a community liaison officer	Possible	Major	High	• Weekly monitoring of enrolment logs • Site induction for researchers • Identification of new study sites	Unlikely	Major	Medium
2	Inadequate funding for new studies	• Research prioritisation framework introduced • Enhanced peer review of new grant applications • All clinical trials include cost-effective studies	Possible	Major	High	• Identify new funding streams • Prioritise pragmatic clinical trials • Consider Registry Clinical Trials	Unlikely	Major	Medium
3	Incomplete documentation of serious adverse events	• GCP training for all researchers • One-day training course for research team • Quality control team in place • External study monitor engaged • Independent Data Safety and Monitoring Committee	Unlikely	Major	High	• Scenario discussions at study sites • Participant education of SAE • Training of local health teams on expected SAE for studies	Unlikely	Minor	Low

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